Metabolic Syndrome and Diabetes

Medical and Surgical Management

Marina Kurian
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Preface

A few years ago, I had the great pleasure of chairing a course with Dr. Bruce Wolfe on Metabolic Syndrome and its management. This was a well-attended course that provided clarity on what we as medical professionals are trying to achieve in this patient population. My coeditors, Dr. Sayeed Ikrammudin and Dr. Bruce Wolfe, presented the nascent biology of the disease and the cause of inflammation with such aplomb that the attendees were truly riveted by the material. There were several other presentations delivered by experts in bariatric surgery on the outcomes of weight loss surgery in metabolic syndrome. At the close of the course, Bruce and I were approached by Richard Hruska, editor at Springer, about creating a textbook based on the course.

As we committed to the book, I wanted Sayeed to be a part of the project. For those of you who don't know either Bruce or Sayeed, they are two of the most thoughtful and consummate scientists I know. Both have spent considerable time delving into disease etiology and incretin effect on diabetes and metabolic syndrome. With their help, we created a textbook that is a resource for all medical professionals and gives the most up-to-date research on the topic. This is a textbook that is comprehensive in its focus on metabolic syndrome with medical and surgical perspectives from experts in the field. This book is a resource for everyone involved in the care of the patient with diabetes and/or metabolic syndrome. Sayeed, Bruce, and I are proud of the finished product, and we know you, the reader, will appreciate the clarity this book provides.

New York, NY, USA — Marina Kurian, M.D., F.A.C.S., F.A.S.M.B.S.

Contents

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Definition, History, and Management of the Metabolic Syndrome and Management Gaps

1

Josep Vidal and Amanda Jiménez

1.1 Historical Perspective

As nicely reviewed by Enzi et al., a report of the association between visceral obesity and cardiovascular disease (CVD) was already provided by Morgagni back in the eighteenth century using macroscopic anatomical description [1]. As summarized below, many have followed and refined the observational skillfulness of the Italian anatomist. Over time, clinical observations on the clustering of cardiovascular risk factors evolved into pathophysiological constructs and, lately, into the clinical entity we now know as the metabolic syndrome (MetS).

Early in the twentieth century, several European physicians suggested that metabolic abnormalities such as hypertension and diabetes often presented in the same individual [2, 3] (Table 1.1). The recognition of the clustering of CVD risk factors was first categorized as a syndrome by Kylin when he proposed the "hypertension–hyperteglycemia–hypeuricemia syndrome" in 1923 [4]. In the mid-twentieth century, Jean Philippe Vague fostered the importance of body fat distribution as determinant of the association of several CVD risk factors in a particular subject. In 1947, Vague first described the sexual dimorphism of body fat distribution [5]. A few years later, he portrayed the closer association between android obesity, diabetes, hypertension, and atherosclerosis as compared to that between CVD risk factors and the gynoid type of body fat distribution [6]. The relationship between body fat distribution and metabolic complications of obesity was later further emphasized by several independent groups. Kassebah et al. hypothesized disparate morphology and metabolic behavior of fat cells accounting for the differential association of CVD risk factors with different body fat distributions [7]. Contemporarily, Albrink described the relationship between obesity, hypertriglyceridemia, and low

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Table 1.1 Chronological overview of the history of the metabolic syndrome

Year	Authors	Contribution
1765	Morgagni JP [1]	Macroscopic anatomic description of the association between visceral obesity and CV disease
1921	Hitzenberger K [2]	Description of the relationship between diabetes mellitus and hypertension
1922	Marañon G [3]	Description of the relationship diabetes mellitus and hypertension
1923	Kylin E [4]	Description of a syndrome of diabetes mellitus, hypertension, and hyperuricemia
1947	Vague JP [5]	Description of the android and gynoid types of obesity
1956	Vague JP [5]	Connection between android obesity and diabetes, hypertension, gout, and atherosclerosis
1966	Camus JP [10]	Description of the metabolic tri-syndrome: gout, diabetes, and hyperlipidemia
1967	Avogaro P [11]	Description of the plurimetabolic syndrome (hyperlipidemia, obesity, diabetes, hypertension)
1968	Menhert H, Kuhlman H [14]	Description of the syndrome of affluence
1977	Haller H [12]	Relationship between the metabolic syndrome and atherosclerosis
1980	Albrink MJ [8]	Relationship between obesity, hypertriglyceridemia, and low HDL-cholesterol
1981	Hanefeld M, Leonhardt W [13]	Metabolic syndrome: T2DM, hyperinsulinemia, obesity, hypertension, hyperlipidemia, gout, and trombophilia
1982	Kissebah AH [7]	Description of the disparate morphology and metabolic behavior of fat cells in different body fat distributions
1988	Reaven GM [17]	Syndrome X (insulin resistance as the common link)
1989	Kaplan NM [20]	The deadly quartet (central adiposity, IGT, hypertriglyceridemia, hypertension)
1991	De Fronzo RA, Ferrannini E [21]	Description of the multifaceted insulin resistance syndrome
1992	Larsson B [9]	Relationship between body fat and sex differences in cardiovascular disease

HDL-cholesterol plasma concentration [8]. Furthermore, in the mid-1990s a Swedish group suggested that body fat distribution or a highly correlated factor (genetic, hormonal, or behavioral) could help explain the sex differences observed in the incidence of coronary heart disease [9]. Terms similar to MetS were used to describe the association of cardiovascular risk factors already in the mid-1960s of last century. Camus named "metabolic tri-syndrome" the association of gout, diabetes, and hypelipidemia [10]. Avogaro proposed the term "plurimetabolic syndrome" to describe the association of obesity, diabetes, hyperlidemia, hypertension and CVD [11]. Finally, in 1977 Haller defined a "metabolic syndrome" as the confluence of obesity, diabetes mellitus, hyperlipoproteinemia, hyperuricemia, and hepatic esteatosis [12]. Of note, the authors underlined the potentiating effect of the

combination of risk in atherosclerosis. The term "metabolic syndrome" was also used by Hanefeld and Leonhardt in 1981 to depict the association of diabetes, hyperinsulinemia, obesity, hypertension, hyperlidemia, gout, and thrombophilia [13]. From the early descriptions of the cluster of CVD risk factors, it was underscored that lifestyle was associated with the presence of the metabolic disturbances [3]. This was the basis for Mehnert and Kuhlmann to jointly name the clinical manifestations described above as "syndrome of affluence" [14].

On the occasion of the Banting Medal address at the 1988 annual meeting of the American Diabetes Association, Gerald M Reaven first introduced the term Syndrome X [15]. According to its pathophysiology, insulin-resistant nondiabetic individuals would be at increased risk to be somewhat glucose intolerant, hypertensive, and present with a form of dyslipidemia best described by the presence of elevated plasma triglycerides and low plasma HDL-cholesterol concentrations. The notion of a syndrome was proposed by Reaven to acknowledge that insulin resistance underlies several downstream manifestations. The number of these alterations present in a particular individual would vary depending upon the presence of additional factors. For instance, type 2 diabetes would not occur in the presence of insulin resistance unless a subject is unable to secrete enough insulin to overcome the defect in insulin action [16]. The X in the name of the entity was used to capture attention to the fact that the importance of insulin resistance as CVD risk factor was relatively unknown [17]. As a whole, the term Syndrome X served Reaven to emphasize the importance of insulin resistance and its manifestations as cardiovascular risk factors. The list of manifestations associated with insulin resistance was further expanded by several authors following the initial description by Reaven and will be discussed in the next chapter in this book. As insulin resistance was deemed the underpinning mechanism of Syndrome X, obesity or body fat distribution were not in the definition of the syndrome. The group by Reaven had shown that not all obese individuals are insulin resistant, and reciprocally nor are all insulin resistant individuals are obese [18]. As derived from the seminal study of the European Group for the Study of Insulin Resistance, only approximately 25 % of the variability in degree of insulin resistance in nondiabetic individuals would be accounted for by differences in degree of obesity [19].

It was only 1 year after Reaven's Banting Medal address, that Kaplan vindicated again the importance of upper-body obesity as major contributor to other CVD risk factors often times present in some individuals [20]. Kaplan defined the deadly quartet as the combination of central adiposity, glucose intolerance, hypertriglyceridemia, and hypertension. The author acknowledged the importance of insulin resistance and the accompanying hyperinsulinemia as key intermediaries in the pathogenesis of the cluster of CVD risk factors. Furthermore, Kaplan recognized that genetic and environmental factors would be involved in its pathogenesis, since each of the different components of the quartet may occur in the absence of the others. However, following on Vague's work, he call into attention the fact that obesity was being oversight as a major contributor to the CVD risk not captured by the traditional CVD risk factors. The inclusion of obesity in a multifaceted syndrome

characterized by insulin resistance/hyperinsulinemia was further endorsed by DeFronzo and Ferrannini in 1991 [21].

In summary, this historical overview clearly underscores that the observations on the confluence of certain CVD risk factors in some individuals more often than by chance are not novel. Although some disagreement on its pathophysiology exists, historical concordance could be found in that such CVD risk factors are tightly linked to our lifestyle and would be alleviated by means of interventions aiming at lifestyle modification.

1.2 The Definition of the Metabolic Syndrome

In 1998, the World Health Organization (WHO) was first in proposing a formal definition of the MetS [22]. Several organizations followed (Table 1.2) [24–30]. Nonetheless, despite this sequence starting 15 years ago, the MetS definition still appears to be a work in progress and is seen rooted in controversy regarding its clinical utility [23].

By providing a definition of the MetS, the group of WHO experts aimed at emphasizing the CVD risk associated with the coexistence in one individual of hypertension, upper body obesity, and dyslipidemia, with or without hyperglycemia [22]. They call attention to the fact that despite each component of the cluster conveying increased CVD risk, the combination of the different component was considered much more powerful. Furthermore, for those with normal glucose tolerance the concurrence of other components would put them at risk for future diabetes. The definition was presented embedded in a report on the diagnosis and classification of diabetes. For the diagnosis of the MetS either some degree of glucose intolerance and/or insulin resistance (as assessed from a hyperinsulinemic euglycemic clamp) was required. The diagnosis of the MetS would be made if two additional risk factors were present (Table 1.2).

Shortly after the WHO report had been published, the European Group for the Study of Insulin Resistance (EGIR) suggested some amendments to the proposed definition (Table 1.2) [24]. The EGIR experts considered as premises that (1) the diagnosis of the MetS was intended at easily identifying a group of patients with mild anomalies which, in combination, increase CVD risk, and (2) that insulin resistance was the underlying mechanism. From that perspective, the EGIR experts proposed fasting plasma insulin as simple measure of insulin sensitivity and to restrict the diagnosis of the MetS to nondiabetic individuals. In the presence of insulin resistance, the MetS would be diagnosed in the presence of two additional risk factors: impaired fasting but nondiabetic hyperglycemia, enlarged waist circumference, mildly elevated blood pressure, and elevated triglycerides and/or low HDL-cholesterol (Table 1.2). To strength the simplicity and feasibility of the diagnosis, the EGIR proposal left out of the definition the microalbuminuria criterion that was part of the WHO proposal.

In 2001, a new set of diagnostic criteria for the MetS was issued by the National Cholesterol Education Program (NCEP-ATPIII) (Table 1.2) [25]. The NCEP-ATPIII

Table 1.2 Components of the metabolic syndrome according to the definitions proposed by different organizations

WHO	EGIR	NCEP-ATP III	IDF	AHA/NHLB	IDF-AHA/NHLB
Glucose intolerance and/or insulin resistance (hyperinsulinemic euglycemic clamp)	**Elevated fasting insulinemia (upper 25th percentile of nondiabetics)**	WC ≥102 cm in males, ≥88 in females	**Elevated waist circumference (Population specific)**	WC ≥102 cm in males, ≥88 in females	Elevated waist circumference (Population specific)
Central obesity (males W/H>0.9, females >0.85) or BMI>30 kg/m^2	FPG ≥110 mg/dl, but not diabetic	FPG ≥110 mg/dl	FPG ≥100 mg/dl or drug therapy for ↑ glucose	FPG ≥100 mg/dl or drug therapy for ↑ glucose	FPG ≥100 mg/dl or drug therapy for ↑ glucose
BP ≥160/90 mmHg	SBP ≥140 mmHg or DBP ≥90 mmHg or drug therapy for ↑ BP	SBP ≥130 mmHg or DBP ≥85 mmHg	SBP ≥130 mmHg or DBP ≥85 mmHg or drug therapy for ↑ BP	SBP ≥130 mmHg or DBP ≥85 mmHg or drug therapy for ↑ BP	SBP ≥130 mmHg or DBP ≥85 mmHg or drug therapy for ↑ BP
Triglycerides ≥150 mg/dl and/or HDL-cholesterol <35 mg/dl in males or <39 mg/dl in females	Triglycerides ≥2.0 mmol/L and/or HDL<1.0 mmol/L	Triglycerides ≥150 mg/dl	Triglycerides ≥150 mg/dl or drug therapy for ↑ triglycerides	Triglycerides ≥150 mg/dl or drug therapy for ↑ triglycerides	Triglycerides ≥150 mg/dl or drug therapy for ↑ triglycerides
Microalbuminuria (UAER ≥20 μg/min or albumin/creatinine ≥20 mg/g)	WC ≥94 cm in males, ≥80 in females	HDL-cholesterol ≤40 mg/dl in males or ≤50 mg/dl in females	HDL-cholesterol ≤40 mg/dl in males or ≤50 mg/dl in females for ↓ glucose	HDL-cholesterol ≤40 mg/dl in males or ≤50 mg/dl in females for ↓ glucose	HDL-cholesterol ≤40 mg/dl in males or ≤50 mg/dl in females for ↓ glucose

WHO World Health Organization, *EGIR* European Group for the study of Insulin Resistance, *NCEP-ATP* National Cholesterol Education Program-Adult Treatment Panel, *IDF* International Diabetes Federation, *AHA/NHLB* American Heart Association/National Heart, Lung, and Blood Institute, *W/H* waist to hip ratio, *BMI* body mass index, *SBP/DPB* systolic/diastolic blood pressure. *WC* waist circumference, *UAER* urinary albumin excretion rate

Bolded components refer to those required for the diagnosis of the metabolic syndrome according to the corresponding organization

criteria aimed at easily identifying subjects in whom the CVD risk reduction associated with LDL-cholesterol lowering therapy could be threatened because of the presence of metabolic abnormalities often times associated with overweight or obesity. It was acknowledged that insulin resistance, a proinflammatory state, and a prothrombotic state were part of the syndrome but were left out of the definition because these were unfeasible to detect in routine clinical practice. At variance with previous definitions no single criterion was required for the diagnosis, but rather the diagnosis of the MetS was made in the presence of any combination of three of a set of five components. As previously endorsed by others, the MetS was considered a risk enhancer of CVD and T2DM. Nonetheless, as suggested by the WHO, the diagnosis of the MetS was applicable to subjects with T2DM.

The American Association of Clinical Endocrinologists (AACE) was next (2003) in joining the work in progress towards a definition of the MetS [26]. The criteria included were similar to those proposed by the WHO and ATP (obesity, elevated blood pressure, elevated triglycerides, low HDL-cholesterol), but the number of risk factors needed was not specified and the diagnosis was left to clinical judgment. As for the EGIR, the diagnosis would no longer apply when T2DM is present. Additional factors to inform clinical judgment included a family history of T2DM, hypertension or CVD, polycystic ovarian syndrome, advancing age, or a sedentary lifestyle.

In 2006, a new proposal came from the International Diabetes Federation (IDF) (Table 1.2) [27]. The proposal aimed at an easy to use and worldwide valid definition of a set of criteria that would allow the identification of subjects at considerably increased risk of developing CVD and/or T2DM. The IDF experts considered the obesity epidemic to be one of the main drivers of the high prevalence of the MetS. The 2001-ATP III definition was used as a starting point to be modified and updated to reflect current knowledge. At variance with the NCEP-ATPIII definition, the IDF proposal included central obesity as required criterion for the diagnosis. The rationale for this requirement was that central obesity was found more strongly correlated with the other MetS components than is any other parameter. Gender and ethnic-group specific cut-points for the waist circumference were proposed to acknowledge group-differences in body fat distribution. Two of for additional factors were required for the diagnosis of the MetS (Table 1.2). Of note, contemporarily to the IDF proposal, the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) slightly modified the NCEP-ATPIII criteria but did not obligatorily mandated an enlarged waist circumference for the diagnosis of MetS to be made [28]. The AHA/NHLBI considered that the different consideration of the obesity criterion between the two proposals would have minor effects since most individuals with the MetS according the AHA/NHLBI criteria would test positive for it.

The remaining differences between the IDF and the AHA/NHLBI were discussed in a joint meeting in 2009 and resulted in a harmonized definition of the MetS (Table 1.2) [29]. As a result, abdominal obesity was not considered any more a prerequisite for the diagnosis but rather given equal consideration to the other four components. The diagnosis would be made in the presence of any combination of at

least three out of the five agreed criteria (Table 1.2). Interestingly, it was recommended that until more data was available the IDF cut-point for waist circumference were used in non-Europeans, and either the IDF (male ≥94, female ≥80) or AHA/NHLBI (male ≥102, female ≥88) for people of European origin. As previously proposed separately by the two organizations the diagnosis of the MetS would not exclude subjects with T2DM.

The final chapter of this evolutionary history was made public in 2010 and came, interestingly, from a WHO expert consultation [30]. In our opinion, that report contains several important statements. First, it was acknowledged that a formal diagnosis of the MetS is rarely made in routine clinical practice and has not been widely adopted in national guidelines for the prediction of CVD or T2DM. Second, the MetS should be considered as a pre-morbid condition rather than a clinical diagnosis. Thus, the diagnosis of the MetS does not apply to those with already existing T2DM or CVD. Third, efforts should be placed in elucidating the mechanisms underlying the clustering of the different components of the MetS rather than in developing new or revised definitions. Finally, it was concluded that despite the MetS could be useful as educational concept, it has limited practical utility as management tool.

In summary, over the last two decades we have witnessed a work in progress in search of clinically useful definition of the MetS. The existence of multiple definitions for the MetS has inevitably led to confusion. Proposals have varied depending on the underlying views of the proponents. It looks as if at the current stage we have not succeeded in our aim.

1.3 What Is in the Diagnosis?

According to the current of state of the art, the MetS could be best conceptualized as a recognizable cluster of physical and biochemical abnormalities occurring in one individual more often than expected by chance and for which the direct underlying cause is not well understood. The use of statistical analysis techniques appears to confirm the view that the different components of the MetS are part of a single entity [31]. In sharp contrast, over the last years the MetS has rather been used as clinical tool for the identification of individuals at high risk for CVD and T2DM. As a result, the concept of the MetS has been distorted and questioned [23, 32].

A recent systematic review and meta-analysis of 87 studies, in which either the NCEP-ATPIII or the AHA/NHLB definition was used, clearly illustrates the predictive value of the MetS for CVD outcomes [33]. The diagnosis of the MetS was associated with a twofold increase in risk for incident CVD, CVD mortality, myocardial infarction, and stroke. Risk estimates varied little whether derived from any of the two definitions. Moreover, the estimated relative risk for CVD mortality, myocardial infarction, and stroke were only slightly smaller when the analysis was restricted to the subgroup of nondiabetic subjects with the MetS. The estimated relative risks were, respectively, 1.75 (95 % CI: 1.19–2.58); 1.62 (95 % CI: 1.31–2.01); and 1.86 (95 % CI: 1.10–3.17). However, to what extent the diagnosis of the MetS accomplishes the goal of identifying individuals at high-risk for CVD is less obvious.

The performance of the MetS as compared to the widely used Framingham Risk Score (FRS) for the identification of subjects at risk for CVD has been reported in several studies including different populations [34–37]. In 2004, Stern et al. found the MetS had a lower sensitivity and was associated with a higher rate of false-positivity as compared to the FRS for the identification of incident CVD when applied to the San Antonio Heart Study population [34]. Likewise, McNeil et al. found the MetS did not improve coronary heart disease prediction beyond the level achieved by the FRS when applied the nondiabetic and CVD-free population participating in the Atherosclerosis Risk in Communities study [35]. Similar results were reported by Woodward [36] and Wannamethee [37] in prospective studies in which either Scottish men or women or British men with no history of CVD at baseline were followed up to 13.7 years and 20 years respectively. Although an in depth discussion of the reasons accounting for the poorer performance of the MetS as compared to the FRS in predicting CVD can be found elsewhere [30] and is beyond the scope of this review, we would like to emphasize three aspects. First, predicting tools such as the FRS may be more informative for risk estimation because of the inclusion of a set of unrelated factors rather than a set of intertwined components arising, potentially, from a single underlying mechanism. Second, whereas the FRS provides an estimate of absolute risk for CVD, the MetS informs on an individual's relative risk compared to those without the MetS. Thus, the diagnosis of the MetS would not represent an equivalent risk for someone with an absolute risk in the low range as compared to someone with a high baseline risk. Finally, in a recent report involving Finnish and Swedish populations, no difference was found between the predictive value of CVD of a full definition of the MetS and its individual components [38]. Thus, discussion of the predictive value of the MetS in predicting CVD clearly exemplifies how the misuse of the MetS conceptual framework has resulted in distortion of its significance.

The ability of the MetS in predicting incident T2DM as compared to simpler measures has also been questioned [23]. It has been shown that the relative risk for incident T2DM is up to five times higher in individuals with the MetS compared with those without the syndrome [39]. Despite some controversy exists, it has been suggested that fasting plasma glucose accounts for a large proportion of the T2DM predictive capacity of the MS [40, 41]. Furthermore, Stern et al. demonstrated that the Diabetes Predicting Model outperformed the MetS in predicting T2DM in the San Antonio Heart Study and Mexico City Diabetes Study [34]. Numerous diabetes risk scores are now available that provide good estimates of the chance of individuals developing diabetes in the mid- or long-term future [42]. For that matter, the MetS does not appear to be the universal ideal diabetes risk score.

To put what is in the diagnosis of the MetS into clinical perspective, we may wonder if being diagnosed with the MetS because of the presence of fasting plasma glucose of 101 mg/dl, systolic blood pressure of 137 mmHg, and fasting triglycerides of 151 mg/dl, would imply a fivefold larger risk for CVD and a twofold larger risk for T2DM as compared with the same individual not fulfilling any of the MetS components because of a fasting plasma glucose of 99 mg/dl, systolic blood pressure of 134 mmHg, and fasting triglycerides of 149 mg/dl. In brief, we could well

conclude that the MetS is not the best available tool for the prediction of CVD or T2DM. Further than this being a scientifically or clinically unresolved question, the low degree of implementation of the MetS as screening tool in CVD or T2DM prevention programs throughout the world would support this view [30]. Nonetheless, this does not detract from the fact that the MetS enfolds the concept of a number of cardiovascular risk factors presenting together in some individuals, and that these risk factors either individually or as group may benefit from lifestyle interventions.

1.4 Current Management Caveats

Major limitations for advancing in the definition of the best management strategies for the MetS include the lack of a consensus definition, the vagueness of its predictive ability for CVD and T2DM outcomes, and the lack of a unifying pathogenic hypothesis (Table 1.3). In the absence of an agreed definition, it is hard to set the proper patient selection criteria to be used in clinical trials evaluating therapeutic strategies and it becomes delicate to compare results across different studies using different definitions. Variation in the strength of association between the 16 potential combinations leading to the diagnosis of the MetS and CVD and/or T2DM hampers accurate trial design. The lack of a unifying underpinning mechanism questions whether the MetS is best treated targeting a single factor or, alternatively, confronting each component separately. At the end of the day, from the management

Table 1.3 Major limitations in the management strategies of the metabolic syndrome

Limitation	Consequence(s)
Lack of consensus definition	– Difficult to set proper patient selection criteria to be used in clinical trials
	– Difficult to compare among clinical trials using different definitions
Vagueness of predictive value for CVD and T2DM outcomes	– Difficult to proper trial design
	– Difficult to ascertain the impact of interventions
	– Difficult to compare among clinical trials with different distribution of combinations leading to diagnosis of the MetS
Lack of unifying hypothesis	– Difficult to identify therapeutic targets aiming at pleiotropic effects
Lifestyle interventions	– Not validated specifically in subjects with the MetS
	– Limited efficacy of current approaches
	– Limited evidence of an effect on cardiovascular outcomes
Bariatric surgery	– Not validated specifically in subjects with the MetS
	– Unfeasible because of the large prevalence of the MetS
Drug therapy targeting each component separately	– Specific therapeutic goals not set for subjects with the MetS

point of view it looks as if we have not gone too far from the historical concept of the "syndrome of affluence" mentioned earlier in this chapter [3, 14]. Lifestyle modification aiming at weight loss and increased physical activity is the foundation of current management of the MetS. Although evidence coming from studies targeting specifically MetS patients is lacking, several studies have shown such lifestyle interventions simultaneously impact more than one component of the MetS [43]. However, it should be emphasized that further than adequate lifestyle modification, targeting each individual component is central to additionally decrease the CVD burden associated with the MetS.

Modest weight loss positively influences all the components of the MetS. Meta-analysis of nine studies of non-pharmacological weight loss interventions for adults with pre-diabetes has shown that weight loss in the 5–10 % range relative to baseline is associated with a significant decrease in the incidence of diabetes [44]. Data from the Diabetes Prevention Program (DPP) would suggest the risk of diabetes is decreased by 16 % for every kilogram of weight loss in subjects at high-risk for diabetes because of impaired glucose tolerance at baseline [45]. Although at 10-years follow-up subjects in the lifestyle intervention of group in the DPP had maintained only a 2 kg weight loss relative to baseline, the incidence of diabetes was still reduced by 34 % compared with the placebo group [46]. Importantly, the prevalence of all the MetS components among the DPP participants meeting the diagnostic criteria at baseline (53 %) was reduced after 3 years of the beginning of the intervention [47]. In a systematic review, systolic blood pressure was found reduced by 4.5 mmHg and diastolic blood pressure by 3.2 mmHg in patients with primary hypertension assigned to weight loss as compared to the corresponding control interventions [48]. Similarly, Dattilo et al. reported on the benefits of modest weight loss on blood lipids and lipoproteins [49]. A review of the several studies that have evaluated the influence of hypocaloric diets differing in macronutrient composition on the MetS is beyond the scope of this review [50]. However, according to the literature, a diet low in saturated fat, higher in unsaturated fats, high in complex carbohydrates and low in sodium taking an individual's personal preferences would appear to be advisable. On the other hand, although there is no specific data on subjects with the MetS, it has been shown that physical activity and aerobic exercise capacity are associated with decreased CVD risk and all-cause and CVD mortality [51]. Physical activity and exercise intervention have been linked to improved blood pressure, increased HDL-cholesterol, and decreased triglycerides [52, 53]. The relative contributions of physical activity and weight loss on improved cardiometabolic profile are difficult to disentangle. Nevertheless, regular exercise appears to play an important role in weight maintenance in those who have successfully lost weight, and there may be additional benefit from the combination of the two elements [54]. Finally, it is important to underscore that there is no conclusive data on the beneficial effects of intentional dietary weight loss interventions on cardiovascular events [55, 56]. The only currently approved weight loss drug orlistat has been shown to increase the proportion of subjects achieving modest weight loss and maintenance, along with diabetes prevention and sustained improvement of CVD risk factors [57]. However, as well as for non-pharmacological weight loss

interventions, evidence is lacking on its impact on CVD events. Admittedly, according to a recent WHO report subjects with T2DM should no longer be diagnosed with the MetS [30]. Nonetheless, although the intensive lifestyle intervention provided in the seminal Look AHEAD trial was associated with sustained modest weight loss and improved CVD risk factors in subjects with T2DM, the trial was terminated earlier because these modifications did not translated ultimately into reductions in CVD events [58]. Interestingly, it has been recently been shown that a Mediterranean diet supplemented either with olive oil or nuts may not only ease the control of the several components of the MetS [59] but also decrease CVD mortality (Estruch R, personal communication).

Bariatric surgery is currently considered the best approach for achieving and maintaining major weight loss in severely obese subjects [60]. Bariatric surgery is associated with changes in all the MetS components, with larger effects associated with techniques associated with larger weight loss [60, 61]. The Swedish Obese Subjects Study demonstrated that bariatric surgery is associated with an 83 % risk reduction of developing T2DM as compared to usual care at 15-years follow [62]. Post-hoc analysis has shown this effect is not limited to subjects with a body mass index >40 kg/m^2 but rather benefits those with any degree of obesity [63]. Furthermore, bariatric surgery has been associated with reduced all-cause mortality and CVD mortality [64–66]. Of relevance to this chapter, the data discussed in this paragraph has not been derived from studies limited to MetS patients. Nonetheless, elevated fasting insulin (a crude estimate of insulin resistance) was found to predict the benefit of bariatric surgery on CVD above and beyond the body mass index [66]. The health benefits of bariatric surgery will be discussed in further depth in upcoming chapters in this book. However, it should be emphasized that according to harmonized definition the MetS is present in approximately 34.3 % of the US population aged >20 years, and in 59.8 % of those in that population presenting with a body mass index in the obesity range [67]. Thus, even in the absence of randomized clinical trials evaluating the effects of bariatric surgery specifically in subjects with the Mets, it would appear unfeasible to make bariatric surgery available to this large amount of subjects.

The use of pharmacotherapy in the MetS could be envisioned as a means of targeting the potentially underlying pathogenic mechanism or as therapy for the individual components of the syndrome. Insulin resistance and impaired adipose tissue endocrine function leading to a low-grade inflammatory state have been suggested as underlying the MetS [24, 27]. Currently, no drug therapy is approved for the latter but metformin or glitazones are available to alleviate insulin resistance. On the other hand, specific therapeutic targets for the control of waist circumference, glycemia, lipid, and blood pressure for MetS patients have not been issued. Rather, the therapeutic goals for glycemia, lipids, and blood pressure are defined based on risk-estimates independent of the presence of the MetS [25, 68, 69].

Metformin therapy was associated with an approximately 31 % reduction in the incidence of T2DM in the DPP [47]. Likewise, time-limited treatment with rosiglitazone reduces the short- (by 60 %) and longer-term (by 39 %) incidence of diabetes [70, 71]. However, the effect of metformin on diabetes prevention and other CVD

risk factors was smaller than that with lifestyle intervention. On the other, although data would suggest metformin reduces the risk of CVD in subjects with T2DM [72], this outcome measure should be demonstrated in nondiabetic subjects as subjects with T2DM would currently be excluded from the MetS category [30]. Finally, the DREAM trial did not only fail to show a positive impact of rosiglitazone on CVD outcomes in subjects with impaired glucose tolerance at baseline, but rather was associated with an increased risk of heart failure [73]. In summary, although insulin resistance is considered at the core of the MetS, data would not endorse its use as first line therapy.

The American Diabetes Association standards of care do acknowledge metformin has a strong evidence base for diabetes prevention and demonstrated long-term safety [68]. It is also stated that for other drugs, issues of cost, side effects, and lack of persistence of effect in some studies require consideration. Finally, metformin use for diabetes prevention is only recommended for those at very-high risk defined as those with a history of gestational diabetes mellitus, the very obese, and/or those with more severe or progressive hyperglycemia. No specific mention is made of those with the MetS.

According to current NCEP-ATPIII guidelines LDL-cholesterol, rather than triglycerides or HDL-cholesterol, is the major CVD modifiable risk factor in subjects with the MetS [25]. It is only after LDL has been treated that the other components of dyslipdemia should be addressed. Therapeutic targets for LDL-cholesterol in MetS patients are to be defined according to the absolute CVD risk estimated using standard methods. Thus, the MetS is not considered a CVD-risk equivalent nor a high-risk category in itself. No specific goal for HDL-C is set by the NCEP-ATPIII guidelines, as there insufficient evidence to specify a therapy goal. If triglycerides are 150–200 mg/dL, a specific drug therapy to reduced triglyceride-rich lipoproteins is not indicated. For those with triglycerides 200–499 mg/dL, a non-HDL cholesterol target is set at 30 mg/dL higher than that for the LDL-cholesterol target set according to the patient absolute risk for CVD. In that setting, statin use to reach the LDL-cholesterol goal continues to be first line-therapy and triglyceride-lowering drug (nicotinic acid or fibrate) be considered as second line. Statins are associated with an increase in HDL-cholesterol (5–10 %) and a reduction in triglycerides (7–30 %). Furthermore, statins are highly effective in decreasing CVD mortality and morbidity [74]. Evidence for CVD reduction for fibrates is not as robust as it is for statins, although data would suggest subjects with atherogenic dyslipidemia may benefit [75]. Thus, data supports that attention should be addressed to the attainment of LDL-cholesterol goals in subjects with the MetS, despite this lipid fraction not being part of the MetS definition.

Management of elevated blood pressure and hypertension is another key target in CVD risk reduction in the MetS patient, although there are no guidelines for blood pressure management specific to this population. The 7th report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (7th JNC) has recommended that target blood pressure should be less than 140/90 mmHg in those without diabetes or chronic kidney disease [69]. According to these guidelines, drug therapy for those with the MetS and falling in the

pre-hypertension category (systolic blood pressue 120–139 mmHg and/or diastolic blood pressure 80–89 mmHg) is not indicated. The MetS is not considered among the compelling indications for individual drug classes in the 7th JNC report. Thus, hypertension in subjects with the MetS should be treated according to the hypertension stage. Of note, the Navigator Trial showed valsartan therapy for 5 years, along with lifestyle modification, in subjects with impaired glucose tolerance was associated with a relative reduction of 14 % in the incidence of T2DM but did not reduce the rate of CVD events [76].

1.5 Conclusions

For more than a century it has been recognized that some CVD risk factors cluster in certain individuals more often than by chance. The term MetS nicely illustrates this concept. However, the MetS is of limited practical utility for the identification of subjects at increased of either CVD or T2DM when used as diagnostic construct. Likewise, the diagnostic of the MetS is of limited utility as management tool. All the components of the MetS benefit from lifestyle modifications aiming at weight loss and increased physical activity. However, it is less clear to what extent the diagnosis of the MetS should guide decisions involving the use of additional therapies either medical or surgical.

References

1. Enzi G, Busetto L, Inelmen EM, Coin A, Sergi G. Historical perspective: visceral obesity and related comorbidity in Joannes Baptista Morgagni's 'De sedibus et causis morborum per anatomen indagata'. Int J Obes Relat Metab Disord. 2003;27:534–5.
2. Hitzenberger K. Uber den Blutdruck bei Diabetes Mellitus. Wiener Arch Innere Med. 1921;2:461–6.
3. Marañon G. Uber Hypertonie and Zuckerkrankheit. Zentralblatt für Innere Medizin. 1922;43:169–76.
4. Kylin E. Studien über das Hypertoni-Hyperglycemi-Hyperurikemi syndrom. Zentralblatt für Innere Medizin. 1923;44:105–12.
5. Vague J. La differentiation sexuelle. Facteur determinant des formes de l'obésite. Presse Med. 1947;55:339–41.
6. Vague J. The degree of masculine differentiation of obesities. A factor determining predisposition to diabetes, atherosclerosis, gout and uric calculous disease. Am J Clin Nutr. 1956;4:20–34.
7. Kissebah AH, Vydelingum N, Murray R, et al. Relation of body fat distribution to metabolic complications of obesity. J Clin Endocrinol Metab. 1982;54:254–60.
8. Albrink MJ, Krauss RM, Lindgrem FT, von der Groeben J, Pan S, Wood PD. Intercorrelations among plasma high density lipoprotein, obesity and triglycerides in a normal population. Lipids. 1980;15:668–76.
9. Larsson B, Bengtsson C, Björntorp P, et al. Is abdominal body fat distribution a major explanation for the sex difference in the incidence of myocardial infarction? The study of men born in 1913 and the study of women, Göteborg, Sweden. Am J Epidemiol. 1992;135:266–73.
10. Camus JP. Goutte, diabète, hyperlipémie: un trisyndrome métabolique. Rev Rhum. 1966;33:10–5.

11. Avogaro P, Crepaldi G. Plurimetabolic syndrome. Acta Diabetol Lat. 1967;4:572–80.
12. Haller H. Epidermiology and associated risk factors of hyperlipoproteinemia. Z Gesamte Inn Med. 1977;32:124–8.
13. Hanefeld M, Leonhardt W. Das Metabolische Syndrom. Dt Gesundh Wesen. 1981;36:545–51.
14. Mehnert H, Kuhlmann H. Hypertonie und Diabetes Mellitus. Dtsch Med J. 1968;19:567–71.
15. Reaven GM. Banting Lecture 1988. Role of insulin resistance in human disease. Diabetes. 1988;37:1595–607.
16. Bogardus C, Lillioja S, Mott DM, Hollenbeck C, Reaven G. Relationship between degree of obesity and in vivo insulin action in man. Am J Physiol. 1985;248:E286–91.
17. Reaven GM. Syndrome X: a short history. Ochsner J. 2001;3:124–5.
18. Kahn SE, Prigeon RL, McCulloch DK, et al. Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function. Diabetes. 1993;42:1663–72.
19. Ferrannini E, Natali A, Bell P, et al. Insulin resistance and hypersecretion in obesity. J Clin Invest. 1997;100:1166–73.
20. Kaplan NM. The deadly quartet. Upper body obesity, glucose intolerance, hypertriglyceridemia and hypertension. Arch Intern Med. 1989;149:1514.
21. DeFronzo RA, Ferrannini E. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia and atherosclerotic cardiovascular disease. Diabetes Care. 1991;14:173–94.
22. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998;15:539–53.
23. Reaven GM. The metabolic syndrome: time to get off the merry-go-round? J Intern Med. 2011;269:127–36.
24. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). Diabet Med. 1999;16:442–3.
25. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA. 2001;285:2486–97.
26. Bloomgarden ZT. American Association of Clinical Endocrinologists (AACE) consensus conference on the insulin resistance syndrome: 25–26 August 2002, Washington, DC. Diabetes Care. 2003;26:1297–303.
27. Alberti KG, Zimmet P, Shaw J, IDF Epidemiology Task Force Consensus Group. The metabolic syndrome--a new worldwide definition. Lancet. 2005;366:1059–62.
28. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005;112:2735–52.
29. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120:1640–5.
30. Simmons RK, Alberti KG, Gale EA, et al. The metabolic syndrome: useful concept or clinical tool? Report of a WHO Expert Consultation. Diabetologia. 2010;53:600–5.
31. Povel CM, Beulens JW, van der Schouw YT, et al. Metabolic syndrome model definitions predicting type 2 diabetes and cardiovascular disease. Diabetes Care. 2013;36:362–8.
32. Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal. Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2005;28:2289–304.
33. Mottillo S, Filion KB, Genest J, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. J Am Coll Cardiol. 2010;56:1113–32.

34. Stern MP, Williams K, González-Villalpando C, Hunt KJ, Haffner SM. Does the metabolic syndrome improve identification of individuals at risk of type 2 diabetes and/or cardiovascular disease? Diabetes Care. 2004;27:2676–81.
35. McNeill AM, Rosamond WD, Girman CJ, et al. The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. Diabetes Care. 2005;28:385–90.
36. Woodward M, Tunstall-Pedoe H. The metabolic syndrome is not a sensible tool for predicting the risk of coronary heart disease. Eur J Cardiovasc Prev Rehabil. 2009;16:210–4.
37. Wannamethee SG. The metabolic syndrome and cardiovascular risk in the British Regional Heart Study. Int J Obes (Lond). 2008;32 Suppl 2:S25–9.
38. Qiao Q, Laatikainen T, Zethelius B, et al. Comparison of definitions of metabolic syndrome in relation to the risk of developing stroke and coronary heart disease in Finnish and Swedish cohorts. Stroke. 2009;40:337–43.
39. Ford ES, Li C, Sattar N. Metabolic syndrome and incident diabetes: current state of the evidence. Diabetes Care. 2008;31:1898–904.
40. Lorenzo C, Williams K, Hunt KJ, Haffner SM. The National Cholesterol Education Program - Adult Treatment Panel III, International Diabetes Federation, and World Health Organization definitions of the metabolic syndrome as predictors of incident cardiovascular disease and diabetes. Diabetes Care. 2007;30:8–13.
41. Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation. 2005;112:3066–72.
42. Noble D, Mathur R, Dent T, Meads C, Greenhalgh T. Risk models and scores for type 2 diabetes: systematic review. BMJ. 2011;343:d7163.
43. Vidal J. Updated review on the benefits of weight loss. Int J Obes Relat Metab Disord. 2002;26 Suppl 4:S25–8.
44. Norris SL, Zhang X, Avenell A, Gregg E, Schmid CH, Lau J. Long-term non-pharmacological weight loss interventions for adults with prediabetes. Cochrane Database Syst Rev. 2005; (2):CD005270
45. Hamman RF, Wing RR, Edelstein SL, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. Diabetes Care. 2006;29:2102–7.
46. Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet. 2009;374:1677–86.
47. Orchard TJ, Temprosa M, Goldberg R, et al. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. Ann Intern Med. 2005;142:611–9.
48. Siebenhofer A, Jeitler K, Berghold A, et al. Long-term effects of weight-reducing diets in hypertensive patients. Cochrane Database Syst Rev. 2011; (9):CD008274.
49. Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. Am J Clin Nutr. 1992;56:320–8.
50. Gregory SM, Headley SA, Wood RJ. Effects of dietary macronutrient distribution on vascular integrity in obesity and metabolic syndrome. Nutr Rev. 2011;69:509–19.
51. Vanhees L, Geladas N, Hansen D, et al. Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health in individuals with cardiovascular risk factors: recommendations from the EACPR. Part II. Eur J Prev Cardiol. 2012;19:1005–33.
52. Cornelissen VA, Fagard RH, Coeckelberghs E, Vanhees L. Impact of resistance training on blood pressure and other cardiovascular risk factors: a meta-analysis of randomized, controlled trials. Hypertension. 2011;58:950–8.
53. Kelley GA, Kelley KS. Impact of progressive resistance training on lipids and lipoproteins in adults: a meta-analysis of randomized controlled trials. Prev Med. 2009;48:9–19.
54. Wu T, Gao X, Chen M, van Dam RM. Long-term effectiveness of diet-plus-exercise interventions vs. diet-only interventions for weight loss: a meta-analysis. Obes Rev. 2009;10: 313–23.

55. Eilat-Adar S, Eldar M, Goldbourt U. Association of intentional changes in body weight with coronary heart disease event rates in overweight subjects who have an additional coronary risk factor. Am J Epidemiol. 2005;161:352–8.
56. Simonsen MK, Hundrup YA, Obel EB, Grønbaek M, Heitmann BL. Intentional weight loss and mortality among initially healthy men and women. Nutr Rev. 2008;66:375–86.
57. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care. 2004;27:155–61.
58. Look AHEAD Research Group, Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. Arch Intern Med. 2010;170:1566–75.
59. Babio N, Bulló M, Salas-Salvadó J. Mediterranean diet and metabolic syndrome: the evidence. Public Health Nutr. 2009;12:1607–17.
60. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, Schoelles K. Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004;292:1724–37.
61. Sjöström L, Lindroos AK, Peltonen M, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med. 2004;351:2683–93.
62. Carlsson LM, Peltonen M, Ahlin S, et al. Bariatric surgery and prevention of type 2 diabetes in Swedish obese subjects. N Engl J Med. 2012;367:695–704.
63. Sjöholm K, Anveden A, Peltonen M, et al. Evaluation of current eligibility criteria for bariatric surgery: diabetes prevention and risk factor changes in the Swedish Obese Subjects (SOS) study. Diabetes Care. 2013;36:1335.
64. Sjöström L, Narbro K, Sjöström CD, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med. 2007;357:741–52.
65. Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. N Engl J Med. 2007;357:753–61.
66. Sjöström L, Peltonen M, Jacobson P, et al. Bariatric surgery and long-term cardiovascular events. JAMA. 2012;307:56–65.
67. Ford ES, Li C, Zhao G. Prevalence and correlates of metabolic syndrome based on a harmonious definition among adults in the US. J Diabetes. 2010;2:180–93.
68. American Diabetes Association. Standards of medical care in diabetes--2013. Diabetes Care. 2013;36 Suppl 1:S11–66.
69. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003;289:2560–72.
70. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators, Gerstein HC, Yusuf S, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet. 2006;368:1096–105.
71. DREAM On (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication Ongoing Follow-up) Investigators, Gerstein HC, Mohan V, et al. Long-term effect of rosiglitazone and/or ramipril on the incidence of diabetes. Diabetologia. 2011;54:487–95.
72. Lamanna C, Monami M, Marchionni N, Mannucci E. Effect of metformin on cardiovascular events and mortality: a meta-analysis of randomized clinical trials. Diabetes Obes Metab. 2011;13:221–8.
73. DREAM Trial Investigators, Dagenais GR, Gerstein HC, Holman R, et al. Effects of ramipril and rosiglitazone on cardiovascular and renal outcomes in people with impaired glucose tolerance or impaired fasting glucose: results of the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial. Diabetes Care. 2008;31:1007–14.

74. Taylor F, Ward K, Moore TH, Burke M, Davey Smith G, Casas JP, Ebrahim S. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2011; (1):CD004816.
75. Lee M, Saver JL, Towfighi A, Chow J, Ovbiagele B. Efficacy of fibrates for cardiovascular risk reduction in persons with atherogenic dyslipidemia: a meta-analysis. Atherosclerosis. 2011;217:492–8.
76. NAVIGATOR Study Group, McMurray JJ, Holman RR, et al. Effect of valsartan on the incidence of diabetes and cardiovascular events. N Engl J Med. 2010;362(16):1477–90.

Extending Current Definitions of the Metabolic Syndrome

2

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2.1 Introduction

Current interest in the concept of the metabolic syndrome (MS) dates back from the late 1980s, when Reaven, in his Banting Lecture at the American Diabetes Association, described a cluster of abnormalities, whose combined risk of developing future diabetes and cardiovascular risk (CVD) is greater than that of the risk of individual components [1]. This cluster was termed "Syndrome X" by Reaven and later came to be known by various other names such as Metabolic Syndrome (MS) and Insulin Resistance Syndrome. The history of the concept of MS and its management are discussed elsewhere in this book. This chapter attempts to analyze the various definitions of MS currently in use and to establish the need to modify it for different ethnic groups and populations, based on currently available evidence.

2.2 Current Criteria Used for MS

The original definition of MS included hyperinsulinemia, impaired glucose tolerance, hypertriglyceridemia, low HDL cholesterol, and hypertension [1]. More expanded definitions have been proposed over the past two decades with the inclusion of alternative parameters like central obesity, microalbuminuria, endothelial dysfunction, inflammation, and prothrombotic state [2]. Further, the scientific community is also debating as to whether the presence of non-alcoholic fatty liver disease

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(NAFLD) should be included as a diagnostic criterion for MS and the varying components used [3, 4]. Unfortunately, the existence of various definitions has led to considerable ambiguity and the question has arisen whether MS should be considered as a specific entity at all. Yet, in its defense, MS has, over time, made physicians and patients aware of the interactions between the individual components of the syndrome and the benefits of lifestyle modifications in its management. The commonly used definitions for MS include those put forward by the WHO (1999) [5], EGIR (1999) [6], NCEP- ATP III (2001) [7], IDF (2005) [8] and these are summarized in Table 2.1. The major distinction between the definitions mainly lies in the risk variables included and the differing levels of importance given to each of these variables.

Apart from the above major definitions there also exist other definitions with minor variations. For instance, in 2004, the NCEP definition was revised by lowering the threshold for fasting glucose to ≥100 mg/dl according to the American Diabetes Association (ADA) criteria for impaired fasting glucose (IFG) [9]. Also the South Asian modified (SAM)—NCEP definition has been introduced for use in individuals of the South Asian ethnicity [9].

2.3 Extending the Current Definitions

Since one of the major disadvantages in diagnosing MS is the variability in the different criteria used, an attempt was made by several major organizations like International Diabetes Federation (IDF) Task Force on Epidemiology and Prevention, National Heart, Lung, and Blood Institute (NHLBI), American Heart Association (AHA), World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity to unify the criteria for diagnosis of MS. It was agreed upon by these organizations that though there should not be an obligatory component for MS diagnosis, waist circumference plus any combination of the other parameters would categorize an individual as having metabolic syndrome. Other than waist circumference, which is ethnicity specific, all other components would have a single set of cut points [10]. Table 2.2 describes these unified criteria in detail.

Initially, the criteria used for identifying people with MS were based on the data derived from Caucasian populations. Since there is sufficient evidence to prove that the currently used criteria may not be able to precisely characterize risk in non-Caucasian populations, this may result in over- or under-estimation of risk. To overcome this, we have proposed the use of a novel parameter called index of central obesity (ICO) which is the ratio of waist circumference to height [18]. Using this index could preclude the need for cut points specific for the ethnic groups. Moreover, bringing such alterations would enhance the continued feasibility, utility and sustenance of the criteria.

The IDF Consensus Group has further highlighted several other parameters that should be tested by further research to determine their predictive power [2]. Elucidating the following additional factors will facilitate the further refinement of the definition and validation of the same in the existing ethnic groups:

Table 2.1 Different criteria used for metabolic syndrome

Components of MS	WHO criteria (1999)	EGIR (1999)	NCEP ATP III criteria (2001)	IDF consensus (2005)
Obesity/abdominal obesity	Body mass index (BMI) ≥30 kg/m^2 and/or waist-to-hip ratio >0.90 (M), >0.85 (F)	Waist circumference ≥94 cm (M), ≥80 cm (F)	Waist circumference ≥102 cm (M), ≥88 cm (F)	Waist circumference ≥90 cm (M), ≥80 cm (F)—South Asians and ethnicity specific cut points
Blood pressure	≥140/≥90 mmHg or on medication	≥140/90 mmHg or on medication	>130/>85 mmHg or on medication	>130/>85 mmHg or on medication
Fasting glucose	Diabetes, impaired glucose tolerance or insulin resistance	IGT or IFG (but not diabetes)	≥110 mg/dl or on medication	≥100 mg/dl or pre-existing DM
Triglycerides	≥150 mg/dl	TG ≥177 mg/dl	≥150 mg/dl	≥150 mg/dl
HDL cholesterol		<39 mg/dl or treated for dyslipidemia	<40 mg/dl (M), <50 mg/dl (F)	<40 mg/dl (M), <50 mg/dl (f)
Insulin-resistance	Glucose uptake below the lowest quartile under hyperinsulinemic, euglycemic conditions	Plasma insulin >75th percentile		
Microalbuminuria	Urinary albumin excretion rate ≥20 μg/min or albumin: creatinine ratio ≥30 mg/g	Not in criteria	Not in criteria	Not in criteria
Metabolic syndrome—definition	Diabetes, impaired glucose tolerance or insulin resistance plus any two or more risk factors	Insulin resistance plus any two of the other risk factors	At least three risk factors	Obesity plus two of the other criteria

Table 2.2 Unified criteria for clinical diagnosis of MS and ethnicity specific cut points for waist circumference [10]

MS components		Categorical cut points	
Increased waist circumference		Population and country-specific definitions	
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator)		≥150 mg/dl (1.7 mmol/l)	
Low HDL-C		<40 mg/dl (1.0 mmol/l) in males; <50 mg/dl (1.3 mmol/l) in females	
Elevated blood pressure/antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator		Systolic ≥130 and/or diastolic ≥85 mmHg	
Elevated fasting plasma glucose (drug treatment is an alternate indicator)		≥100 mg/dl	
Waist circumference cut points for different ethnic groups			
		Recommended waist circumference threshold for abdominal obesity (cm)	
Population	Organization	Men	Women
Europid	IDF [9]	≥94	≥80
Caucasian	WHO [11]	≥94 (↑risk) ≥102 (↑↑risk)	≥80 (↑risk) ≥88 (↑↑risk)
United states	AHA/NHLBI (ATP III) [12]	≥102	≥88
Canada	Health Canada [13]	≥102	≥88
European	European Cardiovascular Societies [14]	≥102	≥88
Asian (including Japanese)	IDF [9]	≥90	≥80
Asian	WHO [15]	≥90	≥80
Japanese	Japanese Obesity Society [16]	≥85	≥90
China	Cooperative Task Force [17]	≥85	≥80
Middle East, Mediterranean	IDF [9]	≥94	≥80
Sub-Saharan African	IDF [9]	≥94	≥80
Ethnic Central and South American	IDF [9]	≥90	≥80

- Abnormal distribution of body fat.
- Vascular dysregulation indicated by endothelial dysfunction and microalbuminura.
- Insulin resistance assessed by fasting insulin and FFA levels.
- Proinflammatory state indicated by elevated hs-CRP, TNF-a, IL-6, and decreased adiponectin.
- Prothrombotic state reflected by the fibrinolytic and clotting factors.
- Hormonal factors in the pituitary–adrenal axis.

2.4 Use of MS for Identifying CVD and Type 2 Diabetes Risk

A number of longitudinal studies have ascribed the cardiovascular risk associated with MS. Meta-analyses have shown that metabolic syndrome was associated with a higher cardiovascular risk in women when compared to men [19]. In subjects

without type 2 DM, it was shown that in the group with MS, the incidence of CVD was 10.2 % as compared to 4.9 % in the group without MS [20]. Irrespective of the definition used, MS was noted to be associated with an increased risk of CVD mortality. In non-obese men with MS, the CVD mortality after a follow-up of 10 years was found to be 1.99 % as compared to 0.53 % in those without MS [21].

Prospective studies show that MS predicts the occurrence of type 2 diabetes. Ford et al. have performed a meta-analysis on the results from 16 prospective studies and concluded that irrespective of the definition of MS, it predicted incident diabetes [22]. Also MS is closely associated with NAFLD (non-alcoholic fatty liver disease), on account of the effects of insulin resistance in increasing hepatic free fatty acid flux by inhibiting lipolysis and increasing de novo lipogenesis [23]. Thus metabolic syndrome can be considered a tool for assessment of CVD and diabetes risk. Recent studies showing an association of metabolic syndrome with polycystic ovary syndrome (PCOs) [24], Parkinson's disease [25], and so on present the possibility of further extensions to the definition of MS and thus increase its utility as a clinical entity.

2.5 Extending MS Definitions to Children and Adolescents

Owing to the exponentially escalating rates of childhood obesity worldwide, diseases of adults have started occurring in children as well. Since the pathogenesis of obesity and metabolic syndrome are intimately interconnected, it is highly likely that the epidemic of childhood obesity would be paralleled by an increase in the prevalence of MS in this population, with grave implications for cardiovascular morbidity and mortality in the future. Though there are many difficulties in directly transposing the adult definition to children, it is commonly defined as the co-occurrence of three or more of the risk factors viz. obesity, dyslipidemia, hypertension, and impaired glucose tolerance. In utero conditions and early childhood environment have been known to predispose children to the development of the component risk factors of MS [26].

2.6 Prevalence and Long-Term Consequences of MS in Children and Adolescents

The prevalence of metabolic syndrome was found to be 38.7 % in a group of moderately obese children and 49.7 % in severely obese children in the United States [27]. In a group of Italian obese children and adolescents aged 6–16 years, the prevalence was found to be 23.3 % according to the WHO definition [28]. In a study done in 2008 on a group of African American and Caucasian children, the prevalence was found to be 18.7 %, 21 %, 13.4 %, 25.1 % by Weiss's definition [27], Cook's criteria [29], Cruz's criteria [30], and Ford's criteria [31] respectively. Despite the significant variability observed, MS was higher in the obese compared to the normal weight children and adolescents in both ethnic groups. Similarly when

MS was assessed in an adolescent population using NCEP III and WHO criteria, it was found to vary from 4.2 to 8.4 % [32]. In a population of Asian Indian children, MS prevalence was found to be 2.2 by the NCEP criteria and 1.5 % by the IDF criteria in the adolescents in the age group of 16–17 years [33]. However, large population-based studies on MS are yet to be carried out in Asian Indian children and adolescents.

The presence of metabolic syndrome or its risk factors in childhood might impose long-term consequences on health during adult life; however, there are only limited longitudinal studies assessing this problem. Subjects with higher BMI, blood pressure, and triglycerides during childhood were found to develop MS in their adult life and further it was observed that a higher risk of MS was found in people in the above 75th percentile of BMI for the age and sex [34]. In the Bogalusa Heart study and the Cardiovascular risk in Young Finns Study, youth with MetS (MS) were at two to three times increased risk of having high carotid intima medial thickness and type 2 diabetes as adults, compared with those free of MetS as youth [35].

2.7 Current Definitions of MS in Children and Adolescents

There are numerous criteria existing to define MS in children, which have created a lot of ambiguity. This is evident from a review by Ford and Li (2008), which reports over 40 definitions used for diagnosis of MS [36]. In parallel, a comparative study of the existing definitions of MS in children showed that the prevalence varied between 0 and 60 % in the same sample of children [37]. This uncertainty is further compounded by the existence of different threshold values for the components of MS like obesity where cut-points like 85th, 95th, and 98th percentile of BMI have been adopted by various definitions. Tables 2.3 lists the key criteria used by various organizations for diagnosing MS in children and adolescents.

Among children and adolescents, BMI is a predictor of coronary artery disease risk and the Centers for Disease Control (CDC) and International Obesity Task Force (IOTF) have proposed obesity cut points for diagnosis of MS [41, 42]. Using a distribution approach, a BMI of above the 85th percentile is considered as the "at risk" category for overweight and a BMI of above 95th percentile is categorized as overweight [27]. Though data from numerous multi-cohort studies have demonstrated a strong association between obesity and MS prevalence, obesity per se cannot be considered as a conclusive marker for identifying children at MS and consequently CAD risk. Distribution of body fat has been shown to play a crucial role in the occurrence of metabolic complications and particularly visceral fat accumulation is associated with childhood MS and CAD risk in future [43]. Though waist circumference is a robust surrogate marker for measuring visceral fat accumulation, reference values for this measure exist only for some developing nations like US, UK, and Canada. Table 2.4 details some of the MS definitions in children that incorporate waist circumference as one of the primary components.

The increasing demand for a clinically accessible tool for the identification of MS in children and adolescents led the IDF to propose a new simple definition built

Table 2.3 Diagnostic criteria for MS in children according to the WHO, NCEP, and IDPAIA criteria

	WHO [38]	NCEP [39]	IDPAIA [40]
Obesity/ abdominal obesity	BMI >95th percentile	Waist >90th percentile	BMI >85th percentile
Blood pressure	SBP >95th percentile for age, sex, and stature NHBPEP	SBP or DBP >90th percentile specific for age and sex	SBP or DBP >90th and 95th percentiles
Fasting plasma glucose	Hyperinsulinemia Prepubertal >15 mU/l (Stage 1 Tanner) Pubertal >30 mU/l (Stages 2–4 Tanner) Postpubertal ≥20 mU/l (Stage 5 Tanner) Fasting glucose ≥6.1 mM/l Glucose intolerance glucose at 120 min ≥7.8 mM/l	Fasting glucose ≥110 mg/dl	Plasma insulin >15 μm/l
Serum Triglycerides	>105 mg/dl for <10 years >136 mg/dl for ≥10 years	>110 mg/dl	>100 mg/dl
Serum HDL cholesterol	HDL <35 mg/dl	HDL ≤40 mg/dl	HDL ≤45 mg/dl LDL >100 mg/dl
Total cholesterol	>95th percentile	NA	>150 mg/dl
Metabolic syndrome	Three or more risk factors	Three or more risk factors	

I DPAIA I Guidelines of prevention of atherosclerosis in childhood and adolescence

Table 2.4 Metabolic syndrome definitions in children and adolescents according to various authors

	Cook et al. [29]	de Ferranti et al. [44]	Weiss et al. [27]	Ford [31]	Cruz and Goran [30]
Obesity/ abdominal obesity	WC ≥90th percentile	WC >75th percentile	BMI-Z score ≥2	WC ≥90th percentile	WC ≥90th percentile
Blood pressure	BP ≥90th percentile	BP >90th percentile	BP >95th percentile	BP ≥90th percentile	BP ≥90th percentile
Fasting glucose	≥110 mg/dl	≥110 mg/dl	Glucose intolerance according to ADA criteria	≥110 mg/dl	Glucose intolerance according to ADA criteria
Triglycerides	≥110 mg/dl	≥100 mg/dl	>95 the percentile	≥110 mg/dl	≥90 the percentile
HDL Cholesterol	≤40 mg/dl	<50 mg/dl (except in boys aged 15–19 years in whom it is <45)	HDL <5th percentile	≤40 mg/dl (age specific, NCEP)	HDL ≤10th percentile
Metabolic syndrome definition	Presence of three or more criteria	Presence of three or more criteria	Presence of three or more criteria	Presence of three or more criteria	Presence of three or more criteria

Unified IDF definition for MS in children and adolescents

Table 2.5 Simplified IDF definition for MS in children and adolescents [45]

Age group: 6 < 10
Obesity: waist circumference ≥90th percentile
According to IDF criteria, MS cannot be diagnosed under 10 years
Age group: 10 < 16
Obesity: waist circumference ≥90th percentile
Triglycerides: ≥150 mg/dl
HDL: <40
Blood pressure: systolic BP >130 or diastolic BP >85
Glucose: FPG >100 or type 2 diabetes
Age group ≥16
Adult criteria

on previous studies that used the modified adult criteria. Since unequivocal evidence supports the association of abdominal obesity with multiple risk factors and cardiovascular risk, waist circumference has been included as the major essential criterion in the IDF definition for MS (Table 2.5). Moreover, among obese young people with similar BMI, insulin sensitivity has been found to be lower in subjects with higher abdominal obesity. In order to account for the ethnic origin of the children and variation in the development of the child, percentiles rather than absolute values of waist circumference are used. However, the IDF suggests that MS should not be diagnosed in children below 10 years, yet advocates that weight reduction should be strongly recommended in such children [45].

2.8 Controversies Regarding the Metabolic Syndrome

Due to the existence of various criteria for metabolic syndrome, there are concerns over the existence of the syndrome itself. Every combination of the proposed risk factors could impart a different degree of risk for the occurrence of CVD [46]. Also the risk for the occurrence of CVD due to MS appears to be equal to that of the sum of its components. There are also other CVD risk factors that are not included as components of MS like the inflammatory markers [47]. Hence MS would not account for the actual underlying CVD risk that an individual is subjected to. Though insulin resistance has been widely accepted as a causative factor in the pathogenesis of MS, it is likely that insulin resistance could be just another demonstration of an underlying causative factor. Even if MS is identified, the patient is treated only for its individual components. There is no unifying treatment strategy for MS as a whole and this might raise questions about the utility of diagnosing MS [48]. Further, it communicates to the patients that they have a disease even if they do not have one and hence detracts from the need to prioritize treatment based on benefits, risks, and cost.

In pediatric population, though efforts have been made to create a unique definition of MS, there is a lot of dispute on the best components of MS to be considered and age, gender and ethnicity specific cut points for the risk components are still

lacking. Further, the definition is complicated by the effect of growth and puberty and this raises the demand for definitions that employ continuous risk scores that could improve the clinical utility of diagnosing MS in the pediatric population [49].

2.9 Utility of the Diagnosis of Metabolic Syndrome

Irrespective of the question of a common etiology underlying the components of MS, identification of MS clearly recognizes individuals at heightened risk for type 2 diabetes and CVD [50–52]. The recommendations proposed by NCEP-ATPIII clearly state that there is a dire need for emphasizing lifestyle interventions to combat CVD risk factors [23]. Hence the diagnosis of MS leads to enhanced treatment strategies. Also research on MS could throw light on the pathophysiological mechanisms that link insulin resistance and CVD risk factors. Overall, the concept of MS has come to stay. It is particularly useful in young obese people and its predictive value on the occurrence of MS in adult life has been consistently demonstrated. This highlights the need for rigorous intervention strategies particularly in youth with MS which can help to stem the looming epidemic of type 2 diabetes and CVD.

References

1. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes. 1988;37:1595–607.
2. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome – a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med. 2006;23:469–80.
3. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet. 2005;365:1415–28.
4. Cornier MA, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ, Stob NR, Van Pelt RE, Wang H, Eckel RH. The metabolic syndrome. Endocr Rev. 2008;29:777–822.
5. World Health Organisation. Definition diagnosis and classification of diabetes mellitus and its complications. Geneva: World Health Organization; 1999.
6. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). Diabetes Med. 1999;16:442–3.
7. National Cholesterol Education Program Coordinating Committee. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in adults (Adult Treatment Panel III) final report. Circulation. 2002;106:3143–421.
8. Alberti KG, Zimmet P, Shaw J, IDF Epidemiology Task Force Consensus Group. The metabolic syndrome – a new worldwide definition. Lancet. 2005;366:1059–62.
9. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005;112:2735–52.
10. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith Jr SC, International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation;

International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120(16):1640–5.
11. WHO. Obesity: preventing and managing the global epidemic, Report of a WHOconsultation. World Health Organ Tech Rep Ser 894. Geneva, Switzerland: WHO; 2000.
12. World Health Organization. Obesity: preventing and managing the global epidemic: Report on a WHO Consultation (WHO Technical Report Series 894). Geneva, Switzerland: World Health Organization; 2000.
13. Health Canada. Canadian guidelines for body weight classification in adults. Ottawa, Canada: Health Canada Publications Centre; 2003. Publication ID No. 4645. ISBN 0-662-33431-0.
14. Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, Dallongeville J, De Backer G, Ebrahim S, Gjelsvik B, Herrmann-Lingen C, Hoes A, Humphries S, Knapton M, Perk J, Priori SG, Pyorala K, Reiner Z, Ruilope L, Sans-Menendez S, Op Reimer WS, Weissberg P, Wood D, Yarnell J, Zamorano JL. ESC Committee for Practice Guidelines. European guidelines on cardiovascular disease prevention in clinical practice: executive summary. Atherosclerosis. 2007;194:1–45.
15. Hara K, Matsushita Y, Horikoshi M, Yoshiike N, Yokoyama T, Tanaka H, Kadowaki T. A proposal for the cutoff point of waist circumference for the diagnosis of metabolic syndrome in the Japanese population. Diabetes Care. 2006;29:1123–4.
16. Oka R, Kobayashi J, Yagi K, Tanii H, Miyamato S, Asano A, Hagishita T, Mori M, Moriuchi T, Kobayashi M, Katsuda S, Kawashiri M, Nohara A, Takeda Y, Mabuchi H, Yamagishi M. Reassessment of the cutoff values of waist circumference and visceral fat for identifying Japanese subjects at risk for the metabolic syndrome. Diabetes Res Clin Pract. 2008;79:474–81.
17. Zhou BF, Cooperative Meta-Analysis Group of the Working Group on Obesity in China. Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults: study on optimal cut-off points of body mass index and waist circumference in Chinese adults. Biomed Environ Sci. 2002;15:83–96.
18. Parikh R, Mohan V, Joshi S. Should waist circumference be replaced by index of central obesity (ICO) in definition of metabolic syndrome? Diabetes Metab Res Rev. 2012;28:3–5.
19. Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation. 2005;112:3066–72.
20. Ingelsson E, Sullivan LM, Murabito JM, Fox CS, Benjamin EJ, Polak JF, Meigs JB, Keyes MJ, O'Donnell CJ, Wang TJ, D'Agostino Sr RB, Wolf PA, Vasan RS. Prevalence and prognostic impact of subclinical cardiovascular disease in individuals with the metabolic syndrome and diabetes. Diabetes. 2007;56:1718–26.
21. Katzmarzyk PT, Janssen I, Ross R, Church TS, Blair SN. The importance of waist circumference in the definition of metabolic syndrome: prospective analyses of mortality in men. Diabetes Care. 2006;29:404–9.
22. Ford ES, Li C, Sattar N. Metabolic syndrome and incident diabetes: current state of the evidence. Diabetes Care. 2008;31(9):1898–904.
23. Grundy SM, Brewer Jr HB, Cleeman JI, Smith Jr SC, Lenfant C, National Heart, Lung, and Blood Institute; American Heart Association. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American heart Association conference on scientific issues related to definition. Arterioscler Thromb Vasc Biol. 2004;24:e13–8.
24. Cırık DA, Dilbaz B. What do we know about metabolic syndrome in adolescents with PCOS? J Turk Ger Gynecol Assoc. 2014;15:49–55.
25. Zhang P, Tian B. Metabolic syndrome: an important risk factor for Parkinson's disease. Oxid Med Cell Longev. 2014;2014:729194.
26. Marcovecchio ML, Chiarelli F. Metabolic syndrome in youth: chimera or useful concept? Curr Diab Rep. 2013;13:56–62.
27. Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, et al. Obesity and the metabolic syndrome in children and adolescents. N Engl J Med. 2004;350:2362–74.
28. Invitti C, Maffeis C, Gilardini L, Pontiggia B, Mazzilli G, Girola A, Sartorio A, Morabito F, Viberti GC. Metabolic syndrome in obese Caucasian children: prevalence using WHO-derived

criteria and association with nontraditional cardiovascular risk factors. Int J Obes (Lond). 2006;30:627–33.
29. Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988-1994. Arch Pediatr Adolesc Med. 2003;157:821–7.
30. Cruz ML, Goran MI. The metabolic syndrome in children and adolescents. Curr Diab Rep. 2004;4:53–62.
31. Ford ES. Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. Diabetes Care. 2005;28:2745–9.
32. Goodman E, Daniels SR, Morrison JA, Huang B, Dolan LM. Contrasting prevalence of and demographic disparities in the World Health Organization and National Cholesterol Education Program Adult Treatment Panel III definitions of metabolic syndrome among adolescents. J Pediatr. 2004;145:445–51.
33. Vikram NK, Misra A, Pandey RM, Luthra K, Bhatt SP. Distribution and cutoff points of fasting insulin in Asian Indian adolescents and their association with metabolic syndrome. J Assoc Physicians India. 2008;56:949–54.
34. Burns TL, Letuchy EM, Paulos R, Witt J. Childhood predictors of the metabolic syndrome in middle-aged adults: the Muscatine study. J Pediatr. 2009;155:S5.e17–26.
35. Magnussen CG, Koskinen J, Chen W, Thomson R, Schmidt MD, Srinivasan SR, Kivimäki M, Mattsson N, Kähönen M, Laitinen T, Taittonen L, Rönnemaa T, Viikari JS, Berenson GS, Juonala M, Raitakari OT. Pediatric metabolic syndrome predicts adulthood metabolic syndrome, subclinical atherosclerosis, and type 2 diabetes mellitus but is no better than body mass index alone: the Bogalusa Heart Study and the Cardiovascular Risk in Young Finns Study. Circulation. 2010;122:1604–11.
36. Ford ES, Li C. Defining the metabolic syndrome in children and adolescents: will the real definition please stand up? J Pediatr. 2008;152:160–4.
37. Golley RK, Magarey AM, Steinbeck KS, Baur LA, Daniels LA. Comparison of metabolic syndrome prevalence using six different definitions in overweight pre-pubertal children enrolled in a weight management study. Int J Obes (Lond). 2006;30:853–60.
38. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications: Report of WHO a Consultation. Part 1: diagnosis and classification of diabetes mellitus. Genebra; 1999.
39. Executive summary of the third report of The National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA. 285:2486e97.
40. Back Giuliano Ide C, Caramelli B, Pellanda L, Duncan B, Mattos S, et al. I guidelines of prevention of atherosclerosis in childhood and adolescence. Arq Bras Cardiol. 2005;85 Suppl 6:4–36.
41. Himes JH, Dietz WH. Guidelines for overweight in adolescent preventive services: recommendations from an expert committee. The Expert Committee on Clinical Guidelines for Overweight in Adolescent Preventive Services. Am J Clin Nutr. 1994;59:307–16.
42. Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, Wei R, Curtin LR, Roche AF, Johnson CL. 2000 CDC Growth Charts for the United States: methods and development. Vital Health Stat. 2002;11(246):1–190.
43. Pouliot MC, Després JP, Lemieux S, Moorjani S, Bouchard C, Tremblay A, Nadeau A, Lupien PJ. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am J Cardiol. 1994;73:460–8.
44. de Ferranti SD, Gauvreau K, Ludwig DS, Neufeld EJ, Newburger JW, Rifai N. Prevalence of the metabolic syndrome in American adolescents: findings from the Third National Health and Nutrition Examination Survey. Circulation. 2004;110:2494–7.
45. Zimmet P, Alberti G, Kaufman F, Tajima N, Silink M, Arslanian S, Wong G, Bennett P, Shaw J, Caprio S, International Diabetes Federation Task Force on Epidemiology and Prevention of Diabetes. The metabolic syndrome in children and adolescents. Lancet. 2007;369:2059–61.

46. Kahn R. Metabolic syndrome: is it a syndrome? Does it matter? Circulation. 2007;115: 1806–10.
47. Indulekha K, Surendar J, Mohan V. High sensitive C-reactive protein, tumor necrosis factor-alpha, interleukin-6 and vascular cell adhesion molecule levels in Asian Indians with metabolic syndrome and insulin resistance (CURES – 105). J Diabetes Sci Technol. 2011;5:982–8.
48. Grundy SM. Does a diagnosis of metabolic syndrome have value in clinical practice? Am J ClinNutr. 2006;83:1248–51.
49. Eisenmann JC. On the use of a continuous metabolic syndrome score in pediatric research. Cardiovasc Diabetol. 2008;7:17.
50. Nilsson PM, Engström G, Hedblad B. The metabolic syndrome and incidence of cardiovascular disease in non-diabetic subjects – a population-based study comparing three different definitions. Diabetes Med. 2007;24:464–72.
51. Butler J, Rodondi N, Zhu Y, Figaro K, Fazio S, Vaughan DE, Health ABC Study, et al. Metabolic syndrome and the risk of cardiovascular disease in older adults. J Am Coll Cardiol. 2006;47:1595–602.
52. Holvoet P, Kritchevsky SB, Tracy RP, Mertens A, Rubin SM, Butler J, et al. The metabolic syndrome, circulating oxidized LDL, and risk of myocardial infarction in well-functioning elderly people in the health, aging, and body composition cohort. Diabetes. 2004;53:1068–73.

Part I

Understanding Diabetes Mellitus

Understanding Diabetes Mellitus: Pathophysiology

3

Meera Shah and Adrian Vella

Type 2 diabetes arises out of a complex interaction between the genes and the environment. It is characterized by hyperglycemia which is the result of inadequate insulin secretion for the prevailing insulin action. In addition, the ability of glucose itself to stimulate its own uptake and suppress its own release—otherwise termed glucose effectiveness—is also impaired. Prolonged hyperglycemia is ultimately a major contributor to the macrovascular and microvascular complications of type 2 diabetes.

3.1 Predisposition to Type 2 Diabetes

Genome-wide association studies (GWAS) have helped identify multiple genetic variants at multiple loci that are associated with type 2 diabetes. In addition to affecting diabetes risk, these and other loci also may affect quantitative traits such as the insulin response to an oral glucose challenge [1]. Interestingly, many of these variants seem to be associated with a decrease in insulin secretion (at least as measured by peripheral insulin concentrations) rather than defects in insulin action. This might be explained by the suggestion that defects in insulin secretion are more important in the pathogenesis of type 2 diabetes. Alternatively, it is reasonable to posit that environmental contributions to defective insulin action far outweigh any genetic contribution, making detection of a genetic contribution harder. Finally, it is also important to note that most GWAS studies examining quantitative traits have used qualitative methodology for the measurement of insulin secretion and action which may be prone to errors such as those introduced by hepatic extraction of insulin [2]. Nevertheless, many of the genes identified by GWAS as being

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associated with type 2 diabetes may help shed light on the pathogenesis of the disease. A few examples are discussed below (Table 3.1) [3]:

The gene encoding transcription factor 7-like 2 (*TCF7L2*) on chromosome 10q, and its association with type 2 diabetes, was discovered in 2006 [4]. Subsequent analysis of data from the Diabetes Prevention Program suggested that the diabetes-associated allele(s) at this locus increased the risk of progression to diabetes and impaired post-challenge insulin secretion [5, 6].

An alanine substitution (Pro12ala) in the peroxisome proliferator-activated receptor γ (*PPARG*) gene has been found to confer a 20 % reduced risk of developing diabetes compared to the more common proline homozygotes [7]. Despite the modest contribution to the risk of diabetes, the *PPAR*-γ receptor is a proven therapeutic target with significant effects on glycemic control. Another therapeutic target is *KCNJ11*, an ATP-sensitive potassium channel involved in the depolarization of the β cell, leading to insulin release. Sulfonylureas can activate these channels and are used in forms of congenital diabetes where there is an activating gene mutation causing loss of depolarization [8]. *KCNQ1* is a gene that encodes a potassium channel protein and mutations in this have been shown to increase the risk of type 2 diabetes in predominantly Asian populations [9].

As noted above, type 2 diabetes is a polygenic disorder with a strong environmental influence. Several monogenic forms of diabetes have also been identified, including maturity-onset diabetes of the young (MODY) and maternally inherited diabetes and deafness (MIDD). The MODY subtypes share the common

Table 3.1 Genetic variants associated with type 2 diabetes with corresponding odds ratios for developing diabetes

Gene	Name	Function	Chromosome	Odds ratio
PPARG	Peroxisome proliferator-activated receptor ϒ	Regulates adipocyte differentiation	3	1.19
KCNJ11	Potassium inwardly rectifying channel, subfamily J, member 11	Part of the sulfonylurea receptor complex and therefore important in insulin secretion	11	1.14
TCF7L2	Transcription factor 7-like 2	Encodes a transcription factor that regulates proglucagon gene expression in the intestine	10	1.37
SLC30A8	Solute carrier family 30 (zinc transporter), member 8	Zinc transporter involved in insulin storage and secretion	8	1.12
HHEX	Hematopoietically expressed homeobox	Transcription factor that is important in pancreatic development	10	1.13
KCNQ1	Potassium voltage-gated channel, KQT-like subfamily, member 1	Encodes protein for potassium channel	11	1.42

characteristics of autosomal dominant inheritance associated with early age of onset of diabetes that is not associated with obesity and, at least initially, is not insulin-requiring. The MODY genes may provide useful insights into the physiology of glucose homeostasis—for example a mutation in glucokinase (MODY2), the enzyme necessary for phosphorylation of glucose, alters the set-point for insulin secretion. European studies have estimated that up to 5 % of patients with type 2 diabetes may in fact have MODY [10].

A small group of patients may have diabetes associated with rare genetic syndromes, including the congenital loss of β cells, pancreatic developmental disorders, and inborn errors of metabolism. Chromosomal disorders such as Turner and Klinefelter syndromes are associated with a higher prevalence of diabetes, in the latter thought partly due to concomitant obesity [11].

3.2 Interaction Between Defects in Insulin Secretion and Insulin Action

Insulin inhibits hepatic glucose production and stimulates glucose uptake in the skeletal muscle. It also stimulates intravascular lipolysis and lipogenesis in the adipose tissue, inhibits lipolysis in adipose tissue and inhibits the production of very low-density lipoprotein (VLDL) in the liver. The net effect of these actions is to lower serum glucose, fatty acid and triglyceride concentrations and to increase lipoprotein lipase activity in the adipocyte. When insulin is unable to perform these actions at concentrations that are normally adequate, a state of insulin resistance is reached.

The relationship between insulin secretion and insulin action has been widely studied and the debate continues as to which one precedes the other in type 2 diabetes. Individuals with impaired fasting glucose (IFG) have been shown to have a similar inverse relationship between insulin secretion and action but their disposition index (a marker of β-cell function) decreases with increasing fasting glucose, suggesting that there is no fixed glucose threshold above which β-cell function deteriorates [12]. This also implies that these defects are seen earlier than the current accepted definitions of impaired fasting glucose, which may in turn have therapeutic implications. Others have noted phenotypic differences between individuals in whom the primary defect is β-cell dysfunction (lean diabetic) and those who have a defect in tissue sensitivity to insulin (obese diabetic) [13], although this is not a reliable clinical tool.

Physiologic studies on individuals with impaired glucose tolerance (IGT) have also confirmed defects in both insulin secretion and insulin action (Fig. 3.1). Hepatic insulin resistance along with impairment in first phase insulin secretion accounts for fasting hyperglycemia seen in IFG [14], although heterogeneity in insulin sensitivity within this group has led to some authors reporting abnormal peripheral insulin sensitivity as well [15]. Individuals with IGT have reduced second-phase insulin secretion (by about 30 % when compared IFG) and greater insulin resistance at the level of the skeletal muscle [14, 16]. Hence IFG and IGT are distinct metabolic

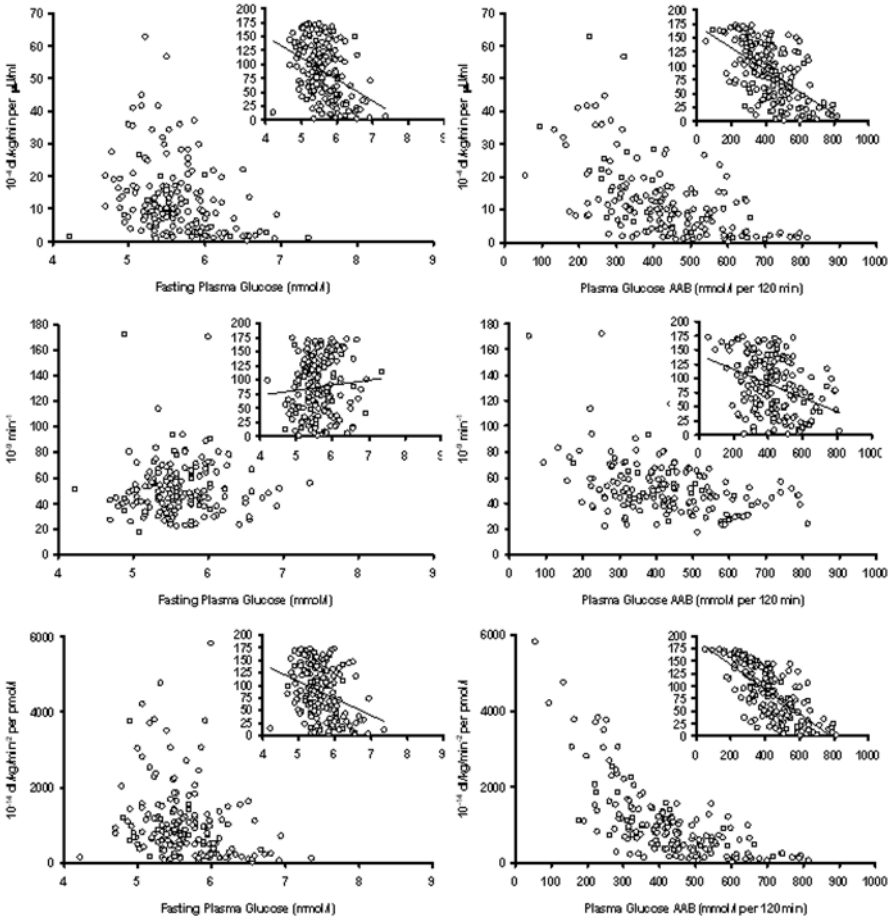

Fig. 3.1 Relationship of insulin action (Si, *top panel*), insulin secretion (ϕ, *middle panel*), and disposition index (DI, *lower panel*) with fasting glucose concentrations (*left*) and area above basal after oral glucose challenge (*right*). The inset panels represent the rank transformed values of Si, ϕ, and DI plotted against fasting and area above basal glucose values. *Reproduced with permission from Sathananthan et al. Clinical Endocrinology (2012) 76, 212–219*

entities and the defects of insulin secretion and action are additive in individuals with combined IFG and IGT. These conclusions seem to hold true even when various methodologies for quantifying insulin secretion and measuring insulin action are taken into account. In addition, for a given percentage body fat, women show decreased insulin action when compared to men highlighting the contribution of gender on glucose metabolism [2].

In type 2 diabetes, fasting hyperglycemia is primarily due to an increase in endogenous hepatic glucose production (EGP). In the post-prandial state, the cause for hyperglycemia is multifactorial. Inadequate suppression of EGP leads to hyperglycemia, which in large part is due to hepatic insulin resistance [17]. The severity

of hepatic insulin resistance has been shown to positively correlate with liver triglyceride content [18]. Insulin resistance at the level of the skeletal muscle also reduces the peripheral uptake of glucose, though this is probably a secondary contributory mechanism. Multiple defects in the insulin signaling cascade have been identified, and insulin-enhanced glucose uptake mediated by glucose transporter 4 (GLUT-4) is diminished [19]. Additionally, insulin action in the liver and peripheral tissues is inhibited by higher circulating concentrations of free fatty acids and triglycerides.

Peripheral insulin concentrations are reflective of pancreatic insulin secretion after having undergone hepatic extraction, which in turn is affected by obesity, ethnicity, and β-cell function [20]. Hepatic insulin extraction is decreased in individuals with type 2 diabetes, thus contributing to peripheral hyperinsulinemia.

Perhaps the best way to characterize the pathogenic mechanisms is via lessons learnt from longitudinal studies involving patients that progress from normal glucose tolerance (NGT) to IGT to type 2 diabetes. The 10 years cumulative incidence of diabetes in individuals with fasting plasma glucose (FPG) in the 100–109 mg/dL range is about 10 %, while that risk doubles if FPG is between 110 and 125 mg/dL [21]. This suggests a continuum in β-cell dysfunction, which is characterized by the progressive loss of the β-cell's ability to compensate for increases in glucose concentrations.

The evolution of a predisposed individual toward diabetes has been studied in large prospective trials. When Pima Indians with NGT were followed over a 5-year period, progressors to diabetes were on average heavier, and showed a faster decline in insulin-stimulated glucose disposal and insulin secretion when compared to non-progressors suggesting that defects in both insulin secretion and action were early occurrences in the pathogenesis of type 2 diabetes [22]. These have been shown to happen between 3 and 6 years before the actual diagnosis of diabetes and are accelerated by weight gain [23].

3.3 Bihormonal Defects and Their Role in the Pathogenesis of Hyperglycemia

In the post-prandial state, type 2 diabetes is characterized by unsuppressed glucagon production and delayed and defective insulin secretion. The main stimulus for insulin secretion and its regulation is the prevailing glucose concentration. Additionally, circulating amino acids, free fatty acids and incretins augment insulin secretion, while catecholamines, cortisol, growth hormone, leptin and tumor necrosis factor-α reduce β-cell response.

Insulin is usually secreted in a pulsatile manner and the amplitude or frequency of pulses increase in response to appropriate stimuli. In people with impaired glucose tolerance and type 2 diabetes, this pulsatility is disordered resulting in inappropriate insulin concentrations for the level of prevailing glucose. Disordered pulsatility also decreases expression of multiple mediators of the insulin signaling cascade [24].

Both prolonged and acute exposure to hyperglycemia adversely affects β-cell function, in part through chronic oxidative stress, with resulting impairment in insulin gene expression and β-cell apoptosis [25]. Low birth weight infants are more susceptible to developing diabetes; one hypothesis is that in utero malnutrition may prime the β cell to adapt poorly to subsequent states of over-nutrition [26].

Individuals with type 2 diabetes also have elevated circulating free fatty acid concentrations which impair β-cell function. Histologically, these islet cells are deposited with amyloid, but these changes interestingly are only subsequent to and do not precede, the defects in insulin secretion [27]. β-cell mass in individuals with type 2 diabetes is also decreased by about 30 %, when compared to non-obese non-diabetic individuals [28].

Alpha-cell mass in the pancreas remains relatively unchanged, and evidence of α-cell dysfunction is seen through impaired glucagon suppression by hyperglycemia and diminished responses to hypoglycemia [29]. It is uncertain whether this results from an inherent defect in the α-cells of people with type 2 diabetes or a manifestation of decreased intra-islet insulin that would normally suppress glucagon secretion.

Shah et al. showed that in response to a mixed meal, impaired glucose tolerance was a result of the lack of glucagon suppression in the presence of relative insulin insufficiency, as seen in the diabetic state (Fig. 3.2) [30]. Further studies using

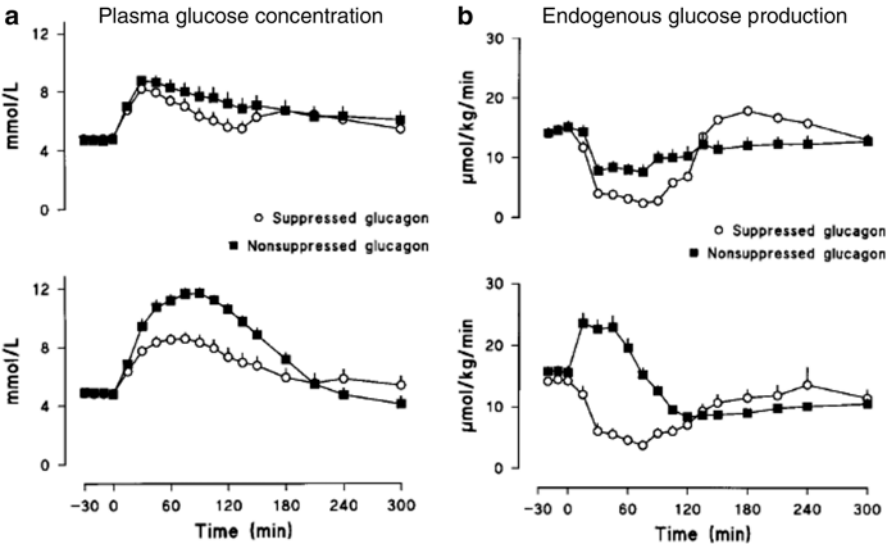

Fig. 3.2 Non-diabetic subjects were infused with a prandial glucose infusion and insulin was infused to mimic a "diabetic" panel B or "non-diabetic" panel A post-prandial profile. Glucagon was then infused at time zero to prevent a fall in glucagon (non-suppressed) or at 2 h to allow a transient fall in glucagon (suppressed). During the "diabetic" insulin profile, lack of glucagon suppression resulted in a marked increase in both the peak glucose concentration and the area above basal of glucose because of impaired suppression of glucose production. *Reproduced with permission from Shah et al. Am J Physiol Endocrinol Metab 277:E283–E290, 1999*

infusions of [1-^{14}C] labeled galactose confirmed this to be mainly as a result of glycogenolysis [31].

Incretin hormones, released by the L cells of the small intestine in response to an enteral nutrient load, augment insulin release and are trophic to β cells. Lower concentrations of incretins such as glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP) have been observed in people with impaired fasting glucose, impaired glucose tolerance and in people with type 2 diabetes [32]. However it is more likely that these changes are a consequence of, and not a cause of the diabetic state and their role in the pathogenesis of type 2 diabetes continues to be debated [33, 34].

3.4 Defects in Carbohydrate Metabolism in Type 2 Diabetes

There is a prolonged elevation of glucose concentrations following a carbohydrate-containing meal in people with type 2 diabetes, and this is a result of a multitude of factors. There is a failure of suppression of EGP in the immediate post-prandial period. Additionally, it takes longer for EGP to reach nadir levels when compared to individuals without diabetes [35]. Post-prandially, the main sources of glucose are from hepatic gluconeogenesis and glycogenolysis, as the rate of appearance of ingested glucose is no different from normal individuals [36]. Both sources of EGP are increased early on in diabetes, perhaps gluconeogenesis to a greater degree [37]. To answer the question if the increase in EGP is due to hepatic insulin resistance, Basu et al. studied individuals with and without type 2 diabetes in a hyperglycemic state while insulin was infused at concentrations that spanned the physiologic range [38]. As expected, EGP was higher in the group with diabetes when compared to those without diabetes at lower and higher concentrations of insulin, suggesting hepatic insulin resistance. Additionally, the liver is also resistant to the inhibitory effect of hyperglycemia per se.

The rate of glucose disappearance is lower in people with type 2 diabetes, and this is due to decreases in both splanchnic and muscle glucose uptake with defects in glucokinase activity likely accounting for the former [39]. Delays in insulin secretion after a meal, as seen in type 2 diabetes, results in higher peak glucose concentrations whereas insulin resistance prolongs hyperglycemia [40]. Therefore, defects in both insulin secretion and action work in concert to promote higher post-prandial glucose concentrations (Fig. 3.3).

Glucose is an important regulator of its own metabolism, a phenomenon termed "glucose effectiveness." When non-diabetic individuals were infused with 35 g of intravenous glucose while their basal insulin levels were clamped, they exhibited a modest rise in plasma glucose concentrations, unlike the stark hyperglycemia seen in patients with type 2 diabetes. This was found to be due to impaired glucose-induced stimulation of glucose uptake and not glucose-induced suppression of glucose production [41]. This regulatory mechanism is lost in people with type 2 diabetes, further contributing to the hyperglycemic state.

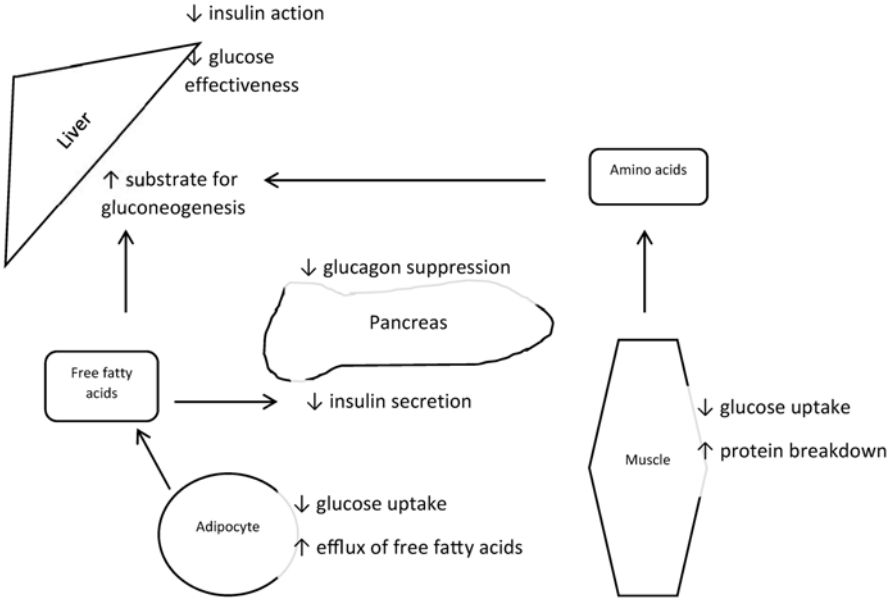

Fig. 3.3 Principle defects in type 2 diabetes. (1) Decreased insulin secretion (*DeFronzo RA, et al.: New concepts in the pathogenesis and treatment of non-insulin-dependent diabetes mellitus. Am J Med 75:52–81, 1983*). (2) Decreased insulin action (*DeFronzo RA, et al.: Effects of insulin on peripheral and splanchnic glucose metabolism in non-insulin-dependent (type II) diabetes mellitus. J Clin Invest 76:149–55, 1985*). (3) Decreased glucagon suppression (*Shah P, et al.: Impact of lack of suppression of glucagon on glucose tolerance in humans. Am J Physiol Endocrinol Metab 277:E283–E290, 1999*). (4) Decreased glucose effectiveness (*Basu A, et al.: Impaired Basal Glucose Effectiveness in NIDDM: Contribution of Defects in Glucose Disappearance and Production, Measured Using an Optimized Minimal Model Independent Protocol. Diabetes 46:421–432, 1997*)

3.5 Defects in Protein Metabolism in Type 2 Diabetes

In contrast to its effect on fat and glucose metabolism, the effects of insulin on whole-body protein synthesis and breakdown appear to be much more diminutive in individuals with type 2 diabetes [42]. This is quite different from individuals with type 1 diabetes, where absolute insulin deficiency results in whole body protein catabolism and defects in skeletal muscle protein synthesis [43]. When free fatty acids are infused to induce insulin resistance, there is a decreased rate of protein breakdown but little to no effect on the rate of protein synthesis as measured by the rate of protein disappearance [44]. There also seems to be post-absorptive insulin resistance of regional protein metabolism, although adiposity and elevated free fatty acid concentrations alone may have contributory roles independent of insulin action [45, 46]. In men, the degree of hyperglycemia seems to correlate directly with increased protein turnover and while this is not evident in women, the presence of lower body obesity seems protective [47]. The mechanisms by which this occurs is

unclear-fatty acids and their metabolites may impact protein metabolism by their effects on the insulin signaling pathway, but other human studies have shown this to be independent of the insulin signaling cascade [48].

Therefore in type 2 diabetes and other insulin-resistant states, there is limited protein catabolism and preserved lean body mass, except in instances where there is poor glycemic control; with adequate glycemic control the defects are normalized [49]. People with type 2 diabetes have also been found to have increased circulating levels of clotting factors such as tissue plasminogen activator and plasminogen activator inhibitor-1 [50], implying abnormal hepatic and endothelial protein synthesis.

3.6 Defects in Fat Metabolism in Type 2 Diabetes

Concentrations of free fatty acids are elevated in individuals with type 2 diabetes in the fasting and post-prandial states, leading to impairment of insulin secretion and insulin-stimulated glucose uptake [51]. Studies have shown that a chronic elevation of free fatty acids impairs β-cell function leading to increased basal insulin secretion but ineffective insulin secretion in the presence of glucose [52]. Excessive amounts of free fatty acids can result in β-cell apoptosis [25], which in rodents at least occurs even in the absence of amyloid deposition, suggesting that free fatty acids alone were toxic to these cells [53].

During the evolution of type 2 diabetes, adipocytes develop resistance to the anti-lipolytic activity of insulin with resulting elevations in free fatty acid concentrations in both the fasting and post-prandial state. As β-cell function declines and insulin secretion is attenuated, the situation worsens. Interestingly, the ability of insulin to suppress lipolysis is affected by body fat distribution; upper body obesity is typically more insulin-resistant than lower body obesity [54].

There are several effects of high free fatty acid levels on the liver. Hepatic insulin extraction is impaired, contributing further to hyperinsulinemia [55]. This in turn promotes the expression of lipogenic enzymes and diminished fatty acid oxidation, leading to increased production of very low-density lipoprotein (VLDL) and triglycerides [56]. In addition, there is upregulation of enzymes involved in gluconeogenesis, with the net result of increasing hepatic glucose output [57].

At the level of the muscle, free fatty acids decrease glucose uptake by inhibiting glucose transport, glucose phosphorylation, and muscle glycogen synthase. These abnormalities are thought to happen early in the pathogenesis of diabetes and as concentrations of intramyocellular lipid increase with weight gain and dietary indiscretion, insulin resistance also increases [58].

Factors released from adipose tissue such as leptin and adiponectin have also been studied in the pathogenesis of type 2 diabetes. Leptin, which is secreted by adipocytes, sends signals to the hypothalamus about fat stores and has biologic effects on the pancreas. Animal models deficient in the pancreatic leptin receptor were found to have reduced insulin secretory response to glucose, poor islet growth, and glucose intolerance when challenged with a high fat diet [59], suggesting that leptin is an

important mediator of obesity-related type 2 diabetes. A deficiency in adiponectin, a cytokine derived from adipocytes, has been shown to correlate with insulin resistance, hyperinsulinemia, obesity, and type 2 diabetes [60]. It has also been shown to adversely affect the cardiovascular risk profile particularly in men [61]. It remains to be seen if either adipokine becomes a viable clinically relevant therapeutic target for diabetes.

References

1. Smushkin G, Vella A. Genetics of type 2 diabetes. Curr Opin Clin Nutr Metab Care. 2010;13:471–7.
2. Sathananthan A, Dalla Man C, Zinsmeister AR, Camilleri M, Rodeheffer RJ, Toffolo G, et al. A concerted decline in insulin secretion and action occurs across the spectrum of fasting and post-challenge glucose concentrations. Clin Endocrinol (Oxf). 2012;76(2):212–9.
3. Stolerman ES, Florez JC. Genomics of type 2 diabetes mellitus: implications for the clinician. Nat Rev Endocrinol. 2009;5:429–36.
4. Grant S, et al. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nat Genet. 2006;38:320–3.
5. Florez JC, Jablonski KA, Bayley N, et al. TCF7L2 polymorphisms and progression to diabetes in the Diabetes Prevention Program. N Engl J Med. 2006;355:241–50.
6. Saxena R, Gianniny L, Burtt NP, et al. Common single nucleotide polymorphisms in TCF7L2 are reproducibly associated with type 2 diabetes and reduce the insulin response to glucose in nondiabetic individuals. Diabetes. 2006;55:2890–5.
7. Altshuler D, et al. The common PPARγ Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes. Nat Genet. 2000;26:76–80.
8. Pearson ER, et al. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. N Engl J Med. 2006;355:467–77.
9. Unoki H, et al. SNPs in KCNQ1 are associated with susceptibility to type 2 diabetes in East Asian and European populations. Nat Genet. 2008;40:1098–102.
10. Ledermann HM. Is maturity-onset diabetes at young age (MODY) morer common in Europe than previously assumed? Lancet. 1995;345:648.
11. Nielsen J, Johansen K, Yde H. Frequency of diabetes mellitus in patients with Klinefelter's syndrome of different chromosome contitutions and the XYY syndrome: plasma insulin and growth hormone level after a glucose load. J Clin Endocrinol Metab. 1969;29:1062–73.
12. Utzschneider KM, Prigeon RL, Carr DB, et al. Impact of differences in fasting glucose and glucose tolerance on the hyperbolic relationship between insulin sensitivity and insulin responses. Diabetes Care. 2006;29:356–62.
13. DeFronzo RA. Lilly lecture 1987. The triumvirate: betacell, muscle, liver. A collusion responsible for NIDDM. Diabetes. 1988;37:667–87.
14. Meyer C, Pimenta W, Woerle HJ, Van Haeften T, Szoke E, Mitrakou A, et al. Different mechanisms for impaired fasting glucose and impaired postprandial glucose tolerance in humans. Diabetes Care. 2006;29:1909–14.
15. Kim SH, Reaven GM. Isolated impaired fasting glucose and peripheral insulin sensitivity. Diabetes Care. 2008;31:347–52.
16. Abdul-Ghani MA, Jenkinson CP, Richardson DK, Tripathy D, DeFronzo RA. Insulin secretion and action in subjects with impaired fasting glucose and impaired glucose tolerance results from the Veterans Administration Genetic Epidemiology Study. Diabetes. 2006;55:1430–5.
17. Mitrakou A, Kelley D, Veneman T, et al. Contribution of abnormal muscle and liver metabolism to postprandial hyperglycemia in NIDDM. Diabetes. 1990;39:1381–90.

18. Ryysy L, Hakkinen AM, Goto T, et al. Hepatic fat content and insulin action on free fatty acids and glucose metabolism rather than insulin absoption are asociated with insulin requirements during insulin therapy in type 2 diabetic patients. Diabetes. 2000;49:749–58.
19. Zierath JR, Krook A, Wallberg-Henriksson H. Insulin action in skeletal muscle from patients with NIDDM. Mol Cell Biochem. 1998;182:153–60.
20. Rossell R, Gomis R, et al. Reduced hepatic insulin extraction in obesity: relationship with plasma insulin levels. J Clin Endocrinol Metab. 1983;56:608.
21. Dinnen SF, et al. Cumulative incidence of diabetes according to initial fasting plasma glucose. Diabetes Care. 1998;21:1408–13.
22. Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest. 1999;104:787–94.
23. Tabák AG, Jokela M, Akbaraly TN, Brunner EJ, Kivimäki M, Witte DR. Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: an analysis from the Whitehall II study. Lancet. 2009;373:2215–21.
24. Porksen N, Hollingdal M, Juhl C, Butler P, Veldhuis JD, Schmitz O. Pulsatile insulin secretion: detection, regulation, and role in diabetes. Diabetes. 2002;51 Suppl 1:S245–54.
25. Poitout V, Robertson RP. Minireview: secondary beta-cell failure in type 2 diabetes – a convergence of glucotoxicity and lipotoxicity. Endocrinology. 2002;143:339–42.
26. Hales C, Barker D. Type 2 (non insulin dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia. 1992;35:595–601.
27. Hayden MR, Sowers JR. Isletopathy in type 2 diabetes mellitus: implications of islet RAS, islet fibrosis, islet amyloid, remodeling, and oxidative stress. Antioxid Redox Signal. 2007;9:891–910.
28. Rahier J, Goebbels R, Henquin J. Cellular composition of the human diabetic pancreas. Diabetologia. 1983;24:366–71.
29. Gerich J. Abnormal glucagon secretion in type 2 (non insulin dependent) diabetes mellitus: causes and consequences. In: Lefebvre P, editor. Bayer centenary symposium: diabetes mellitus-pathophysiology and therapy. New York: Springer; 1988. p. 127–33.
30. Shah P, Basu A, Basu R, Rizza R. Impact of lack of suppression of glucagon on glucose tolerance in humans. Am J Physiol Endocrinol Metab. 1999;277:E283–90.
31. Shah P, Vella A, Basu A, Basu R, Schwenk WF, Rizza RA. Lack of suppression of glucagon contributes to postprandial hyperglycemia in subjects with type 2 diabetes mellitus. J Clin Endocrinol Metab. 2000;85:4053–9.
32. Laakso M, Zilinskaite J, Hansen T, Boesgaard TW, Vanttinen M, Stancakova A, et al. Insulin sensitivity, insulin release and glucagon-like peptide-1 levels in persons with impaired fasting glucose and/or impaired glucose tolerance in the EUGENE2 study. Diabetologia. 2008;51:502–11.
33. Smushkin G, Sathananthan A, Man CD, Zinsmeister AR, Camilleri M, Cobelli C, et al. Defects in GLP-1 response to an oral challenge do not play a significant role in the pathogenesis of prediabetes. J Clin Endocrinol Metab. 2012;97(2):589–98.
34. Knop FK, Vilsbøll T, Højberg PV, Larsen S, Madsbad S, et al. Reduced incretin effect in type 2 diabetes: cause or consequence of the diabetic state? Diabetes. 2007;56:1951–9.
35. Firth RG, Bell PM, Marsh HM, Hansen I, Rizza RA. Postprandial hyperglycemia in patients with noninsulin-dependent diabetes mellitus: role of hepatic and extrahepatic tissues. J Clin Invest. 1986;77:1525–32.
36. Butler PC, Rizza R. Contribution to postprandial hyperglycemia and the effect on initial splanchnic glucose clearance of hepatic glucose cycling in glucose-intolerant or NIDDM patients. Diabetes. 1991;40:73–81.
37. Basu R, Schwenk WF, Rizza RA. Both fasting glucose production and disappearance are abnormal in people with “mild” and “severe” type 2 diabetes. Am J Physiol Endocrinol Metab. 2004;287:E55–62.

38. Basu R, Basu A, Johnson CM, Schwenk WF, Rizza RA. Insulin dose response curves for stimulation of splanchnic glucose uptake and suppression of endogenous glucose production differ in nondiabetic humans and are abnormal in people with type 2 diabetes. Diabetes. 2004;53:2042–50.
39. Basu A, Basu R, Shah P, Vella A, Johnson CM, Nair KS, et al. Effects of type 2 diabetes on the ability of insulin and glucose to regulate splanchnic and muscle glucose metabolism: evidence for a defect in hepatic glucokinase activity. Diabetes. 2000;49:272–83.
40. Basu A, Alzaid A, Dinneen S, Caumo A, Cobelli C, Rizza RA. Effects of a change in the pattern of insulin delivery on carbohydrate tolerance in diabetic and nondiabetic humans in the presence of differing degrees of insulin resistance. J Clin Invest. 1996;97:2351–61.
41. Basu A, Caumo A, Bettini F, et al. Impaired basal glucose effectiveness in NIDDM: contribution of defects in glucose disappearance and production, measured using an optimized minimal model independent protocol. Diabetes. 1997;46:421–32.
42. Luzi L, Petrides AS, De Fronzo RA. Different sensitivity of glucose and amino acid metabolism to insulin in NIDDM. Diabetes. 1993;42:1868–77.
43. Nair KS, Ford GC, Ekberg K, Fernqvist-Forbes E, Wahren J. Protein dynamics in whole body and in splanchnic and leg tissues in type I diabetic patients. J Clin Invest. 1995;95: 2926–37.
44. Katsanos CS, Aarsland A, Cree MG, Wolfe RR. Muscle protein synthesis and balance responsiveness to essential amino acids ingestion in the presence of elevated plasma free fatty acid concentration. J Clin Endocrinol Metab. 2009;94:2984–90.
45. Chevalier S, Marliss EB, Morais JA, Lamarche M, Gougeon R. Whole-body protein anabolic response is resistant to the action of insulin in obese women. Am J Clin Nutr. 2005;82:355–65.
46. Short KR, Irving BA, Basu A, Johnson CM, Nair KS, Basu R. Effects of type 2 diabetes and insulin on whole-body, splanchnic, and leg protein metabolism. J Clin Endocrinol Metab. 2012;97:4733–41.
47. Gougeon R, Morais JA, Chevalier S, Pereira S, Lamarche M, Marliss EB. Determinants of whole-body protein metabolism in subjects with and without type 2 diabetes. Diabetes Care. 2008;31:128–33.
48. Kalhan SC. Fatty acids, insulin resistance, and protein metabolism. J Clin Endocrinol Metab. 2009;94(8):2725–7.
49. Gougeon R, Marliss EB, Jones PJ, Pencharz PB, Morais JA. Effect of exogenous insulin on protein metabolism with differing nonprotein energy intakes in type 2 diabetes mellitus. Int J Obes Relat Metab Disord. 1998;22:250–61.
50. Sobel BE, Woodcock-Mitchell J, Schneider DJ, et al. Increased plasminogen activator inhibitor type 1 in coronary artery atherectomy specimens from type 2 diabetic compared with non diabetic patients: a potential factor predisposing to thrombosis and its persistence. Circulation. 1998;97:2213–21.
51. Boden G, Chen XS. Effects of fat on glucose uptake and utilization in patients with non-insulin-dependent diabetes. J Clin Invest. 1995;96(3):1261.
52. Zhou YP, Grill VE. Long term exposure to fatty acids and ketones inhibits beta-cell function in human pancreatic islets of Langerhans. J Clin Endocrinol Metab. 1995;80:1584–90.
53. McGarry JD. Banting lecture 2001: dysregulation of fatty acid metabolism in the etiology of type 2 diabetes. Diabetes. 2002;51:7–18.
54. Meek SE, Nair KS, Jensen MD. Insulin regulation of regional free fatty acid metabolism. Diabetes. 1999;48:10–4.
55. Bergman RN. Non-esterified fatty acids and the liver. Why is insulin secreted into the portal vein? Diabetologia. 2000;43:946–52.
56. McGarry JD, Dobbins RL. Fatty acids, lipotoxicity and insulin secretion. Diabetologia. 1999;42:128–38.
57. Massillon D, Barzilai N, Hawkins M, Prus-Wertheimer D, Rossetti L. Induction of hepatic glucose-6-phosphatase gene expression by lipid infusion. Diabetes. 1997;46:153–7.

58. Krssak M, Petersen KF, Dresner A, DiPietro L, Vogel SM, Rothman DL, et al. Intramyocellular lipid concentrations are correlated with insulin sensitivity in humans: a 1H NMR spectroscopy study. Diabetologia. 1999;42:113–6.
59. Morioka T, Asilmaz E, Hu J, Dishinger JF, Kurpad AJ, Elias CF, et al. Disruption of leptin receptor expression in the pancreas directly affects beta cell growth and function in mice. J Clin Invest. 2007;117(10):2860.
60. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest. 2006;116(7):1784.
61. Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB. Plasma adiponectin levels and risk of myocardial infarction in men. JAMA. 2004;291(14):1730.

Medical Approaches to Weight-Centric Management of Obese Patients with Type 2 Diabetes

4

Donna H. Ryan

4.1 Introduction and Purpose

The traditional approach to management of type 2 diabetes has been targeting both glycemic control and associated risk factors that drive cardiovascular disease risk (blood pressure, dyslipidemia, pro-thrombotic tendency). This approach emphasizes a "treating to goal" approach to blood pressure, hemoglobin A1c and LDL, primarily through prescribing antihypertensives, antidiabetics and lipid-lowering medications and by assuring that all patients are on aspirin. This approach pays slight attention to weight management as a way to reduce all components that are contributing to cardiovascular risk. This is changing, in part driven by the observation of dramatic improvement in the metabolic and cardiovascular risk profile of patients with type 2 diabetes who undergo bariatric surgery. This has sparked respect for weight loss as a powerful remediator of dysglycemia and even of cardiovascular risk in persons with type 2 diabetes. The metabolic and weight loss response with bariatric surgery has also stimulated interest in gut peptides as potential medical therapies for both producing and sustaining weight loss and improving multiple metabolic benefits, as well. A new development is the adoption by medical societies of recommendations that physicians who treat patients with type 2 diabetes should restructure their treatment approaches to more weight-centric approaches, as evidenced by the 2013 American Association of Clinical Endocrinologists (AACE) Comprehensive Diabetes Management Algorithm [1].

The primary focus of this chapter is to explore the role of *medical approaches* (*as opposed to surgical approaches*) *using lifestyle intervention to achieve weight management* as a pathway to improving the metabolic profile, symptoms, and

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functionality of patients with type 2 diabetes. The chapter will review the evidence for health benefit from medically induced weight loss in persons with type 2 diabetes, and will limit its scope to interventions that use lifestyle alone, without adjunctive medications.

Evidence for the protean and powerful effects of weight loss, even modest amounts of weight loss, will primarily derive from the Look AHEAD Study. This randomized controlled study [2] of lifestyle intervention versus support condition is chosen to illustrate the impact of weight loss in individuals with type 2 diabetes because of its diverse population (overall there were 59 % women, 37 % ethnic minorities, 14 % had prior cardiovascular disease, the average BMI was 36 kg/m^2) and the average duration of diabetes was 6.8 years) [3], large size (>5000 participants), relatively long period of follow-up (publication of results of at least 8 years minimum observation), excellent delivery of a state-of-the-art lifestyle intervention [4] and excellent retention (8-year retention was 94 %, when deceased persons were removed from the denominator) [5].

The discussion will be organized around eight questions, as follows:

1. Can persons with diabetes successfully lose weight?
2. What is the effect of weight loss achieved with lifestyle intervention on glycemic measures, cardiovascular risk factors, and concomitant medications use in persons with type 2 diabetes?
3. Can persons with diabetes and severe obesity achieve weight loss and associated health benefits with modest weight loss?
4. Can lifestyle intervention in overweight and obese persons with type 2 diabetes reduce cardiovascular events?
5. Can lifestyle intervention induce diabetes remission?
6. What is the prevalence of obstructive sleep apnea in persons with diabetes? Can weight loss improve sleep apnea?
7. What are the benefits of lifestyle intervention on improvement in feeling and function (Quality of Life, Depression, Mobility, Sexual Dysfunction, Urinary Stress Incontinence).
8. What's the bottom line? Does lifestyle intervention for overweight and obese persons with type 2 diabetes reduce health care costs?

4.2 Efficacy of Lifestyle Intervention in Patients with Diabetes

Look AHEAD has provided a framework for comparing intensive lifestyle intervention with a control condition (diabetes support and education). A number of ancillary studies, substudies and subanalyses of this large trial have yielded answers to all the above questions. One must be cautious and recognize the limitations of relying on this one study. While more studies might be needed for a definitive determination, the quality of the studies and the quantity of data make Look AHEAD often the best source to judge the effect of lifestyle intervention.

1. Can persons with diabetes successfully lose weight? It is well known that persons with type 2 diabetes lose less weight than persons without type 2 diabetes [6]. Some of the reasons for this are the use of medications for diabetes that promote weight gain, such as insulin, thiazolidinediones and insulin secretagogues [7]. Persons with diabetes are also more likely to be taking common medications for chronic disease management that also promote weight gain, such as many antidepressants and beta-blockers for hypertension [7]. In the Look AHEAD Intensive Lifestyle Intervention, those persons who were on insulin, other diabetes medications or no medications lost 7.4 ± 7.2, 8.7 ± 6.9, and 9.3 ± 6.8 %, respectively at one year [8].

   Weight loss is also more difficult in patients with type 2 diabetes because when patients enter negative energy balance, the risk of hypoglycemia increases and patients may eat to defend against hypoglycemia. In Look AHEAD, a medication management algorithm [4] was used to reduce hypoglycemia risk with weight loss. Medications were reduced at the start of negative energy balance, with the degree of reduction based on baseline glycemic control. Persons with lower hemoglobin A1c or lower plasma glucose levels were deemed to be at higher risk and requiring greater medication reduction, especially for insulin and insulin secretagogues. Once weight had reached plateau and energy balance was neutral, patients were monitored for glycemia and medications readjusted.

   Other challenges to successful weight loss in persons with type 2 diabetes include the possible presence of established cardiovascular disease and peripheral neuropathy, which make exercise more challenging. Patients who are managing a chronic disease may have competing demands on their time and this may make it difficult to adhere to the behavioral components that are predictive of weight loss success. In Look AHEAD, there was a direct and linear relationship between the amount of weight loss in the first year and quartile of visit attendance, use of meal replacements and minutes of physical activity, emphasizing the importance of adherence to weight loss success [8]. Further, there was a graded relationship between baseline A1c and amount of weight loss, with those with A1c ≥9 % losing less weight over the first year than those with A1c 7–8.9 %. Those with A1c <7 % lost most weight over the first year [9].

   Look AHEAD is ample demonstration that one should not be nihilistic about a person with type 2 diabetes being able to lose weight. Figure 4.1 demonstrates the weight loss over 8 years in Look AHEAD. The mean weight loss at 1 year was −8.6 % of initial weight for those in the Intensive Lifestyle Intervention group vs. −0.7 % for those in the control condition, Diabetes Support and Education ($P < 0.001$) [10]. At 4 years, mean weight loss was −4.7 % of initial weight for those in the Intensive Lifestyle Intervention group vs. −1.1 % for those in Diabetes Support and Education ($P < 0.001$) [11]. At 8 years [5], mean weight loss stayed the same as at 4 years for those in the Intensive Lifestyle Intervention (−4.7 %) and the support condition weight loss was −2.1 %. These results are displayed graphically year by year in Fig. 4.1.

   In terms of predictors of success over the long term, a 4 years analysis of patterns associated with success again revealed that attendance at counseling sessions and amount of physical activity were related to 4 years weight loss in a graded fashion with greater adherence translating into more weight loss [12].

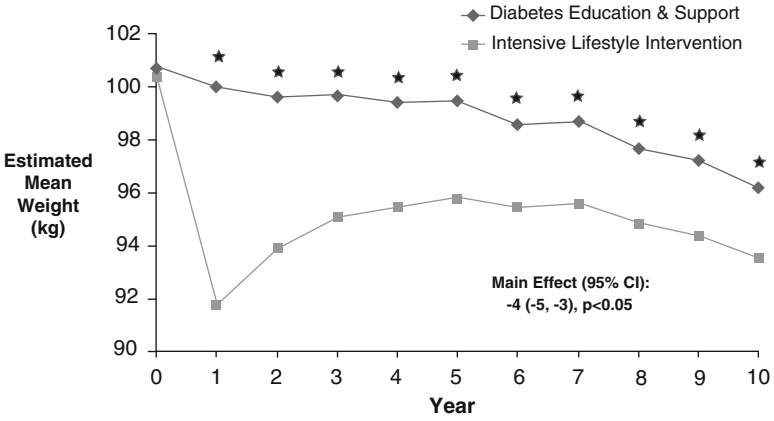

Fig. 4.1 Weight loss in Look AHEAD over minimum 8 years of observation. Mean (+SE) weight loss from baseline among participants in the Intensive Lifestyle Intervention (ILI; $n=2570$) and Diabetes Support and Education (DSE; $n=2575$). Differences between groups are significant ($P<0.001$ for all years). The between-group difference in weight loss after 8 years minimum follow-up was 2.6 %

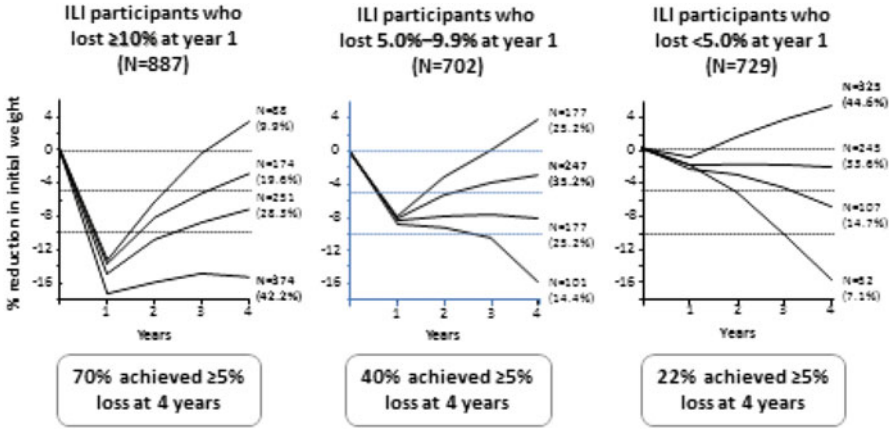

Fig. 4.2 Weight loss (percent loss from baseline) at 1 year in Look AHEAD predicts probability of clinically significant weight loss at 4 years. Participants in the Intensive Lifestyle Intervention (ILI) were categorized according to 1 year loss. The proportion who achieved ≥10 %, 5–9.9 %, and <5 % were, respectively, 38, 30, and 31 %. Of those who lost ≥10 % in year 1, 70 % achieved 5 % or more weight loss in year 4. Of those who lost 5–9.9 % in year 1, 40 % achieved 5 % or more weight loss in year 4. Of those who achieved <5 % in year 1, only 22 % achieved 5 % or more loss at year 4 [12]

However, for participants in the Intensive Lifestyle Intervention, initial weight loss was a strong predictor of ultimate weight loss [12]. This is illustrated graphically in Fig. 4.2, which shows that weight loss at year 1 was predictive of ability to achieve significant weight loss at year 4. The initial weight loss was highly variable in year 1, with roughly one-third achieving 5 % loss or less, one-third

achieving 5–9.9 % loss and one-third achieving ≥10 % loss. If one looks at ≥5 % weight loss at year 4, 70 % of those who achieve ≥10 % in year 1 meet this benchmark at year 4, while only 40 % of those who lost 5–9.9 % in year 1 did and only 22 % of those who lost less than 5 % at year 1 did so. Clearly, initial weight loss is important, because it is predictive of ultimate weight loss.

We will use the Look AHEAD study and the weight loss achieved and sustained over the 1, 4, and 8 years of observation to demonstrate effects on metabolic risk factors, symptoms, and functional issues in patients with type 2 diabetes.

2. What is the effect of weight loss achieved with lifestyle intervention on glycemic measures, cardiovascular risk factors, and concomitant medication use in persons with type 2 diabetes? The impact of negative energy balance on glycemia is immediate. But once weight loss has reached a plateau, and weight is stable there is a strong effect on glycemia of even modest weight loss, such as was achieved in Look AHEAD. As demonstrated in Table 4.1, the glycemic changes associated

Table 4.1 Weight loss and risk factor changes at years 1 and 4 for Look AHEAD intensive lifestyle intervention and diabetes support and education participants

	Year 1 ILI	Year 1 DSE	*P*-value	Year 4 ILI	Year 4 DSE	*P*-value
Weight change (kg)	−8.6	−0.63	<0.001	−4.66	−1.01	<0.0001
Weight change (%)	−8.6	−0.7	<0.001	−4.7	−1.1	<0.001
A1c (%)	−0.64	−0.14	<0.001	−0.20	−0.08 %	<0.001
Glucose (mg %)	−21.5	−7.2	<0.001			
% on insulin, none at baseline	1.7	3.7	<0.001	6.9	11	<0.001
% on insulin, baseline use	80.6	91.6	<0.001	77.4	88	<0.001
% on hypertension medications, none at baseline	16.4	21.9	<0.001	43	47.2	<0.001
% on hypertension medications, baseline use	81.3	89.9	<0.001	85	92.7	<0.001
Systolic blood pressure (mmHg)	−6.8	−2.8	<0.001	−4.66	−3.41	0.01
Diastolic blood pressure (mmHg)	−3.0	−1.8	<0.001	−3.44	−3.19	0.29
LDL (mg/dL)	−5.2	−5.7	0.49	−18.88	−22.77	0.01
HDL (mg/dL)	+3.4	+1.4	<0.001	+3.95	+2.58	0.001
TG (mg/dL)	−30.3	−14.6	<0.001	−22.91	−27.51	0.13
% on Lipid-lowering medication, none at baseline	17.6	25.3	<0.001	47.2	53.2	<0.001
Albumen-to creatinine ration (>30.0 μg/mg) (%)	−3.9	−1.5	0.002			
Fitness increase from baseline (%)	20.4	5.0	<0.001	5.1	1.1	<0.001

with weight loss at years 1 [10] and 4 [11] demonstrated clinically significant reductions in hemoglobin A1c for those who were in the intensive lifestyle intervention, both at year 1 and at year 4. This improvement occurred in the presence of lesser medication use. Of patients who were not on insulin at baseline, there were fewer who started insulin in the lifestyle intervention group, compared to those on diabetes support and education [11]. In addition, at year 1, there were significant benefits associated with lifestyle intervention in systolic blood pressure, HDL cholesterol, reduction in lipid lowering and antihypertensive medications and in fitness; these benefits persisted at year 4. The significant benefits seen with lifestyle intervention at year 1 did not persist to year 4 for diastolic blood pressure and triglycerides. Albumen/creatinine ratio was significantly improved with lifestyle intervention in year 1.

3. Can persons with diabetes and severe obesity achieve weight loss and associated health benefits with modest weight loss? This is a frequent question, since many health professionals have a negative perception of persons with more severe obesity being able to loss enough weight to derive health benefit. The ability to lose weight and the changes in risk factors has been evaluated in the large Look AHEAD population among individuals with class I, II, and III obesity [13, 14]. These results are illustrated in Fig. 4.3. There was no significant difference

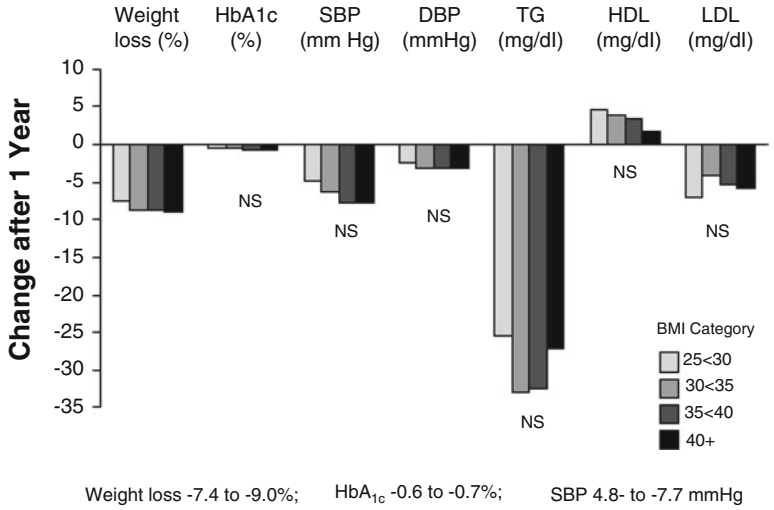

Fig. 4.3 Persons with obesity and type 2 diabetes at all levels of obesity can lose weight and improve risk factors, even those with severe obesity. BMI categories are shown in bars depicting the change at 1 year in weight (%), HbA1c (%), systolic blood pressure (SBP; mmHg), diastolic blood pressure (DBP; mmHg), triglycerides (TG; mg/dL), high-density lipoprotein cholesterol (HDL; mg/dL), and low-density lipoprotein cholesterol (LDL; mg/dL). There is no significant difference among risk factors by BMI category. There is no significant difference by obesity category; however, the weight loss in the overweight category is significantly less than the obese categories, albeit without clinical significance [13]

among classes of those persons with diabetes and any class of BMI, in terms of proportion of weight lost at year 1 and 4, although those in the overweight category loss slightly less weight which was significantly different from the obese categories. Further, the impact of this modest weight loss (roughly 9 %) on improvements was the same for all cardiovascular risk factors, across all BMI classes [13]. Therefore there is no reason to be overly pessimistic about lifestyle intervention, even in those with BMI 0.40 kg/m^2.

4. Can lifestyle intervention in overweight and obese persons with type 2 diabetes reduce cardiovascular events? Despite the above noted reductions in glycated hemoglobin and initial fitness and intermediate cardiovascular endpoints, after a median follow-up of 9.6 years, the Look AHEAD study was stopped for futility. The composite primary outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina) occurred in 403 patients in the intervention group and 418 in the control group. At the end of the study, the difference in weight loss was only 2.5 % between the two groups [15]. It may take more weight loss to achieve benefits in reduction in cardiovascular events. In the SOS study, which demonstrated risk reduction for cardiovascular events [16] and also mortality [17], the difference between the surgical weight loss and the control groups was 16 % [16, 17], much more than the lifestyle intervention in Look AHEAD. Also, among individuals with no cardiovascular disease at baseline in Look AHEAD, the hazard ratio for the endpoint was 0.86 (0.72–1.02) compared to 1.13 (0.90–1.42). Thus, lifestyle-induced weight loss may be simply ineffective for secondary prevention of cardiovascular diseases and may be more appropriate for primary prevention. Whatever the case, we are unable to demonstrate randomized clinical trial evidence for reduction of cardiovascular events and mortality with weight loss achieved through lifestyle intervention.
5. Can lifestyle intervention induce diabetes remission? In Look AHEAD, some patients in both treatment groups (lifestyle and support) achieved partial or complete remission of type 2 diabetes, defined as transition from meeting diabetes criteria to a prediabetes or nondiabetic level of glycemia (fasting plasma glucose <126 mg/dL and hemoglobin A1c <6.5 % with no antihyperglycemic medication) [18]. The lifestyle group had more episodes of remission (partial or complete), with prevalences of 11.5 % (95 % CI, 10.1–12.8 %) during the first year and 7.3 % (95 % CI, 6.2–8.4 %) at year 4, compared with 2.0 % for the support group at both time points (95 % CIs, 1.4–2.6 % at year 1 and 1.5–2.7 % at year 4) ($P < 0.001$ for each) [18]. There were 9.2 % (95 % CI, 7.9–10.4 %), 6.4 % (95 % CI, 5.3–7.4 %), and 3.5 % (95 % CI, 2.7–4.3 %) of lifestyle participants who had continuous, sustained remission for at least 2, at least 3, and 4 years, respectively, compared with less than 2 % of DSE participants (1.7 % [95 % CI, 1.2–2.3 %] for at least 2 years; 1.3 % [95 % CI, 0.8–1.7 %] for at least 3 years; and 0.5 % [95 % CI, 0.2–0.8 %] for 4 years) [18]. Of course these results are extremely modest, but they do provide at least preliminary evidence that complete or partial remission may be possible in type 2 diabetes with medical management, especially if greater weight loss can be achieved and sustained.

6. What is the prevalence of obstructive sleep apnea in persons with diabetes? Can weight loss improve sleep apnea? Both obesity and type 2 diabetes are risk factors for obstructive sleep apnea (OSA). In the Sleep AHEAD study, participants at one site ($n=305$) participated in unattended somnography at baseline [19]. Over 86 % of participants had OSA with an apnea–hypopnea index (AHI) of 5 events/h. There were 30.5 % of the participants with moderate OSA ($15<AHI<30$), and 22.6 % had severe OSA ($AHI\geq 30$), with severe obesity being associated with greater risk for severe OSA. At this study site, at year 1 [19], participants in the lifestyle intervention lost 10.8 kg vs. 0.6 kg ($P<0.00$ l) for the support condition and the adjusted (SE) decrease from baseline in AHI was 9.7 (2.0) events per hour ($P<0.001$). There were more than three times as many participants in the intervention group than in the support group with total remission of OSA, and the prevalence of severe OSA among ILI participants was half that of the DSE group [19]. Most interestingly, there is a graded response to weight loss in AHI improvement (see Fig. 4.4) [19]. In the 51 participants who lost 10 or more kg, the reduction in AHI was significantly better than those who lost weight [19]. After 4 years, despite weight regain, benefits persisted with greater maintenance of weight loss associated with greater improvements in AHI [20]. Remission of OSA at 4 years was five times more common with intensive lifestyle intervention (20.7 %) than diabetes support and education (3.6 %) [20].
7. What are the benefits of weight loss on hepatic steatosis in persons with type 2 diabetes? In a substudy population, 96 participants in Look AHEAD underwent proton magnetic resonance spectroscopy (MRS) to quantify fatty infiltration of the liver, with hepatic steatosis defined as 5.5 % being non-alcoholic fatty liver disease [21]. Figure 4.5 shows the relationship between weight loss and reduction of hepatic steatosis as measured by MRS and the greater the weight loss the

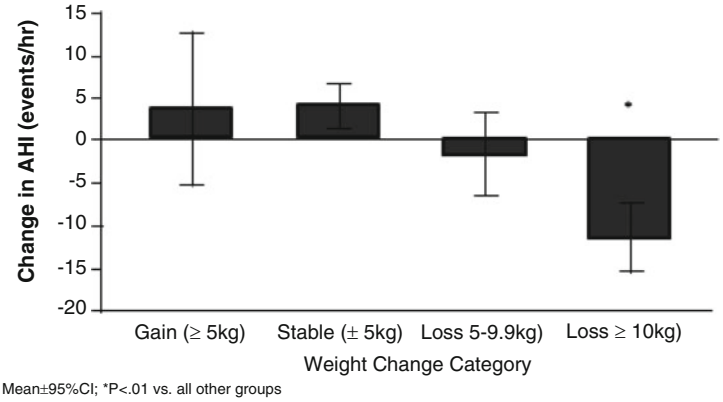

Fig. 4.4 A graded response in weight loss produces a graded response in obstructive sleep apneal with lifestyle intervention for persons with overweight and obesity and type 2 diabetes. In the Sleep AHEAD Study, a Substudy of Look AHEAD, the change in apnea–hypopnea index (AHI) is shown in mean events per hour +95 % Confidence Intervals (CI) according to the category of weight loss. There is significant reduction in AHI beginning at 10 kg or greater weight loss [19]

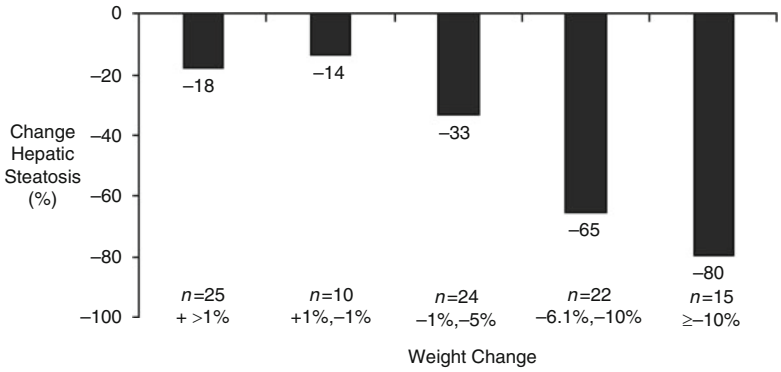

Fig. 4.5 Median percent change in hepatic steatosis measured by 1H Magnetic Resonance Spectroscopy (MRS) by percent weight change. There is a graded relationship between the amount of weight loss category and the percent change in hepatic steatosis measured by MRS. Those with the largest weight loss (≥10 %) had a significantly higher median percent reduction in steatosis of 79.5 % vs. 13.7 % for those with weight loss of +1 to −1 % [21]

greater the reduction in hepatic steatosis. However, while there were group differences in steatosis, with the lifestyle intervention group reducing steatosis on average 50.8 % (vs. 22.8 % in the support group; $P>0.04$), there were no group differences in mean ALT and ASP.

8. What are the benefits of lifestyle intervention on improvement in feeling and function (Quality of Life, Depression, Mobility, Sexual Dysfunction, and Urinary Stress Incontinence)? While reducing risks for other diseases is important, equally important is improving how patients feel and function. There is a known graded response to weight loss achieved through lifestyle intervention and improvement in quality of life as measured by the Impact of Weight—Quality of Life Assessment Tool [22]. Indeed, in Look AHEAD, at year 1, *quality of life* improved more in the group undertaking lifestyle intervention than those in the support condition [23].

   In Look AHEAD, there were fewer patients who developed potentially significant symptoms of *depression* (defined as Beck Depression Inventory [24] score ≥10) in the lifestyle intervention group as compared to the support condition [25]. At 1 year, the incidence of BDI ≥10 was significantly lower in the ILI than in the DSE group (6.3 % vs. 9.6 %; $P<0.001$) indicating that weight loss does not precipitate depression and may protect from it. Furthermore participants in the lifestyle intervention with and without symptoms of depression at baseline lost 7.8 ± 6.7 % and 8.7 ± 6.9 %, respectively, a difference not considered clinically meaningful.

   Look AHEAD also assessed functionality. For participants in the lifestyle intervention, compared to the support condition, there was attenuation in the decline in *mobility* that occurs with aging [26]. For adults with knee pain, there was improvement in function for those in the lifestyle intervention, compared to those who were in the support condition [27].

In overweight and obese women with type 2 diabetes participating in Look AHEAD, *urinary stress incontinence* improved in those who were randomized to the lifestyle intervention as compared to the control condition [28]. Look AHEAD demonstrated the same finding in men [29]. *Sexual dysfunction* was also studied in Look AHEAD and there was improvement in measures of sexual function for participants in the lifestyle intervention compared to the support condition. There was improvement in erectile function for men [30] and sexual dysfunction in women [31].

9. What is the bottom line? Does lifestyle intervention for obese and overweight persons with type 2 diabetes reduce health care costs? A recently published analysis from Look AHEAD [32] analyzed the impact of the lifestyle intervention on use and costs of medical services, with the support condition as comparator. In the lifestyle group, annual hospitalizations were reduced by 11 % ($P=0.004$) and hospital days by 15 % ($P=0.01$). The cost savings for hospitalizations were 10 % less in the lifestyle group ($P=0.04$). Medication cost savings were 7 % less in the lifestyle group compared to the support group ($P<0.001$). Over 10 years, the relative cost savings per person in the lifestyle group were $5280 (95 % CI = $3385-$7175). However, there were no differences in outpatient costs and the savings were not observed in those with a history of cardiovascular disease. The costs of conducting the Look AHEAD intervention have not been reported so cost-effectiveness cannot yet be calculated [32].

4.3 Summing Up and Path Forward

The benefits of weight loss in type 2 diabetes span improvement in risk factors, reduction in the need for concomitant medications, improvements in a variety of measures of feeling and function, partial remission of type 2 diabetes, and reductions in health care costs. However, even with the best lifestyle interventions, some patients are not able to achieve 5 % weight loss and long-term maintenance of weight loss is extremely challenging. The next steps are to develop effective strategies to first, maximize initial weight loss so as to maximize initial health benefits; and second, to develop effective strategies to improve the maintenance of the reduced body weight.

The most optimistic path forward would almost certainly derive from advanced understanding of the biology of energy balance regulation and targeting appetite and other metabolic pathways with pharmacotherapy. Indeed, there would be little room to advance on intensity of lifestyle intervention. Look AHEAD had a minimum of 32 90-min face-to-face sessions with a trained interventionist in the first year. This would be difficult and expensive to duplicate in practice. Turning to pharmacotherapy, there are now four new medications approved for long-term use in weight management (phentermine/topiramate ER, lorcaserin, liraglutide 3 mg and naltrexone/bupropion SR) and one older medication (orlistat). All of these medications

have demonstrated efficacy in overweight and obese patients with type 2 diabetes [33–36]. In every case, when medications are used with lifestyle therapy, there are greater numbers of patients who achieve a meaningful benchmark—5 % weight loss—than those who are receiving placebo and the lifestyle intervention. Further, the average weight loss is greater in pharmacotherapy-treated arm, meaning that the impact on targeted health outcomes is likely to be greater. Last, medications will sustain weight loss as long as they are taken.

Finding ways to achieve successful weight loss in patients with type 2 diabetes is an imperative considering the disease burden that type 2 diabetes imposes on the US population. Addressing these two issues—obesity and type 2 diabetes—will go a long way to addressing the root cause of the epidemic of non-communicable diseases of the twenty-first century.

References

1. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, Dagogo-Jack S, Davidson MB, Einhorn D, Garvey WT, Grunberger G, Handelsman Y, Hirsch IB, Jellinger PS, McGill JB, Mechanick JI, Rosenblit PD, Umpierrez G, Davidson MH, American Association of Clinical Endocrinologists. American Association of Clinical Endocrinologists' comprehensive diabetes management algorithm 2013. Endocr Pract. 2013;19 Suppl 1:1–48.
2. The Look AHEAD Research Group. Look AHEAD (Action for Health in Diabetes): design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. Control Clin Trials. 2003;24(5):610–28.
3. The Look AHEAD Research Group. Baseline characteristics of the randomised cohort from the Look AHEAD (Action for Health in Diabetes) research study. Diab Vasc Dis Res. 2006;3(3):202–15.
4. The Look AHEAD Research Group. The Look AHEAD Study: a description of the lifestyle intervention and the evidence supporting it. Obesity (Silver Spring). 2006;14(5):737–52.
5. The Look AHEAD Research Group. Eight-year weight losses with an intensive lifestyle intervention: the Look AHEAD Study. Obesity. 2014;22:5–13.
6. Guare JC, Wing RR, Grant A. Comparison of obese NIDDM and nondiabetic women: short- and long-term weight loss. Obes Res. 1995;3:329–35.
7. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacologic management of obesity: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015;100(2):342–62.
8. Wadden T, West D, Neiberg R, The Look AHEAD Research Group, et al. One-year weight losses in the Look AHEAD study: factors associated with success. Obesity. 2009;17(4):713–22.
9. Espeland M, Bray G, Neiberg R, The Look AHEAD Research Group, et al. Describing patterns of weight changes using principal components analysis: results from the Action for Health in Diabetes (Look AHEAD) research group. Ann Epidemiol. 2009;19(10):701–10.
10. The Look AHEAD Research Group. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. Diabetes Care. 2007;30(6):1374–83.
11. The Look AHEAD Research Group. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four year results of the Look AHEAD trial. Arch Intern Med. 2010;170(17):1566–75.
12. Wadden T, Neiberg R, Wing R, The Look AHEAD Research Group, et al. Four-year weight losses in the Look AHEAD study: factors associated with success. Obesity. 2011;19(10):1987–98.

13. Unick J, Beavers D, Jakicic J, The Look AHEAD Research Group, et al. The effectiveness of lifestyle interventions for individuals with severe obesity and type 2 diabetes: results from the Look AHEAD trial. Diabetes Care. 2011;34(10):2152–7.
14. Unick JL, Beavers D, Bond DS, et al. The long-term effectiveness of a lifestyle intervention in severely obese individuals. Am J Med. 2013;126:236–42.
15. The Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med. 2013;369:145–54.
16. Sjostrom L, Peltonen M, Jacobson P, et al. Bariatric surgery and long-term cardiovascular events. JAMA. 2012;307(1):56–65.
17. Sjostrom L, Narbro K, Sjostrom D, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med. 2007;357:741–52.
18. Gregg EW, Chen H, Wagenknecht LE, et al. Association of an intensive lifestyle intervention with remission of type 2 diabetes. JAMA. 2012;308:2489–96.
19. Foster G, Sanders M, Millman R, The Sleep AHEAD Ancillary Study, et al. Obstructive sleep apnea among obese patients with type 2 diabetes. Diabetes Care. 2009;32(6):1017–9.
20. Kuna ST, Reboussin DM, Borradaile KE, The Sleep AHEAD Research Group of the Look AHEAD Research Group, et al. Long-term effect of weight loss on obstructive sleep apnea severity in obese patients with type 2 diabetes. Sleep. 2013;36(5):641–649A.
21. Lazo M, Solga S, Horska A, The Fatty Liver Subgroup of the Look AHEAD Research Group, et al. Effect of a 12-month intensive lifestyle intervention on hepatic steatosis in adults with type 2 diabetes. Diabetes Care. 2010;33(10):2156–63.
22. Crosby. Manual for the IWQOL-LITE measure. www.qualityoflifeconsulting.com. Accessed 10 Sept 2014.
23. Williamson D, Rejeski J, Lang W, The Look AHEAD Research Group, et al. Impact of a weight management program on health-related quality of life in overweight adults with type 2 diabetes. Arch Intern Med. 2009;169(2):163–71.
24. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961;4:561–71.
25. Faulconbridge L, Wadden T, Rubin R, The Look AHEAD Research Group, et al. One-year changes in symptoms of depression and weight in overweight/obese individuals with type 2 diabetes in the Look AHEAD study. Obesity. 2012;20(4):783–93.
26. Rejeski WJ, Ip EH, Bertoni AG, et al. Lifestyle change and mobility in obese adults with type 2 diabetes. N Engl J Med. 2012;366:1209–17.
27. Foy CG, Lewis CE, Hairston KG, The Look AHEAD Research Group, et al. Intensive lifestyle intervention improves physical function among obese adults with knee pain: findings from the Look AHEAD trial. Obesity. 2011;19:83–93. Erratum, Obesity (Silver Spring) 2011;19:233.
28. Phelan S, Kanaya AM, Subak LL, et al. Weight loss prevents urinary incontinence in women with type 2 diabetes: results from the Look AHEAD trial. J Urol. 2012;187:939–44.
29. Breyer BN, Phelan S, Hogan PE, The Look AHEAD Research Group, et al. Intensive lifestyle intervention reduces urinary incontinence in overweight/obese men with type 2 diabetes: results from the Look AHEAD trial. J Urol. 2014;192(1):144–9.
30. Wing R, Rosen R, Fava J, Bahnson J, et al. Effects of weight loss intervention on erectile function in older men with type 2 diabetes in the Look AHEAD trial. J Sex Med. 2010;7 (1 Pt 1):156–65.
31. Wing RR, Bond DS, Gendrano IN, The Sexual Dysfunction Subgroup of the Look AHEAD Research Group, et al. Effect of intensive lifestyle intervention on sexual dysfunction in women with type 2 diabetes: results from an ancillary Look AHEAD study. Diab Care. 2013;36:2937–44.
32. Espeland MA, Glick HA, Bertoni A et al., the Look AHEAD Research Group. Impact of an intensive lifestyle intervention on use and cost of medical services among overweight and obese adults with Type 2 diabetes. Diabetes Care. 2014;37(9):2548–56.
33. O'Neil PM, Smith SR, Weissman NJ, et al. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. Obesity. 2012;20(7):1426–36.

34. Garvey WT, Ryan DH, Bohannon NJV, et al. Weight loss therapy in type 2 diabetes: effects of phentermine and topiramate extended-release. Diabetes Care. 2014;37(12):3309–16.
35. Hollander P, Gupta AK, Plodkowski R, The COR-Diabetes Study Group, et al. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. Diabetes Care. 2013;36(12):4022–9.
36. FDA Briefing Document NDA 206321. LIraglutide 3.0 mg. Endocrinologic and Metabolic Advisory Committee. 11 Sept 2014. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM413317.pdf. Accessed 25 Sept 2014.

Adipocyte Dysfunction, Inflammation, and Insulin Resistance in Obesity

5

Cyrus Jahansouz

Only recently has the complexity of adipose tissue become more apparent and appreciated. The two well-known forms of adipose tissue have been recognized: brown and white. Historically, these have been seen as two separate entities, with brown adipose tissue (BAT) primarily playing its role in thermogenesis through uncoupling protein 1, and white adipose tissue (WAT) with its role as fat storage [1–4]. Even this concept is riddled with controversy given the transdifferentiation and plasticity that exists between these two, as observed with alterations in temperature, pregnancy and lactation, and fasting and obesity [5, 6]. This chapter, however, focuses on white adipose tissue, and its derangement with the onset and progression of obesity and insulin resistance. It begins with a brief overview characterizing white adipose tissue and the adipocyte, and then proceeds to a discussion regarding the multifaceted dysfunction that accompanies obesity.

5.1 White Adipose Tissue

Less than 50 % of white adipose tissue is composed of preadipocytes and lipid-filled adipocytes [7, 8]. White adipose tissue is also composed not only of precursors, but also stromal cells, endothelial cells, fibroblasts, and a multitude of immune cells including macrophages, lymphocytes, natural killer cells, and mast cells [5, 9, 10]. M1 Macrophages, induced by pro-inflammatory cytokines, are found in equal amounts to M2 macrophages, induced by anti-inflammatory cytokines [11]. The mature adipocytes are responsible for synthesis, storage (in the form of the lipid droplet), and mobilization of triglycerides [12, 13]. Adipocytes are organized into

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lobules separated and surrounded by loose connective tissue organized in an extracellular matrix composed primarily of collagen [13].

In humans, the major fat depots are intra-abdominal including omental and mesenteric (visceral), lower body including gluteal, intramuscular, subcutaneous lower body, and subcutaneous upper body fat [14] The distribution of WAT within these sites varies significantly between sexes and individuals, with central obesity portending a higher risk of diabetes, dyslipidemia, and several other comorbidities, along with mortality [15]. The importance of this distribution is noteworthy even in normal weight individuals with centrally focused obesity [16]. Significant functional regional differences lie with regards to free fatty acid (FFA) release, hyperplasia and/or hypertrophy, preadipocyte characteristics, and adipocytokine secretion [14, 17–19].

Innervation to WAT is primarily mediated via the sympathetic nervous system (SNS). Youngstrom and Bartness supplied evidence when single neuron tract tracing was used to demonstrate postganglionic sympathetic innervation bidirectionally [20]. Along with insulin, SNS is a primary mediator of lipolysis in WAT [21]. Mansfield first observed this in 1913 after witnessing that patients with hemiplegia and cancer cachexia only mobilized lipid from their neurally intact leg [21, 22]. Further evidence in support of SNS function has been observed in a number of animal models in which surgical denervation of SNS to WAT blocks or attenuates lipolysis with food deprivation [23–26].

5.2 Brief Overview: Adipocyte Function

As noted above, the lipid droplets composing the adipocytes are specialized in energy storage and release. Glucose transport and lipogenesis are stimulated by insulin. Once activated by insulin, glucose transport activity is redistributed from intracellular to the plasma membrane [27, 28]. The transport is mediated via membrane transporters belonging to the Major Facilitator Superfamily, part of the Glut protein family [29]. Most studied is Glut4, whose role has been highlighted in scenarios in which mice without Glut4 in adipose tissue develop adipocyte and systemic insulin resistance, whereas mice with overexpression are protected [30, 31]. The uptaken glucose then serves as the substrate for pyruvate and glycerol-3-phosphate and then the production of triglycerides. The other manner of increasing lipid storage is via direct uptake, in which insulin remains the main regulator. Fatty acids delivered via diet are esterified and bound to a glycerol backbone, and then stored as triglycerides in the lipid droplet. Triglycerides can then be hydrolyzed back into fatty acids and 2-monoacylglycerol by lipoprotein lipase (LPL). Notably, the LPL gene promoter is activated by the transcription factors sterol regulatory element-binding protein (SREBP) 1 and 2, and peroxisome proliferator-activated receptor γ (PPARγ) [32, 33]. While PPARγ is expressed in many tissues, it is 30–40-fold higher in WAT [34]. Its importance in lipid homeostasis is no more highlighted in serving as the main target for the thiazolidinedione receptor class of

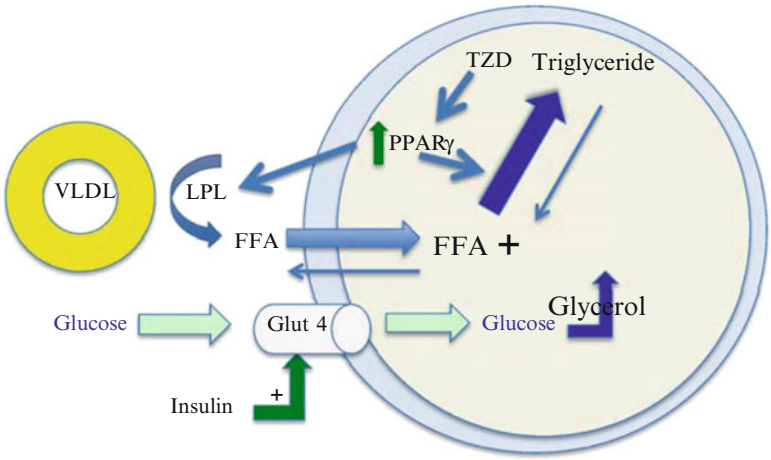

Fig. 5.1 Lean adipose in insulin-sensitive state. The adipocyte is responsive to insulin stimulation, thus prompting glucose uptake via Glut4 transporter, and free fatty acid uptake (FFA). Glucose is converted to glycerol and is combined with FFA to form triglycerides. PPARγ promotes triglyceride synthesis and lipoprotein lipase activity. As noted, the drug class of thiazolidinediones (TZD) increases PPARγ activity. Adapted from Guilherme et al. [60]

insulin-sensitizing drugs, in serving its role in adipogenesis [35–37]. Thus, adipocytes have a crucial role in controlling circulating FFA levels (Fig. 5.1).

More recently, the endocrine role of adipocytes has been gaining attention given its relative complexity and underlying pathologic involvement in a number of disease states. Adipose tissue synthesizes and secretes a number of different proteins with systemic action, termed adipocytokines, or adipokines [38–40]. While more than 100 different adipokines have been identified, proteomic studies have indicated the possibility of several hundreds. Their roles vary, and include controlling appetite, insulin sensitivity, blood pressure, hemostasis, and inflammation [12, 41, 42]. They also affect several organs, including the liver, pancreas, and muscle, along with the central nervous system [43]. The adipocyte's role in inflammation has been of particular interest given its ability to secrete a variety of the well-known cytokines and chemokines including TNF-α, IL-1β, IL-6, IL-10, and several others [44, 45]. Few others have garnered particular interest as well, notably leptin and adiponectin. Leptin, first identified by Friedman and colleagues in 1994, serves a primarily antidiabetic role modulating food intake and energy expenditure, regulating hepatic lipogenesis, and enhancing muscle fatty acid oxidation [43, 46–48]. It has been shown to protect mice from obesity as well [49]. Thus, leptin concentration increases as the proportion of stored fat increases [50]. Adiponectin has roles in insulin sensitizing, as an anti-inflammatory agent, and is anti-atherogenic in character [51–53].

5.3 Obesity and Changes to the Adipocyte and WAT

Globally, it has long been observed that the prevalence of obesity has been on the rise. This is not only true in the adult population, but also alarmingly so in the pediatric population, with potentially significant impact on the future of health care [54]. Long-known associated risks of obesity include type 2 diabetes mellitus (T2DM), cardiovascular disease, arthritis, and increased mortality, among others [55–58]. These pathologic outcomes are the product of significant changes resulting primarily from an energy imbalance, and start at the level of cellular mechanisms involving the adipocyte, its relation its neighboring cells, and beyond with its interplay with the body as a whole.

With persistent consumption of calories in excess of expenditure naturally comes the demand for increasing storage capacity. During states of excess, lipogenic enzymes, localized in the cytoplasm and endoplasmic reticulum (ER), synthesize triglyceride, which is then incorporated into the fat droplet. Adipocytes have a significant capacity to synthesize and store triglycerides. Early on, adipocytes compensate for the increase FFA load by increased expression of enzymes associated with triglyceride synthesis [59]. With progression, accommodation occurs via hypertrophy and hyperplasia [60]. Regional tissue variability associated with adipogenesis has been observed. Intraperitoneal (visceral) fat general enlarges via hypertrophy, whereas regions of subcutaneous fat tend to expand via hyperplasia [61]. It has been suggested in animal models that hyperplasia occurs first in increasing the number of preadipocytes, and then proceeding to mature adipocytes [62]. While much remains to be delineated, larger cells release more FFA, which may underlie the significance of fat distribution and elevated free fatty acid levels in obesity. This was portrayed in a mouse model in which overdevelopment of subcutaneous adipose tissue resulted improved glucose and lipid homeostasis [63]. Thus, and not surprisingly, visceral adipose tissue is significantly linked to increased risk of cardiovascular disease and a strong predictor for developing T2DM, and may act as a surrogate marker for ectopic fat distribution, namely the liver and muscle [64, 65]. Another regional difference is the significantly greater FFA release in upper body in addition to the aforementioned visceral fat, when compared to the nonobese or lower body-obese state. Hence, lower body stores, mainly the gluteo-femoral region, may be viewed as a protective metabolic region [66]. Aging and sedentary lifestyles also serve as factors in increasing the ratio of visceral to subcutaneous fat [67].

Histologically, beyond the changes to the adipocytes themselves, macrophage infiltration increases in WAT. Macrophages typically organize in a ring around the adipocyte; such organization is specific to adipose tissue, and more prevalent in visceral WAT than subcutaneous WAT, and intimates their role in the phagocytosis of necrotic adipocytes [68]. In contrast to the relative balance of M1 and M2 macrophages, these macrophages are M1, and thus pro-inflammatory in nature. T-cell infiltration is also present in WAT without an increase in systemic circulation, presumably due to dysfunctional adipokine release, discussed below [69]. Not surprisingly, accompanying the pro-inflammatory state is fibrosis of the extracellular matrix, organized in clusters and fibrotic bundles, and surrounding adipocytes [70].

Interestingly, M2 macrophages expressing higher levels of tumor growth factor β (TGFβ), which stimulates collage VI production, were found in greater number. They also express increased IL-1, suggesting more of a pro-inflammatory role contrasting M2 macrophages in the non-obese state [71]. It has been shown that patients with a higher degree of adipose tissue fibrosis were found to lose less fat mass after gastric bypass, and that fibrosis may serve a protective role in omental WAT in limiting hypertrophy and its associated deleterious effects [70].

5.4 Excessive FFA, Ectopic Fat Deposition, and Insulin Resistance

Naturally, with progression of obesity comes an increased release of FFAs into the blood stream [72]. Circulating levels of FFAs are a significant mediator connecting obesity with insulin resistance. Elevated levels have been shown to cause insulin resistance in both animals and humans, with an acute decrease in levels resulting in enhanced insulin activity and peripheral glucose uptake [73, 74]. With the accumulation of fatty acids and its metabolites, activation via phosphorylation of serine kinases such as JNK and IKK results in blocking and inactivating insulin receptors. Said mechanism is present in a multitude of cells including adipocytes, myocytes, and hepatocytes [75–77]. Knockout mouse models of JNK and IKK show resistance to the effects of high fat diet on insulin receptor signaling [78, 79]. JNK is required for FFA-mediated macrophage release of inflammatory cytokines such as TNFα, IL-6, and MCP-1 [80]. Additionally, FFAs may induce insulin resistance via their activation of Toll-like receptors (TLR) on adipocytes and macrophages, as mutation of TLR4 prevents obesity and insulin resistance in mice on a high fat diet [60, 81, 82]. Mice with myeloid-specific TLR4 deletion became obese on a high fat diet but were protected from insulin resistance [83]. Cells from TLR4 knock out mice were unresponsive to the inflammatory effects of FFAs [82, 84]. One of the end results is decreased membrane mediated glucose transport via disruption of Glut4. As such, hyperinsulinemia ensues as compensation [84] (Fig. 5.2).

At a cellular level, obesity decreases the rate of lipid turnover, and is related to decreased catecholamine stimulated lipolysis given the sympathetic innervation of WAT [85–87]. The primary mediators of lipolysis are adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and monoglyceride lipase (MGL) [88]. HSL is responsible for converting triacylglycerol to diacylglycerol and monoacylglycerol, while ATGL participates in fat mobilization and MGL in the final hydrolysis of the 2-monoacylglycerols produced by HSL [89]. ATGL is important for basal lipolysis, whereas HSL is important during catecholamine-stimulated lipolysis, via the SNS, as previously noted [90]. Obesity results in significantly decreased HSL and ATGL in obese patients. Regionally, ATGL is not significantly different between omental and subcutaneous storage depots, but HSL does differ and is much higher in omental stores correlating with adipocyte size and fasting plasma insulin concentrations [91]. The activity of HSL is further affected by a blunted catecholamine response seen in obesity, correlating with the notion that catecholamines exert their

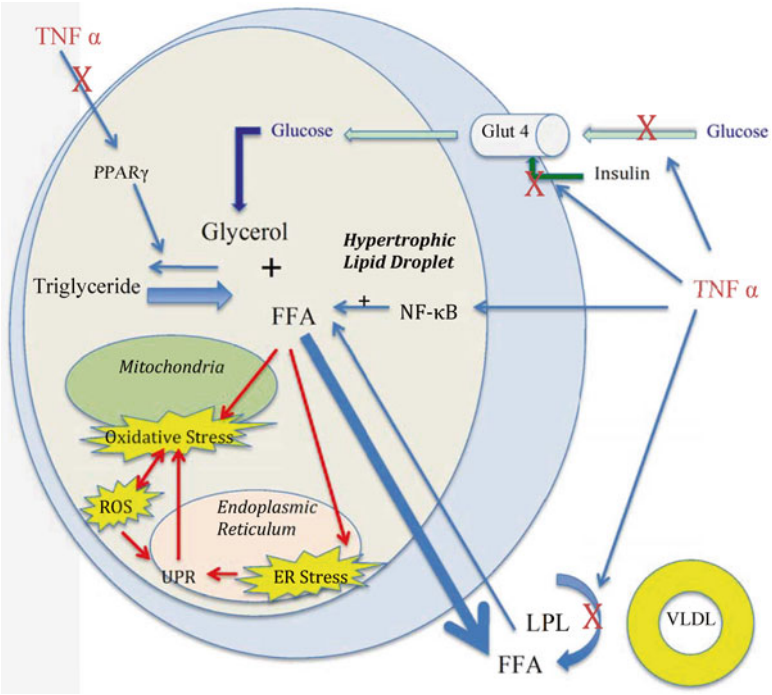

Fig. 5.2 Hypertrophic adipocyte in inflammatory state. Adipocyte hypertrophy results in increased free fatty acid (FFA). With the increased FFA comes mitochondrial oxidative stress and endoplasmic reticulum stress. This in turn results in increased reactive oxidative species (ROS) and activation of the unfolded protein response (UPR). Inflammatory cytokines like TNFα lead to increased activation of the proinflammatory pathway NF-κB, decreased cellular insulin responsiveness, and decreased PPARγ and lipoprotein lipase activity. Adapted from Guilherme et al. and de Ferranti et al. [60, 101]

strongest influence over visceral fat [92]. Hypertrophy, observed more so in visceral obesity, correlates with a decrease in lipolytic activity governed by a higher density of α-2 adrenergic receptors, and a lower density of lipolytic β-1/2 adrenergic receptors presumably in an effort to limit contributing to the already elevated circulating FFA levels [92, 93].

Once FFA storage capacity has been met coupled with the decreased lipid mobilization, a spillover effect is observed, at which point organs are exposed to the deleterious effects of unoxidized FFA. Increased hepatic FFA uptake results in hepatic steatosis, then worsening insulin resistance and hyperglycemia in addition to leading to nonalcoholic steatotic hepatitis (NASH) [94]. Evidence suggests that hepatic fat is strongly associated with insulin resistance [95, 96]. As visceral fat increases, so does hepatic delivery via the splanchnic bed, more selectively so than increases in subcutaneous fat do [94]. This in turn stimulates hepatic VLDL-triglyceride production [97]. FFA deposition and intracellular accumulation may also be observed in muscle, pancreatic β-cells, and the heart, which exacerbate

insulin resistance perpetuating a vicious cycle [98]. Elevated circulating FFA is also associated with inhibition of carbohydrate oxidation and glycogen synthesis in muscle [99]. The direct lipotoxicity to pancreatic β-cells is significant as it can lead to their dysfunction and apoptosis hindering their capacity to accommodate the metabolic derangement at a time of increased insulin requirements [100, 101]. In rodents, lipid accumulation in cardiac myocytes results in cellular damage and ventricular dysfunction [98]. The effects of ectopic distribution of adipose tissue are observed as well in lipodystrophic patients with defects in triglyceride storage in adipose tissue, and in mice without WAT, as both populations exhibit severe insulin resistance. Upon surgical transplantation of functional adipose tissue in mice, there is a dramatic reversal of hyperglycemia, hyperinsulinemia, and insulin resistance [102, 103].

As noted earlier, the effective nature of thiazolidinediones is due to their action on PPARγ receptors which stimulate FFA uptake by subcutaneous adipocytes resulting in decreased ectopic fat distribution and the increased insulin sensitivity [104]. PPARγ is also present in macrophages where they negatively regulate a multitude of inflammatory genes [105]. In PPARγ knockout mice, insulin resistance is impaired, and worsens following high-fat feeding [106, 107]. An important aspect of adipocyte dysfunction arises from downregulation of PPARγ by inflammatory cytokines, and in particular TNFα, both from macrophages and adipocytes. TNFα has been shown to negatively impact PPARγ in many ways, including transcription, posttranscription, and translation [108]. When treated with TNFα, PPARγ mRNA is more rapidly turned over in adipocytes [109]. Another factor negatively affecting PPARγ expression in preadipocytes and adipocytes is hypoxia. This may also be the underlying reason for the inhibited adipocyte differentiation in a hypoxic state [110].

5.5 Hypoxia and Inflammation

As indicated by the histologic changes accompanying obesity, inflammatory changes are a significant driver of pathogenicity as well. With the advent of hyperplasia and more so hypertrophy comes macrophage infiltration and aggregation around necrotic adipocytes. Adipocytes enlarge to accommodate for the increased FFA load. However, their growth will then reach a limit given restraints from oxygen tension, which could explain the ensuing cell death and initiation of macrophage infiltration [68, 111]. The degree of infiltration correlates with obesity and insulin resistance regardless of BMI. Thus, of two similarly obese patients, the patient with increased macrophage infiltration will exhibit worse insulin resistance [112]. The concept of hypoxia-induced inflammation is supported given that adipocytes can increase in size to up to 200 μM in the obese state which is similar to or greater than that of normal oxygen diffusion distance, and although lean patients have the ability to increase postprandial blood flow to WAT, no such increase in blood flow is observed in obese patients [113, 114]. Both qualitative and quantitative studies via the hypoxyprobe system and needle-type fiber-optic O_2 sensor,

respectively, have also demonstrated hypoxia present in adipose tissue in the obese mouse model [8, 115, 116]. Macrophage tissue infiltration is evident in hypoxic tissue areas as well, thus providing a link between hypoxia, adipocyte stress and apoptosis, and inflammation [114]. In humans, the PO_2 of oxygen has been observed to be decreased in the adipose tissue of obese patients, when compared to lean counterparts, with PO_2 levels inversely correlating with percent body fat [117].

One of the main aspects lending support to hypoxia as a factor in inflammation is the up-regulation of hypoxic induced factors, mainly hypoxia-inducible factor 1α (HIF-1α), a key regulator of oxygen homeostasis [118]. Using a transgenic mouse model of HIF-1α overexpression, adipose tissue fibrosis and increased local inflammation are observed [119]. With selective pharmacologic and genetic inhibition of HIF-1α activity, high-fat diet-fed obese mice demonstrated significant metabolic improvements and reduced inflammation in WAT [120]. A key role in the increased inflammation may be the role HIF-1α has in downregulating the expression of PPARγ [110].

5.6 Inflammation, Endoplasmic Reticulum, and Mitochondria

As the demand for increased lipid storage expands, so does the capacity and activity of the adipocyte endoplasmic reticulum, which is responsible for synthesizing proteins, forming lipid droplets, and regulating cholesterol [101]. Thus, with obesity and increasing FFA load, ER "stress" develops. This state is characterized by its functional disturbance in which case proper folding and modification of proteins and lipid droplet creation are disturbed [101]. The ER is able to identify the imbalance in supply and production via the Unfolded Protein Response (UPR), which is subsequently activated through its three arms: PKR-like eukaryotic initiation factor 2α kinase (PERK), inositol-requiring enzyme-1 (IRE-1), and activating transcription factor-6 (ATF-6) [121, 122]. PERK activation leads to decreased protein translation and increased expression of a multitude of genes, including those related to apoptosis [123]. Another UPR response is to induce transcription of chaperones to assist with the increasing volume of unfolded proteins. IRE-1 contributes to the increase in chaperone proteins produced to assist with the unfolded protein load, while ATF-6 is responsible for increasing the expression of ER degradation-enhancing α-mannosidase like protein (EDEM) facilitating the clearance of chaperone proteins [124, 125]. The increased chaperone load is likely responsible for the increased oxidative stress via increased reactive oxidative species (ROS) from mediating oxidation-reduction reactions [121, 126]. IRE-1 also upregulates JNK and IKK resulting in increased expression of inflammatory genes responsible for increased cytokine production [127, 128]. While the goal of such changes brought about by UPR are for preserving cell function and stressor accommodation, the end result of inadequate adaptation may yet be apoptosis [121].

Mitochondria also exhibit signs of distress, not only in adipocytes, but in multiple organs as well. Increases in FFA causes increased release of ROS in obese

patients [129]. Lipid infusion in lean human subjects results in decreased mRNAs for many mitochondrial genes [130]. Mitochondrial dysfunction is evident in the pancreas, liver, and muscle as well [125, 131, 132]. In the pancreas, insulin production is negatively affected by ROS. In muscle, there is decreased fat oxidation and ectopic fat accumulation contributing to insulin resistance [133]. Increased intramyocellular lipid content has been observed with down-regulation of genes encoding mitochondrial respiratory complexes I–IV, and genes responsible for cytochrome c oxidase complexes I and III which are subunits of the electron transport chain [134, 135]. PPARγ is responsible for controlling mitochondrial gene subsets, and with its reduced activity may contribute to the decreased mitochondrial function [136]. Also contributing to the decreased mitochondrial function is the increased amount of inflammatory cytokines [137]. Notably, with the mitochondrial dysfunction comes decreased fatty acid oxidation and metabolites that inhibit glucose transport [138].

The presence of ROS associated with obesity is thought to play a central role in the decreased mitochondrial activity [139]. Once again, with the elevated FFA levels in obesity comes increased ROS [140]. In diabetic patients, endothelial cells portray elevated ROS via NADPH oxidase activation [141]. Mice overexpressing superoxide dismutase 2 have decreased levels of ROS, improved hepatic insulin sensitivity, and normalization of glucose and insulin levels [142]. In rats, soleus muscle exposure to nitric oxide donors caused decreased insulin sensitivity, and were associated with decreased insulin-stimulated phosphorylation of insulin receptor (IR) and insulin receptor substrate-1 (IRS-1), critical in the insulin intracellular signaling pathway [143]. Other kinases are also activated, including JNK and NFκB, further inhibiting IRS-1 progressing insulin resistance [144–146].

Uncoupling proteins (UCP) are mitochondrial inner membrane proteins that mediate the coupling of electrons through the electron transport chain, primarily allowing for a proton leak through the inner membrane [147]. UCP2 is expressed in several tissues, and because of its distribution in multiple tissues, it has been hypothesized to have a significant role in decreasing ROS, thus protecting against oxidative stress [148, 149]. At the same time, several studies have shown that increased UCP2 production leads to decreased insulin secretion from pancreatic β cells, predisposing to diabetes mellitus [150–152]. In UCP2 knockout mice, pancreatic islets have increased insulin secretion in response to glucose when compared to wild-type mice [153]. Furthermore, double-mutant leptin/UCP2 knockouts also have improved beta cell function independent of obesity [153]. FFAs seem to be a key mediator of UCP2 as in preadipocytes, UCP2 mRNA expression increases significantly when exposed to FFAs [154].

5.7 Inflammation and Adipocytokines

The complex role of the adipocyte as an endocrine organ has gained significant attention given its ability to secrete several different types of factors. With the infiltration of macrophages into adipose tissue, cytokine secretion accompanies and

influences the adipose tissue environment. FFAs have been shown to strongly stimulate TNF-α production in macrophages via TLR4 receptor activating NFκB [155]. Further activation from ER stress and UPR along with secretion from adipocytes also increases local TNF-α concentration [121]. Conversely, TNF-α secretion inhibits lipoprotein lipase activity, thus increasing FFA release from adipocytes [156]. Thus, a vicious paracrine loop develops that perpetuates the macrophage-adipocyte inflammatory state [157]. TNF-α leads to activation of JNK1 via phosphorylation of IRS-1 and its inhibition, as mentioned above, linking TNF-α with insulin resistance [158]. The cycle is worsened as adipocyte hypertrophy develops given their capacity for increased FFA release [63]. TNF-α also decreases adiponectin secretion, whose actions result in increased insulin sensitivity by decreasing hepatic glucose production and increasing fatty acid oxidation in both liver and muscle [159]. Multiple studies have implicated low adiponectin levels as a strong indicator for the development of insulin resistance and T2DM [160, 161]. Adiponectin-deficient mice develop insulin resistance in the setting of elevated TNF-α and reduced responsiveness to PPARγ [161]. Adiponectin acts via its two receptors, AdipoR1 and AdipoR2. AdipoR1 is universally expressed whereas AdipoR2 is primarily localized to the liver. Mouse knockouts of these two receptors have increased lipid accumulation, and inflammation, and exhibit increased insulin resistance [43, 160, 162].

Whereas adiponectin production is decreased in hypertrophic and inflamed tissue, leptin production is significantly increased [50]. In leptin-deficient mice models and humans, leptin administration leads to decreased hyperphagia and reduced body mass [163]. However, it has also been seen to increase IL-6 and TNF-α production by macrophages [164]. Leptin acts via a number of different pathways including the JAK-STAT pathway which regulates the expression of anorexic neuropeptides, and the phosphatylinositol-3-kinase pathway which stimulates insulin sensitivity in peripheral tissues [43, 165]. The interesting concept of leptin resistance, similar to insulin resistance, has also been proposed, and been shown in states of inflammation whereby subsequent metabolic stress negatively regulates leptin signaling [166]. Similar resistance has been proposed to be evident in the hypothalamus as well [167]. Overall, energy expenditure and appetite remains poorly controlled even as leptin levels increase in obese patients [43, 163].

Other chemokines play important roles in attracting macrophages and perpetuating the inflammatory response, including IL-6 and monocyte chemotactic protein I (MCP-I). Other factors are also released from adipocytes, which increase macrophage diapedesis, including PECAM-I and ICAM-I [168–170].

5.8 Conclusion

The complexity that characterizes insulin resistance is underscored by the remarkable evolution of our understanding of the adipocyte and its role in metabolic homeostasis. The mechanisms underlying the progression from an insulin sensitive state to that of adipocyte dysfunction, inflammation, and local and systemic insulin resistance are complex, and include a series of vicious cycles that perpetuate the

inflammatory state. As we continue to delineate the mechanisms that accompany the changes in the adipocyte correlating with obesity, potential therapeutic targets will continue to emerge. For now, surgery will continue to serve as one of the mainstays in the treatment of obesity, and will remain a source for potential answers in reversing some of the deleterious effects of obesity and insulin resistance.

References

1. Cannon B, Hedin A, Nedergaard J. Exclusive occurrence of thermogenin antigen in brown adipose tissue. FEBS Lett. 1982;150:129–32.
2. Cannon B, Nedergaard J. Brown adipose tissue: function and physiological significance. Physiol Rev. 2004;84:277–359.
3. Cinti S, Zancanaro C, Sbarbati A, Cicolini M, Vogel P, Ricquier D, Fakan S. Immunoelectron microscopical identification of the uncoupling protein in brown adipose tissue mitochondria. Biol Cell. 1989;67:359–62.
4. Frontini A, Rousset S, Cassard-Doulcier AM, Zingaretti C, Ricquier D, Cinti S. Thymus uncoupling protein 1 is exclusive to typical brown adipocytes and is not found in thymocytes. J Histochem Cytochem. 2007;55:183–9.
5. Cinti S. The adipose organ: morphological perspectives of adipose tissues. Proc Nutr Soc. 2001;60:319–28.
6. Cinti S. Transdifferentiation properties of adipocytes in the adipose organ. Am J Physiol Endocrinol Metab. 2009;297(5):E977–86. doi:10.1152/ajpendo.00183.2009.
7. Hausman GJ. Anatomical and enzyme histochemical differentiation of adipose tissue. Int J Obes. 1985;9 Suppl 1:1–6.
8. Trayhurn P. Hypoxia and adipocyte physiology: implications for adipose tissue dysfunction in obesity. Annu Rev Nutr. 2014;34:207–36. doi:10.1146/annurev-nutr-071812-161156.
9. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante Jr AW. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest. 2003;112(12):1796–808.
10. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, Sole J, Nichols A, Ross JS, Tartaglia LA, Chen H. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest. 2003;112(12):1821–30.
11. Aron-Wisnewsky J, Tordjman J, Poitou C, Darakhshan F, Hugol D, Basdevant A, Aissat A, Guerre-Millo M, Clément K. Human adipose tissue macrophages: m1 and m2 cell surface markers in subcutaneous and omental depots and after weight loss. J Clin Endocrinol Metab. 2009;94(11):4619–23. doi:10.1210/jc.2009-0925.
12. Trayhurn P. Hypoxia and adipose tissue dysfunction in obesity. Physiol Rev. 2013;93(1):1–21. doi:10.1152/physrev.00017.2012.
13. Bastard J, Feve B. Physiology and physiopathology of adipose tissue. Paris: Springer; 2013.
14. Tchkonia T, Thomou T, Zhu Y, Karagiannides I, Pothoulakis C, Jensen MD, Kirkland JL. Mechanisms and metabolic implications of regional differences among fat depots. Cell Metab. 2013;17(5):644–56. doi:10.1016/j.cmet.2013.03.008.
15. Shuster A, Patlas M, Pinthus JH, Mourtzakis M. The clinical importance of visceral adiposity: a critical review of methods for visceral adipose tissue analysis. Br J Radiol. 2012;85(1009):1–10. doi:10.1259/bjr/38447238.
16. Kahn SE, Prigeon RL, Schwartz RS, Fujimoto WY, Knopp RH, Brunzell JD, Porte Jr D. Obesity, body fat distribution, insulin sensitivity and Islet beta-cell function as explanations for metabolic diversity. J Nutr. 2001;131(2):354S–60.
17. Peinado JR, Jimenez-Gomez Y, Pulido MR, Ortega-Bellido M, Diaz-Lopez C, Padillo FJ, Lopez-Miranda J, Vazquez-Martínez R, Malagón MM. Cellular and molecular basis of

functional differences among fat depots. Proteomics. 2010;10(18):3356–66. doi:10.1002/pmic.201000350.
18. Tchoukalova YD, Votruba SB, Tchkonia T, Giorgadze N, Kirkland JL, Jensen MD. Regional differences in cellular mechanisms of adipose tissue gain with overfeeding. Proc Natl Acad Sci U S A. 2010;107(42):18226–31. doi:10.1073/pnas.1005259107.
19. Tchkonia T, Morbeck DE, Von Zglinicki T, Van Deursen J, Lustgarten J, Scrable H, Khosla S, Jensen MD, Kirkland JL. Fat tissue, aging, and cellular senescence. Aging Cell. 2010;9(5):667–84. doi:10.1111/j.1474-9726.2010.00608.x.
20. Youngstrom TG, Bartness TJ. Catecholaminergic innervation of white adipose tissue in the Siberian hamster. Am J Physiol. 1995;268(3 Pt 2):R744–51.
21. Bartness TJ, Liu Y, Shrestha YB, Ryu V. Neural innervation of white adipose tissue and the control of lipolysis. Front Neuroendocrinol. 2014;35:473. doi:10.1016/j.yfrne.2014.04.001. pii: S0091-3022(14)00043-0.
22. Mansfeld G, Muller F. Der Einfluss der Nervensystem auf die Mobilisierung von Fett. Arch Physiol. 1913;152:61–7.
23. Hales CN, Luzio JP, Siddle K. Hormonal control of adipose tissue lipolysis. Biochem Soc Symp. 1978;43:97–135.
24. Bray GA, Nishizawa Y. Ventromedial hypothalamus modulates fat mobilisation during fasting. Nature. 1978;274(5674):900–2.
25. Bamshad M, Aoki VT, Adkison MG, Warren WS, Bartness TJ. Central nervous system origins of the sympathetic nervous system outflow to white adipose tissue. Am J Physiol. 1998;275(1 Pt 2):R291–9.
26. Bartness TJ, Shrestha YB, Vaughan CH, Schwartz GJ, Song CK. Sensory and sympathetic nervous system control of white adipose tissue lipolysis. Mol Cell Endocrinol. 2010;318(1-2):34–43. doi:10.1016/j.mce.2009.08.031.
27. Suzuki K, Kono T. Evidence that insulin causes translocation of glucose transport activity to the plasma membrane from an intracellular storage site. Proc Natl Acad Sci U S A. 1980;77(5):2542–5.
28. Cushman SW, Wardzala LJ. Potential mechanism of insulin action on glucose transport in the isolated rat adipose cell. Apparent translocation of intracellular transport systems to the plasma membrane. J Biol Chem. 1980;255(10):4758–62.
29. Thorens B, Mueckler M. Glucose transporters in the 21st century. Am J Physiol Endocrinol Metab. 2010;298(2):E141–5. doi:10.1152/ajpendo.00712.2009.
30. Abel ED, Peroni O, Kim JK, Kim YB, Boss O, Hadro E, Minnemann T, Shulman GI, Kahn BB. Adipose-selective targeting of the GLUT4 gene impairs insulin action in muscle and liver. Nature. 2001;409(6821):729–33.
31. Carvalho E, Kotani K, Peroni OD, Kahn BB. Adipose-specific overexpression of GLUT4 reverses insulin resistance and diabetes in mice lacking GLUT4 selectively in muscle. Am J Physiol Endocrinol Metab. 2005;289(4):E551–61.
32. Schoonjans K, Peinado-Onsurbe J, Lefebvre AM, Heyman RA, Briggs M, Deeb S, Staels B, Auwerx J. PPARalpha and PPARgamma activators direct a distinct tissue-specific transcriptional response via a PPRE in the lipoprotein lipase gene. EMBO J. 1996;15(19):5336–48.
33. Schoonjans K, Gelman L, Haby C, Briggs M, Auwerx J. Induction of LPL gene expression by sterols is mediated by a sterol regulatory element and is independent of the presence of multiple E boxes. J Mol Biol. 2000;304(3):323–34.
34. Tontonoz P, Hu E, Graves RA, Budavari AI, Spiegelman BM. mPPAR gamma 2: tissue-specific regulator of an adipocyte enhancer. Genes Dev. 1994;8:1224–34. doi:10.1101/gad.8.10.1224.
35. Lehmann JM, Moore LB, Smith-Oliver TA, Wilkison WO, Willson TM, Kliewer SA. An antidiabetic thiazolidinedione is a high affinity ligand for peroxi-some proliferator-activated receptor gamma (PPAR gamma). J Biol Chem. 1995;270:12953–6. doi:10.1074/jbc.270.22.12953.
36. Spiegelman BM. PPAR-gamma: adipogenic regulator and thiazolidinedione receptor. Diabetes. 1998;47:507–14. doi:10.2337/diabetes.47.4.507.

37. Tang QQ, Lane MD. Adipogenesis: from stem cell to adipocyte. Annu Rev Biochem. 2012;81:715–36. doi:10.1146/annurev-biochem-052110-115718.
38. Bastard JP, Maachi M, Lagathu C, Kim MJ, Caron M, Vidal H, Capeau J, Feve B. Recent advances in the relationship between obesity, inflammation and insulin resistance. Eur Cytokine Netw. 2006;17(1):4–12.
39. Antuna-Puente B, Fève B, Fellahi S, Bastard JP. Adipokines: the missing link between insulin resistance and obesity. Diabetes Metab. 2008;34(1):2–11.
40. Frühbeck G, Gómez-Ambrosi J, Muruzabal FJ, Burrell MA. The adipocyte: a model for integration of endocrine and metabolic signaling in energy metabolism regulation. Am J Physiol Endocrinol Metab. 2001;280(6):E827–47.
41. Dahlman I, Elsen M, Tennagels N, Korn M, Brockmann B, Sell H, Eckel J, Arner P. Functional annotation of the human fat cell secretome. Arch Physiol Biochem. 2012;118(3):84–91. doi: 10.3109/13813455.2012.685745.
42. Rajala MW, Scherer PE. The adipocyte: at the crossroads of energy homeostasis, inflammation, and atherosclerosis. Endocrinology. 2003;144(9):3765–73.
43. Cao H. Adipocytokines in obesity and metabolic disease. J Endocrinol. 2014;220(2):T47–59. doi:10.1530/JOE-13-0339.
44. Coppack SW. Pro-inflammatory cytokines and adipose tissue. Proc Nutr Soc. 2001;60(3):349–56.
45. Rosen ED, Spiegelman BM. Adipocytes as regulators of energy balance and glucose homeostasis. Nature. 2006;444:847–53.
46. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature. 1994;372:425–32.
47. Cohen P, Miyazaki M, Socci ND, Hagge-Greenberg A, Liedtke W, Soukas AA, Sharma R, Hudgins LC, Ntambi JM, Friedman JM. Role for stearoyl-CoA desaturase-1 in leptin-mediated weight loss. Science. 2002;297:240–3.
48. Kamohara S, Burcelin R, Halaas JL, Friedman JM, Charron MJ. Acute stimulation of glucose metabolism in mice by leptin treatment. Nature. 1997;389:374–7.
49. Wang MY, Orci L, Ravazzola M, Unger RH. Fat storage in adipocytes requires inactivation of leptin's paracrine activity: implications for treatment of human obesity. Proc Natl Acad Sci U S A. 2005;102(50):18011–6.
50. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, Ohannesian JP, Marco CC, McKee LJ, Bauer TL, et al. Serum immunoreactive-leptin concentrations in normal- weight and obese humans. N Engl J Med. 1996;334(5):292–5.
51. Brakenhielm E, Veitonmaki N, Cao R, Kihara S, Matsuzawa Y, Zhivotovsky B, Funahashi T, Cao Y. Adiponectin-induced antiangiogenesis and antitumor activity involve caspase-mediated endothelial cell apoptosis. Proc Natl Acad Sci U S A. 2004;101(8):2476–81.
52. Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, Mori Y, Ide T, Murakami K, Tsuboyama-Kasaoka N, Ezaki O, Akanuma Y, Gavrilova O, Vinson C, Reitman ML, Kagechika H, Shudo K, Yoda M, Nakano Y, Tobe K, Nagai R, Kimura S, Tomita M, Froguel P, Kadowaki T. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med. 2001;7(8):941–6.
53. Yokota T, Oritani K, Takahashi I, Ishikawa J, Matsuyama A, Ouchi N, Kihara S, Funahashi T, Tenner AJ, Tomiyama Y, Matsuzawa Y. Adiponectin, a new member of the family of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and the functions of macrophages. Blood. 2000;96(5):1723–32.
54. World Health Organization. World health statistics. Geneva: World Health Organization; 2014.
55. Picot J, Jones J, Colquitt JL, Gospodarevskaya E, Loveman E, Baxter L, Clegg AJ. The clinical-effectiveness and cost- effectiveness of bariatric (weight loss) surgery for obesity: a systematic review and economic evaluation. Health Technol Assess. 2009;13(41):1–190. doi:10.3310/hta13410. 215-357, iii-iv.
56. Colquitt JL, Picot J, Loveman E, Clegg AJ. Cochrane Database Syst Rev. 2009;(2):CD003641. doi: 10.1002/14651858.CD003641.pub3.

57. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. JAMA. 1999;282(16):1523–9.
58. Adams KF, Schatzkin A, Harris TB, Kipnis V, Mouw T, Ballard-Barbash R, Hollenbeck A, Leitzmann MF. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. N Engl J Med. 2006;355(8):763–78.
59. Frayn KN, Shadid S, Hamlani R, Humphreys SM, Clark ML, Fielding BA, Boland O, Coppack SW. Regulation of fatty acid movement in human adipose tissue in the postabsorptive- to-postprandial transition. Am J Physiol. 1994;266:E308–17.
60. Guilherme A, Virbasius JV, Puri V, Czech MP. Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. Nat Rev Mol Cell Biol. 2008;9(5):367–77. doi:10.1038/nrm2391.
61. Tchkonia T, Giorgadze N, Pirtskhalava T, Tchoukalova Y, Karagiannides I, Forse RA, DePonte M, Stevenson M, Guo W, Han J, Waloga G, Lash TL, Jensen MD, Kirkland JL. Fat depot origin affects adipogenesis in primary cultured and cloned human pre- adipocytes. Am J Physiol Regul Integr Comp Physiol. 2002;282(5):R1286–96.
62. Avram MM, Avram AS, James WD. Subcutaneous fat in normal and diseased states 3. Adipogenesis: from stem cell to fat cell. J Am Acad Dermatol. 2007;56:472–92.
63. Kim JY, van de Wall E, Laplante M, Azzara A, Trujillo ME, Hofmann SM, Schraw T, Durand JL, Li H, Li G, Jelicks LA, Mehler MF, Hui DY, Deshaies Y, Shulman GI, Schwartz GJ, Scherer PE. Obesity-associated improvements in metabolic profile through expansion of adipose tissue. J Clin Invest. 2007;117(9):2621–37.
64. Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature. 2006;444(7121):881–7. Review.
65. Thomas EL, Parkinson JR, Frost GS, Goldstone AP, Doré CJ, McCarthy JP, Collins AL, Fitzpatrick JA, Durighel G, Taylor-Robinson SD, Bell JD. The missing risk: MRI and MRS phenotyping of abdominal adiposity and ectopic fat. Obesity (Silver Spring). 2012;20(1):76–87. doi:10.1038/oby.2011.142.
66. Guo Z, Hensrud DD, Johnson CM, Jensen MD. Regional postprandial fatty acid metabolism in different obesity phenotypes. Diabetes. 1999;48(8):1586–92.
67. Gavi S, Feiner JJ, Melendez MM, Mynarcik DC, Gelato MC, McNurlan MA. Limb fat to trunk fat ratio in elderly persons is a strong determinant of insulin resistance and adiponectin levels. J Gerontol A Biol Sci Med Sci. 2007;62(9):997–1001.
68. Cinti S, Mitchell G, Barbatelli G, Murano I, Ceresi E, Faloia E, Wang S, Fortier M, Greenberg AS, Obin MS. Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. J Lipid Res. 2005;46(11):2347–55.
69. Nishimura S, Manabe I, Nagasaki M, Eto K, Yamashita H, Ohsugi M, Otsu M, Hara K, Ueki K, Sugiura S, Yoshimura K, Kadowaki T, Nagai R. CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. Nat Med. 2009;15(8):914–20. doi:10.1038/nm.1964.
70. Divoux A, Tordjman J, Lacasa D, Veyrie N, Hugol D, Aissat A, Basdevant A, Guerre-Millo M, Poitou C, Zucker JD, Bedossa P, Clément K. Fibrosis in human adipose tissue: composition, distribution, and link with lipid metabolism and fat mass loss. Diabetes. 2010;59(11):2817–25. doi:10.2337/db10-0585.
71. Henegar C, Tordjman J, Achard V, Lacasa D, Cremer I, Guerre-Millo M, Poitou C, Basdevant A, Stich V, Viguerie N, Langin D, Bedossa P, Zucker JD, Clement K. Adipose tissue transcriptomic signature high- lights the pathological relevance of extracellular matrix in human obesity. Genome Biol. 2008;9:R14.
72. Campbell PJ, Carlson MG, Nurjhan N. Fat metabolism in human obesity. Am J Physiol. 1994;266:E600–5.
73. Kelley DE, Mokan M, Simoneau JA, Mandarino LJ. Interaction between glucose and free fatty acid metabolism in human skeletal muscle. J Clin Invest. 1993;92:91–8.
74. Santomauro AT, Boden G, Silva ME, Rocha DM, Santos RF, Ursich MJ, Strassmann PG, Wajchenberg BL. Overnight lowering of free fatty acids with Acipimox improves insulin

resistance and glucose tolerance in obese diabetic and nondiabetic subjects. Diabetes. 1999;48:1836–41.
75. Capurso C, Capurso A. From excess adiposity to insulin resistance: the role of free fatty acids. Vascul Pharmacol. 2012;57(2-4):91–7. doi:10.1016/j.vph.2012.05.003.
76. Greene MW, Sakaue H, Wang L, Alessi DR, Roth RA. Modulation of insulin- stimulated degradation of human insulin receptor substrate-1 by Serine 312 phosphorylation. J Biol Chem. 2003;278(10):8199–211.
77. Gao Z, Zhang X, Zuberi A, Hwang D, Quon MJ, Lefevre M, Ye J. Inhibition of insulin sensitivity by free fatty acids requires activation of multiple serine kinases in 3T3–L1 adipocytes. Mol Endocrinol. 2004;18(8):2024–34.
78. Hirosumi J, Tuncman G, Chang L, Görgün CZ, Uysal KT, Maeda K, Karin M, Hotamisligil GS. A central role for JNK in obesity and insulin resistance. Nature. 2002;420(6913):333–6.
79. Yuan M, Konstantopoulos N, Lee J, Hansen L, Li ZW, Karin M, Shoelson SE. Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted disruption of Ikkβ. Science. 2001;293:1673–7.
80. Solinas G, Vilcu C, Neels JG, Bandyopadhyay GK, Luo JL, Naugler W, Grivennikov S, Wynshaw-Boris A, Scadeng M, Olefsky JM, Karin M. JNK1 in hematopoietically derived cells contributes to diet-induced inflammation and insulin resistance without affecting obesity. Cell Metab. 2007;6:386–97.
81. Shi H, Kokoeva MV, Inouye K, Tzameli I, Yin H, Flier JS. TLR4 links innate immunity and fatty acid-induced insulin resistance. J Clin Invest. 2006;116:3015–25.
82. Tsukumo DM, Carvalho-Filho MA, Carvalheira JB, Prada PO, Hirabara SM, Schenka AA, Araújo EP, Vassallo J, Curi R, Velloso LA, Saad MJ. Loss-of-function mutation in Toll-like receptor 4 prevents diet-induced obesity and insulin resistance. Diabetes. 2007;56:1986–98.
83. Saberi M, Woods NB, de Luca C, Schenk S, Lu JC, Bandyopadhyay G, Verma IM, Olefsky JM. Hematopoeitic cell specific deletion of Toll-like receptor 4 ameliorates hepatic and adipose tissue insulin resistance in high fat-fed mice. Cell Metab. 2009;10(5):419–29. doi:10.1016/j.cmet.2009.09.006.
84. Olefsky JM, Glass CK. Macrophages, inflammation, and insulin resistance. Annu Rev Physiol. 2010;72:219–46. doi:10.1146/annurev-physiol-021909-135846.
85. Arner P, Bernard S, Salehpour M, Possnert G, Liebl J, Steier P, Buchholz BA, Eriksson M, Arner E, Hauner H, Skurk T, Rydén M, Frayn KN, Spalding KL. Dynamics of human adipose lipid turnover in health and metabolic disease. Nature. 2011;478(7367):110–3. doi:10.1038/nature10426.
86. Arner P, Andersson DP, Thörne A, Wirén M, Hoffstedt J, Näslund E, Thorell A, Rydén M. Variations in the size of the major omentum are primarily determined by fat cell number. J Clin Endocrinol Metab. 2013;98:E897–901.
87. Sam S, Mazzone T. Adipose tissue changes in obesity and the impact on metabolic function. Transl Res. 2014;164:284. doi:10.1016/j.trsl.2014.05.008. pii: S1931-5244(14)00176-5.
88. Fredrikson G, Tornqvist H, Belfrage P. Hormone-sensitive lipase and monoacylglycerol lipase are both required for complete degradation of adipocyte triacylglycerol. Biochim Biophys Acta. 1986;876:288–93.
89. Zimmermann R, Strauss JG, Haemmerle G, Schoiswohl G, Birner-Gruenberger R, Riederer M, Lass A, Neuberger G, Eisenhaber F, Hermetter A, Zechner R. Fat mobilization in adipose tissue is promoted by adipose triglyceride lipase. Science. 2004;306:1383–6.
90. Rydén M, Jocken J, van Harmelen V, Dicker A, Hoffstedt J, Wirén M, Blomqvist L, Mairal A, Langin D, Blaak E, Arner P. Comparative studies of the role of hormone-sensitive lipase and adipose triglyceride lipase in human fat cell lipolysis. Am J Physiol Endocrinol Metab. 2007;292:E1847–55.
91. Berndt J, Kralisch S, Klöting N, Ruschke K, Kern M, Fasshauer M, Schön MR, Stumvoll M, Blüher M. Adipose triglyceride lipase gene expression in human visceral obesity. Exp Clin Endocrinol Diabetes. 2008;116:203–10.

92. Lafontan M, Langin D. Lipolysis and lipid mobilization in human adipose tissue. Prog Lipid Res. 2009;48(5):275–97. doi:10.1016/j.plipres.2009.05.001.
93. Lafontan M, Berlan M. Fat cell alpha 2-adrenoceptors: the regulation of fat cell function and lipolysis. Endocr Rev. 1995;16:716–38.
94. Lewis GF, Carpentier A, Adeli K, Giacca A. Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. Endocr Rev. 2002;23(2):201–29.
95. Fabbrini E, Magkos F, Mohammed BS, Pietka T, Abumrad NA, Patterson BW, Okunade A, Klein S. Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. Proc Natl Acad Sci U S A. 2009;106(36):15430–5. doi:10.1073/pnas.0904944106.
96. Boden G, Chen X. Effects of fat on glucose uptake and utilization in patients with non-insulin-dependent diabetes. J Clin Invest. 1995;96:1261–8.
97. Kissebah AH, Adams PW, Wynn V. Plasma free fatty acid and triglyceride transport kinetics in man. Clin Sci Mol Med. 1974;47:259–78.
98. Schaffer JE. Lipotoxicity: when tissues overeat. Curr Opin Lipidol. 2003;14:281–7.
99. Roden M, Price TB, Perseghin G, Petersen KF, Rothman DL, Cline GW, Shulman GI. Mechanism of free fatty acid-induced insulin resistance in humans. J Clin Invest. 1996;97:2859–65.
100. Lupi R, Dotta F, Marselli L, Del Guerra S, Masini M, Santangelo C, et al. Prolonged exposure to free fatty acids has cytostatic and pro-apoptotic effects on human pancreatic islets: evidence that beta cell death is caspase mediated, partially dependent on ceramide pathway, and Bcl-2 regulated. Diabetes. 2002;51:1437–42.
101. de Ferranti S, Mozaffarian D. The perfect storm: obesity, adipocyte dysfunction, and metabolic consequences. Clin Chem. 2008;54(6):945–55. doi:10.1373/clinchem. 2007.100156.
102. Gavrilova O, Marcus-Samuels B, Graham D, Kim JK, Shulman GI, Castle AL, Vinson C, Eckhaus M, Reitman ML. Surgical implantation of adipose tissue reverses diabetes in lipoatrophic mice. J Clin Invest. 2000;105(3):271–8.
103. Langin D. In and out: adipose tissue lipid turnover in obesity and dyslipidemia. Cell Metab. 2011;14:569–70.
104. Wang YX. PPARs: diverse regulators in energy metabolism and metabolic diseases. Cell Res. 2010;20:124–37.
105. Ricote M, Li AC, Willson TM, Kelly CJ, Glass CK. The peroxisome proliferator-activated receptor-γ is a negative regulator of macrophage activation. Nature. 1998;391(6662):79–82.
106. Hevener AL, Olefsky JM, Reichart D, Nguyen MT, Bandyopadyhay G, Leung HY, Watt MJ, Benner C, Febbraio MA, Nguyen AK, Folian B, Subramaniam S, Gonzalez FJ, Glass CK, Ricote M. Macrophage PPARγ is required for normal skeletal muscle and hepatic insulin sensitivity and full antidiabetic effects of thiazolidinediones. J Clin Invest. 2007;117(6):1658–69.
107. Odegaard JI, Ricardo-Gonzalez RR, Goforth MH, Morel CR, Subramanian V, Mukundan L, Red Eagle A, Vats D, Brombacher F, Ferrante AW, Chawla A. Macrophage-specific PPARγ controls alternative activation and improves insulin resistance. Nature. 2007;447(7148):1116–20.
108. Zhang B, Berger J, Hu E, Szalkowski D, White-Carrington S, Spiegelman BM, Moller DE. Negative regulation of peroxisome proliferator-activated receptor-γ gene expression contributes to the antiadipogenic effects of tumor necrosis factor-α. Mol Endocrinol. 1996;10:1457–66.
109. Christianson JL, Nicoloro S, Straubhaar J, Czech MP. Stearoyl CoA desaturase 2 is required for PPARγ expression and adipogenesis in cultured 3T3-L1 cells. J Biol Chem. 2007;283:2906–16.
110. Yun Z, Maecker HL, Johnson RS, Giaccia AJ. Inhibition of PPARγ2 gene expression by the HIF-1-regulated gene DEC1/Stra13: a mechanism for regulation of adipogenesis by hypoxia. Dev Cell. 2002;2(3):331–41.
111. Trayhurn P, Wang B, Wood IS. Hypoxia in adipose tissue: a basis for the dysregulation of tissue function in obesity? Br J Nutr. 2008;100(2):227–35. doi:10.1017/S0007114508971282.

112. Strissel KJ, Stancheva Z, Miyoshi H, Perfield 2nd JW, DeFuria J, Jick Z, Greenberg AS, Obin MS. Adipocyte death, adipose tissue remodeling, and obesity complications. Diabetes. 2007;56:2910–8.
113. Goossens GH, Bizzarri A, Venteclef N, Essers Y, Cleutjens JP, Konings E, Jocken JW, Cajlakovic M, Ribitsch V, Clément K, Blaak EE. Increased adipose tissue oxygen tension in obese compared with lean men is accompanied by insulin resistance, impaired adipose tissue capillarization, and inflammation. Circulation. 2011;124(1):67–76. doi:10.1161/CIRCULATIONAHA.111.027813.
114. Karpe F, Fielding BA, Ilic V, Macdonald IA, Summers LK, Frayn KN. Impaired postprandial adipose tissue blood flow response is related to aspects of insulin sensitivity. Diabetes. 2002;51(8):2467–73.
115. Rausch ME, Weisberg SP, Vardhana P, Tortoriello DV. Obesity in C57BL/6J mice is characterised by adipose tissue hypoxia and cytotoxic T-cell infiltration. Int J Obes (Lond). 2008;32(3):451–63.
116. Ye J, Gao Z, Yin J, He Q. Hypoxia is a potential risk factor for chronic inflammation and adiponectin reduction in adipose tissue of ob/ob and dietary obese mice. Am J Physiol Endocrinol Metab. 2007;293(4):E1118–28.
117. Pasarica M, Sereda OR, Redman LM, Albarado DC, Hymel DT, Roan LE, Rood JC, Burk DH, Smith SR. Reduced adipose tissue oxygenation in human obesity: evidence for rarefaction, macrophage chemotaxis, and inflammation without an angiogenic response. Diabetes. 2009;58(3):718–25. doi:10.2337/db08-1098.
118. Cancello R, Henegar C, Viguerie N, Taleb S, Poitou C, Rouault C, Coupaye M, Pelloux V, Hugol D, Bouillot JL, Bouloumié A, Barbatelli G, Cinti S, Svensson PA, Barsh GS, Zucker JD, Basdevant A, Langin D, Clément K. Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss. Diabetes. 2005;54(8):2277–86.
119. Halberg N, Khan T, Trujillo ME, Wernstedt-Asterholm I, Attie AD, Sherwani S, Wang ZV, Landskroner-Eiger S, Dineen S, Magalang UJ, Brekken RA, Scherer PE. Hypoxia-inducible factor 1alpha induces fibrosis and insulin resistance in white adipose tissue. Mol Cell Biol. 2009;29(16):4467–83. doi:10.1128/MCB.00192-09.
120. Sun K, Halberg N, Khan M, Magalang UJ, Scherer PE. Selective inhibition of hypoxia-inducible factor 1α ameliorates adipose tissue dysfunction. Mol Cell Biol. 2013;33(5):904–17. doi:10.1128/MCB.00951-12.
121. Gregor MF, Hotamisligil GS. Thematic review series: adipocyte biology. adipocyte stress: the endoplasmic reticulum and metabolic disease. J Lipid Res. 2007;48(9):1905–14.
122. Mori K. Tripartite management of unfolded proteins in the endoplasmic reticulum. Cell. 2000;101(5):451–4.
123. Su Q, Wang S, Gao HQ, Kazemi S, Harding HP, Ron D, Koromilas AE. Modulation of the eukaryotic initiation factor 2 alpha-subunit kinase PERK by tyrosine phosphorylation. J Biol Chem. 2008;283:469–75.
124. Ozcan U, Yilmaz E, Ozcan L, Furuhashi M, Vaillancourt E, Smith RO, Görgün CZ, Hotamisligil GS. Chemical chaperones reduce ER stress and restore glucose homeostasis in a mouse model of type 2 diabetes. Science. 2006;313(5790):1137–40.
125. Eizirik DL, Cardozo AK, Cnop M. The role for endoplasmic reticulum stress in diabetes mellitus. Endocr Rev. 2008;29(1):42–61.
126. Haynes CM, Titus EA, Cooper AA. Degradation of misfolded proteins prevents ER-derived oxidative stress and cell death. Mol Cell. 2004;15(5):767–76.
127. Wu J, Kaufman RJ. From acute ER stress to physiological roles of the unfolded protein response. Cell Death Differ. 2006;13:374–84.
128. Deng J, Lu PD, Zhang Y, Scheuner D, Kaufman RJ, Sonenberg N, Harding HP, Ron D. Translational repression mediates activation of nuclear factor kappa B by phosphorylated translation initiation factor 2. Mol Cell Biol. 2004;24(23):10161–8.
129. Wojtczak L, Schonfeld P. Effect of fatty acids on energy coupling processes in mitochondria. Biochim Biophys Acta. 1993;1183:41–57.

130. Richardson DK, Kashyap S, Bajaj M, Cusi K, Mandarino SJ, Finlayson J, DeFronzo RA, Jenkinson CP, Mandarino LJ. Lipid infusion decreases the expression of nuclear encoded mitochondrial genes and increases the expression of extracellular matrix genes in human skeletal muscle. J Biol Chem. 2005;280(11):10290–7.
131. Qatanani M, Lazar MA. Mechanisms of obesity-associated insulin resistance: many choices on the menu. Genes Dev. 2007;21:1443–55.
132. Petersen KF, Befroy D, Dufour S, Dziura J, Ariyan C, Rothman DL, DiPietro L, Cline GW, Shulman GI. Mitochondrial dysfunction in the elderly: possible role in insulin resistance. Science. 2003;300(5622):1140–2.
133. Coletta DK, Mandarino LJ. Mitochondrial dysfunction and insulin resistance from the outside in: extracellular matrix, the cytoskeleton, and mitochondria. Am J Physiol Endocrinol Metab. 2011;301:749–55.
134. Chanseaume E, Malpuech-Brugère C, Patrac V, Bielicki G, Rousset P, Couturier K, Salles J, Renou JP, Boirie Y, Morio B. Diets high in sugar, fat, and energy induce muscle type specific adaptations in mitochondrial functions in rats. J Nutr. 2006;136(8):2194–200.
135. Heilbronn LK, Gan SK, Turner N, Campbell LV, Chisholm DJ. Markers of mitochondrial biogenesis and metabolism are lower in overweight and obese insulin-resistant subjects. J Clin Endocrinol Metab. 2007;92:1467–73.
136. Evans RM, Barish GD, Wang YX. PPARs and the complex journey to obesity. Nat Med. 2004;10:355–61.
137. Yasuhara R, Miyamoto Y, Akaike T, Akuta T, Nakamura M, Takami M, Morimura N, Yasu K, Kamijo R. Interleukin-1beta induces death in chondrocyte-like ATDC5 cells through mitochondrial dysfunction and energy depletion in a reactive nitrogen and oxygen species-dependent manner. Biochem J. 2005;389:315–23.
138. Lowell BB, Shulman GI. Mitochondrial dysfunction and type 2 diabetes. Science. 2005;307:384–7.
139. Bloch-Damti A, Bashan N. Proposed mechanisms for the induction of insulin resistance by oxidative stress. Antioxid Redox Signal. 2005;7:1553–67.
140. Lambertucci RH, Hirabara SM, Silveira Ldos R, Levada-Pires AC, Curi R, Pithon-Curi TC. Palmitate increases superoxide production through mitochondrial electron transport chain and NADPH oxidase activity in skeletal muscle cells. J Cell Physiol. 2008;216:796–804.
141. Inoguchi T, Li P, Umeda F, Yu HY, Kakimoto M, Imamura M, Aoki T, Etoh T, Hashimoto T, Naruse M, Sano H, Utsumi H, Nawata H. High glucose level and free fatty acid stimulate reactive oxygen species production through protein kinase C-dependent activation of NADPH oxidase in cultured vascular cells. Diabetes. 2000;49:1939–45.
142. Zhai L, Ballinger SW, Messina JL. Role of reactive oxygen species in injury-induced insulin resistance. Mol Endocrinol. 2011;25:492–502.
143. Carvalho-Filho MA, Ueno M, Hirabara SM, Seabra AB, Carvalheira JB, de Oliveira MG, Velloso LA, Curi R, Saad MJ. S-nitrosation of the insulin receptor, insulin receptor substrate 1, and protein kinase B/Akt: a novel mechanism of insulin resistance. Diabetes. 2005;54:959–67.
144. Krebs M, Roden M. Molecular mechanisms of lipid-induced insulin resistance in muscle, liver and vasculature. Diabetes Obes Metab. 2005;7:621–32.
145. Talukdar I, Szeszel-Fedorowicz W, Salati LM. Arachidonic acid inhibits the insulin induction of glucose-6-phosphate dehydrogenase via p38 MAP kinase. J Biol Chem. 2005;280:40660–7.
146. Martins AR, Nachbar RT, Gorjao R, Vinolo MA, Festuccia WT, Lambertucci RH, Cury-Boaventura MF, Silveira LR, Curi R, Hirabara SM. Mechanisms underlying skeletal muscle insulin resistance induced by fatty acids: importance of the mitochondrial function. Lipids Health Dis. 2012;11:30.
147. Diano S, Horvath TL. Mitochondrial uncoupling protein 2 (UCP2) in glucose and lipid metabolism. Trends Mol Med. 2012;18(1):52–8. doi:10.1016/j.molmed.2011.08.003.

148. Diao J, Allister EM, Koshkin V, Lee SC, Bhattacharjee A, Tang C, Giacca A, Chan CB, Wheeler MB. UCP2 is highly expressed in pancreatic alpha-cells and influences secretion and survival. Proc Natl Acad Sci U S A. 2008;105(33):12057–62. doi:10.1073/pnas.0710434105.
149. Emre Y, Hurtaud C, Karaca M, Nubel T, Zavala F, Ricquier D. Role of uncoupling protein UCP2 in cell-mediated immunity: how macrophage-mediated insulitis is accelerated in a model of autoimmune diabetes. Proc Natl Acad Sci U S A. 2007;104(48):19085–90.
150. Souza BM, Assmann TS, Kliemann LM, Gross JL, Canani LH, Crispim D. The role of uncoupling protein 2 (UCP2) on the development of type 2 diabetes mellitus and its chronic complications. Arq Bras Endocrinol Metabol. 2011;55(4):239–48.
151. Affourtit C, Brand M. On the role of uncoupling protein 2 in pancreatic beta cells. Biochim Biophys Acta. 2008;1777(7-8):973–9.
152. Brand M, Affourtit C, Esteves T, Green K, Lambert A, Miwa S, et al. Mitochondrial superoxide: production, biological effects, and activation of uncoupling proteins. Free Radic Biol Med. 2004;37(6):755–67.
153. Zhang C, Baffy G, Perret P, Krauss S, Peroni O, Grujic D, et al. Uncoupling protein-2 negatively regulates insulin secretion and is a major link between obesity, beta cell dysfunction, and type 2 diabetes. Cell. 2001;105(6):745–55.
154. Thompson M, Kim D. Links between fatty acids and expression of UCP2 and UCP3 mRNAs. FEBS Lett. 2004;568(1-3):4–9.
155. Nguyen MT, Satoh H, Favelyukis S, Babendure JL, Imamura T, Sbodio JI, Zalevsky J, Dahiyat BI, Chi NW, Olefsky JM. JNK and tumor necrosis factor-alpha mediate free fatty acid-induced insulin resistance in 3T3-L1 adipocytes. J Biol Chem. 2005;280:35361–71.
156. Wang S, Soni KG, Semache M, Casavant S, Fortier M, Pan L, Mitchell GA. Lipolysis and the integrated physiology of lipid energy metabolism. Mol Genet Metab. 2008;95:117–26.
157. Hajer GR, van Haeften TW, Visseren FL. Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. Eur Heart J. 2008;29(24):2959–71. doi:10.1093/eurheartj/ehn387.
158. Aguirre V, Uchida T, Yenush L, Davis R, White MF. The c-Jun NH(2)-terminal kinase promotes insulin resistance during association with insulin receptor substrate-1 and phosphorylation of Ser(307). J Biol Chem. 2000;275:9047–54.
159. Goldstein BJ, Scalia R. Adiponectin. A novel adipokine linking adipocytes and vascular function. J Clin Endocrinol Metab. 2004;89:2563–8.
160. Yamauchi T, Nio Y, Maki T, Kobayashi M, Takazawa T, Iwabu M, Okada-Iwabu M, Kawamoto S, Kubota N, Kubota T, Ito Y, Kamon J, Tsuchida A, Kumagai K, Kozono H, Hada Y, Ogata H, Tokuyama K, Tsunoda M, Ide T, Murakami K, Awazawa M, Takamoto I, Froguel P, Hara K, Tobe K, Nagai R, Ueki K, Kadowaki T. Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. Nat Med. 2007;13:332–9.
161. Maeda N, Shimomura I, Kishida K, Nishizawa H, Matsuda M, Nagaretani H, Furuyama N, Kondo H, Takahashi M, Arita Y, Komuro R, Ouchi N, Kihara S, Tochino Y, Okutomi K, Horie M, Takeda S, Aoyama T, Funahashi T, Matsuzawa Y. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. Nat Med. 2002;8:731–7.
162. Yamauchi T, Kamon J, Ito Y, Tsuchida A, Yokomizo T, Kita S, Sugiyama T, Miyagishi M, Hara K, Tsunoda M, Murakami K, Ohteki T, Uchida S, Takekawa S, Waki H, Tsuno NH, Shibata Y, Terauchi Y, Froguel P, Tobe K, Koyasu S, Taira K, Kitamura T, Shimizu T, Nagai R, Kadowaki T. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. Nature. 2003;423:762–9.
163. Munzberg H, Myers Jr MG. Molecular and anatomical determinants of central leptin resistance. Nat Neurosci. 2005;8:566–70.
164. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol. 2006;6:772–83.
165. St-Pierre J, Tremblay ML. Modulation of leptin resistance by protein tyrosine phosphatases. Cell Metab. 2012;15:292–7.

166. Zhang X, Zhang G, Zhang H, Karin M, Bai H, Cai D. Hypothalamic IKKbeta/NF-kappaB and ER stress link overnutrition to energy imbalance and obesity. Cell. 2008;135:61–73.
167. Baskin DG, Figlewicz LD, Seeley RJ, Woods SC, Porte Jr D, Schwartz MW. Insulin and leptin: dual adiposity signals to the brain for the regulation of food intake and body weight. Brain Res. 1999;848:114–23.
168. Kanda H, Tateya S, Tamori Y, Kotani K, Hiasa K, Kitazawa R, Kitazawa S, Miyachi H, Maeda S, Egashira K, Kasuga M. MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity. J Clin Invest. 2006;116(6):1494–505.
169. Nomiyama T, Perez-Tilve D, Ogawa D, Gizard F, Zhao Y, Heywood EB, Jones KL, Kawamori R, Cassis LA, Tschöp MH, Bruemmer D. Osteopontin mediates obesity-induced adipose tissue macrophage infiltration and insulin resistance in mice. J Clin Invest. 2007; 117(10):2877–88.
170. Curat CA, Miranville A, Sengenès C, Diehl M, Tonus C, Busse R, Bouloumié A. From blood monocytes to adipose tissue resident macrophages: induction of diapedesis by human mature adipocytes. Diabetes. 2004;53(5):1285–92.

Bile Acids, the Microbiome and Metabolic Disease-Implications for Surgery

6

Cyrus Jahansouz

6.1 Obesity, Diabetes Mellitus, and the Microbiome

Perhaps one of the most exciting frontiers of medicine is the exploration of the human gut flora, or the microbiome. While it remains with potential as a target for future therapeutics, defining a healthy microbiome and pathologic variant remains a daunting task. In a pioneering study to further characterize healthy variation, the Human Microbiome Project Consortium in 2012 presented the microbiota of 242 healthy Western subjects from 18 different anatomic sites, including the distal gut, and while significant interindividual variation existed, metabolic pathways remained stable [1, 2]. As indicated by Arumugam et al., *Bacteroidetes* phyla dominate the gut microbiome. In their analysis, 33 samples across several nations formed three distinct clusters: *Bacteroidetes*, *Prevotella*, and *Ruminococcus* [3]. Generally, the gut microbiome is shared among family members with variation present in each individual's microbial community [4]. Diet does have a critical impact [4–6]. As an example, in a comparison of microbiome in children from Europe and from rural Africa, the microbiome of African children displayed significantly increased bacterial richness and diversity, leading the authors to conclude that gut microbiome coevolved with their polysaccharide-rich diet [6].

6.2 Changes in the Microbiome in Obesity and T2DM

Obesity is associated with a significant decrease in microbiome diversity and richness [5]. In a study of obese and non-obese Danish individuals, obese individuals shared an "inflammatory" phenotype, having a higher prevalence of *Bacteroides*

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and *R. gnavus*, which have been associated with Inflammatory Bowel Disease [6–8]. Patients characterized as having a low gene count had a greater prevalence of obesity, insulin resistance, fatty liver, and low-grade inflammation than patients with a high gene count. Low gene count patients were also more prone to gaining more weight over time [5, 9]. In another study by Vrieze et al., male humans with metabolic syndrome were the recipients of either autologous microbiota or that of lean donors. Six weeks after small intestinal infusion, recipients from lean donors experienced increased insulin sensitivity, along with increased levels of butyrate-producing microbiota [10]. Perhaps one of the most telling studies was performed by Ridaura et al. who transplanted fecal microbiota from adult twin pairs discordant for obesity into germ-free mice. Not only were these obesity-associated phenotypes transmissible, cohousing with lean co-twin's microbial recipient prevented increasing body mass and adverse metabolic outcomes [11]. Diet had an integral role, and when mice were fed a low-fat, high-fiber diet, they were protected against the effects of obese microbiota [12].

Correlations between shifts in the microbiome and obesity have been observed, although causality remains to be discerned. In general, one of the noteworthy observations has been the increased ratio of the phylum Firmicutes to the phylum Bacteroidetes seen with obesity [13–15]. This concept was initially proposed by Turnbaugh et al. who also demonstrated that obese microbiome has perhaps an increased capacity to harvest energy from the diet [16]. Further support for the Firmicutes to Bacteroidetes ratio was lent after the observation that this ratio is decreased with percentage reduction in body weight [13]. However, this observation has been met with some controversy, as other studies have failed to identify the difference in this ratio between obese and lean patients [17, 18]. Perhaps controversy in this regard lies in the fact that these are entire phylum changes, and more specific family and species levels changes should be pursed to characterize pathogen with phenotypic changes. For example, Zhang et al. assessed contributions of host genetics and diet in altering the microbiome in mice. Sixty-five species-level phylotypes were correlated with differences induced by diet, with diet explaining 57 % of the total structural variation in gut microbiome. Genetic mutation accounted for 12 %. Barrier-protecting *Bifidobacterium* species were nearly absent in all animals, with an observed increase in *Desulfovibrionaceae*, a sulfate-reducing and endotoxin-producing bacteria, in all animals with impaired glucose tolerance [19].

Not surprisingly, T2DM in humans is associated with microbial shifts as well. In a study by Qin et al., a protocol for a metagenome-wide association study was developed to study 345 Chinese individuals. Patients with T2DM portrayed moderate intestinal dysbiosis as indicated by a decrease in butyrate-producing *Roseburia intestinalis* and *F. prausnitzii*, along with an increase in opportunistic pathogens including *Bacteroides caccae*, *Clostridiales*, and *Escherichia coli*. Lean patients in this study exhibited an enriched population of butyrate-producing bacteria [20]. Similarly, Karlsson et al. studied the gut meganome in 145 European women with normal, impaired, or diabetic glucose control. This group similarly displayed increases in *Clostridiales* species, and decreases in *Roseburia intestinalis* and *F. prausnitzii* [21, 22]. They also illustrated increased Proteobacteria, increased

expression of microbial genes involved in oxidative stress, and decreased genes involved in vitamin synthesis [9, 21, 22]. Another protective bacterium identified is *Akkermansia municiphila*, a mucin-degrading bacterium, negatively associated with type 1 and type 2 diabetes mellitus [20], while *Bacteroidetes* and *Prevotella* are increased in proportion to a decrease in *Firmicutes* and *Clostridia* [21–23].

6.3 Implicated Metabolic Pathways: LPS and Increased Gut Barrier Leak

Circulating lipopolysaccharide (LPS) is an integral and early step in the development of insulin resistance and diabetes having been observed in mice and humans [24–26]. Mice fed a high fat diet had two to three times increased levels of circulating LPS [26]. CD-14 mutant mice, which are resistant to LPS, are also resistant to high-fat diet-induced insulin resistance [26, 27]. Cani et al. administered antibiotics to mice on a high-fat diet, demonstrating that changes in the gut microbiome are responsible for endotoxemia and the subsequent inflammatory cascade, correlating strongly with intestinal permeability [27]. In patients with diabetes mellitus, LPS levels are significantly elevated, leading to increased secretion of pro-inflammatory cytokines [4, 28]. In mice fed a high-fat diet for 3 months, LPS was elevated in the presence of diabetes, and related this to increased gut permeability in the ileum and cecum [29]. Obese patients and rodents exhibit increased richness of LPS-producing bacteria, notably increased *Enterobacteriacaea* and *Desulfovibrionaceae*, corresponding with increased circulating LPS [30]. In obese human adolescents undergoing an exercise and diet program, fecal *Enterobacteriaceae* was significantly decreased [31, 32]. Once systemic, LPS binds LPS-binding protein and is recognized by CD14 and TLR4 [33, 34]. This in turn leads to a pro-inflammatory response and production of inflammatory cytokines potentially linking the microbiome to the diabetic phenotype [35].

6.4 Changes Following Bariatric Surgery

Following the gastric bypass, there is an increase in richness and diversity of the gut microbiome associated with white adipose tissue genes [36]. In a study comparing nine individuals, with three in each of normal weight, morbidly obese, and post-gastric bypass groups, *Firmicutes* was dominant in the first two groups, but decreased in post-gastric bypass individuals with a proportional increase in Gammaproteobacteria [15]. *Akkermansia* was also increased in the post-gastric bypass population. Graessler et al. compared patients before and 3 months following gastric bypass, having also observed a reduction in Firmicutes, with an increase in *Proteobacteria*. However, they also observed a decrease in *F. prausnitzii* correlating directly with fasting blood glucose levels [37]. Furet et al. observed an increase in *F. Prausnitzii* correlating with improved circulating CRP and IL6 in 30 patients with T2DM following gastric bypass. In an interesting and telling study performed by Liou et al.,

shifts observed following RYGB are conserved between humans, mice and rats, observing an increase in *Gammaproteobacteria* (*Escherichia*) and *Verrucomicrobia* (*Akkermansia*). Transferring gut microbiota from mice having undergone RYGB to germ-free mice resulted in weight loss and decreased fat mass relative to recipients of microbiota from mice following sham surgery [38].

In a study by Monte et al., 15 morbidly obese patients with T2DM underwent RYGB, with blood samples collected on day of surgery and 180 days after surgery. Interestingly, systemic inflammation as measured by multiple cytokines, including MCP-1 and CRP, and bacterial LPS were significantly reduced following surgery, possibly linking this improvement in systemic inflammation as a mechanism underlying metabolic improvement [39].

Certainly, further characterization of the microbiome is required; more important may be the role species have in altering gut physiology translating to systemic changes, particularly in diabetes. Much of this may involve gaining a stronger understanding of gut immunology at the enterocyte level given the known systemic inflammation that characterizes white adipose tissue in T2DM.

6.5 Possible Mediators of Change

6.5.1 Bile Acids

Obese patients exhibit an attenuated fasting and post-prandial bile acid response compared to lean individuals [40]. Following RYGB, both fasting and post-prandial plasma bile acid responses are increased, and have been shown to correlate with improvement in glucose metabolism [41, 42]. Bile acids serve as ligands for both G-protein-coupled receptor TGR5, which increases GLP-1 production, and nuclear hormone receptor farnesoid X receptor (FXR) [43]. FXR induces formation of fibroblast growth factor-19, which enters portal circulation and inhibits bile acid synthesis via *CYP7A1*. Primary bile acids cholic acid and chenodeoxycholic acids are synthesized from cholesterol in the liver via *CYP7A1*. In the gut, the microbiome converts primary bile acids into secondary bile acids by dehydroxylation, creating deoxycholic and lithocholic acids. Greater than 95 % of bile acids are reabsorbed by the gut and are transported back to the liver [40, 44, 45].

In an interesting study performed at the University of Cincinnati, mouse FXR knockout models undergoing vertical sleeve gastrectomy (VSG) highlighted the significance of the FXR receptor and the bile acid pathway in mediating metabolic improvement. FXR knockouts portray substantially reduced weight loss and decreased improvement in glucose tolerance following VSG. Along with these observations, changes in microbiome were also observed between wild-type mice undergoing VSG, and FXR knockouts undergoing VSG. Knockouts showed decreased abundance of one genus in the *Porphyromonadaceae* family in Knockout-VSG model. *Roseburia* was also increased in wild-type VSG model relative to wild-type shams, while no difference was observed between the knockout and sham FXR knockout models [46].

The intimate and complex relationship between bile acids and the microbiome is one that requires further research as we continue toward identifying physiologic roles for the multitude of bacterial species that comprise our gut microbiome.

6.5.2 Short-Chain Fatty Acids

Short-chain fatty acids (SCFAs) including acetate, butyrate, and propionate are main colonic bacterial fermentation products that serve as main energy sources and have been established as essential nutrients acting as signaling molecules [47, 48]. Two orphan G-protein-coupled receptors, FFAR2 (formerly gpr 3) and FFAR3 (formerly gpr41), have been identified as being activated by SCFAs [49].

At this time, it is appreciated that the SCFA–FFAR2 interaction has a significant effect on inflammatory responses. Priopionate and butyrate have been observed to reduce low-grade inflammation and increase leptin [50, 51]. Butyrate-producing bacteria have been particularly implicated in studies involving fecal transplantation as a therapeutic modality for insulin resistance [52]. Oral administration of acetate and propionate reduced glycemia in diabetic KK-A (y) and wild-type rats [53]. Interestingly, incubation of human colonic epithelial cell line with butyrate has shown to increase transepithelial resistance by promoting assembly of tight junction, highlighting a potential correlation with metabolic endotoxemia and gut barrier leak highlighted earlier [54]. Along these lines, propionate and butyrate reduce expression of pro-inflammatory cytokines TNF-α and IL-6 in human adipose tissue, while butyrate has been shown to increase the secretion of the anti-inflammatory cytokine IL-10 by human monocytes exposed to bacteria [55, 56].

Substantial knowledge has been gained from mouse knockout models as well. FFAR2 knockout mice display exacerbated or unresolved inflammation in models of colitis, arthritis, and asthma [57]. Kimura et al. demonstrated that FFAR2 knockout mice are obese on a normal diet, whereas mice overexpressing FFAR2 remain lean even on a high fat diet. This difference is abolished under germ-free conditions or after antibiotics. Furthermore, SCFA-mediated activation of FFAR2 suppresses insulin signaling in adipocytes thus inhibiting fat accumulation in adipose tissue [58]. De Vadder et al. were able to show that perhaps one mechanism by which SCFAs, particularly propionate and butyrate, mediate their influence is via activation of intestinal gluconeogenesis (IGN). Butyrate activates IGN gene expression via a cAMP-dependent mechanism, while propionate interestingly activates IGN via a gut-brain neural circuit involving FFAR3. This relationship is abolished with capsaicin-induced periportal nervous deafferentiation in rats [59].

Altogether, as more data are accumulating, it is becoming clearer the impact the gut microbiome has on human metabolism, particularly through SCFAs. How we may utilize these findings from a therapeutic perspective in alleviating diabetes remains to be seen.

6.6 Conclusion

Interest in the microbiome has increased considerably over the past few years, especially with the discovery of a divergence and pattern observed in obese and diabetic humans relative to lean and healthy humans. These changes in the microbiome strongly correlate along the spectrum of metabolic disease. How the human gut interacts with specific bacterial species remains a significant, but necessary challenge to overcome. We, in the field of bariatric surgery, have an important role in elucidating this puzzle given our significant capacity to alter the microbiome following surgery. These changes clearly correlate with the dramatic metabolic improvement following bariatric surgery. The challenge has always been to isolate important physiologic changes following surgery, and relating them to the well-established phenotypic changes that occur. This is no different as it relates to the human gut microbiome.

References

1. Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. Nature. 2012;486(7402):207–14. doi:10.1038/nature11234.
2. Sweeney TE, Morton JM. The human gut microbiome: a review of the effect of obesity and surgically induced weight loss. JAMA Surg. 2013;148(6):563–9. doi:10.1001/jamasurg.2013.5.
3. Arumugam M, Raes J, Pelletier E, Le Paslier D, Yamada T, Mende DR, Fernandes GR, Tap J, Bruls T, Batto JM, Bertalan M, Borruel N, Casellas F, Fernandez L, Gautier L, Hansen T, Hattori M, Hayashi T, Kleerebezem M, Kurokawa K, Leclerc M, Levenez F, Manichanh C, Nielsen HB, Nielsen T, Pons N, Poulain J, Qin J, Sicheritz-Ponten T, Tims S, Torrents D, Ugarte E, Zoetendal EG, Wang J, Guarner F, Pedersen O, De Vos WM, Brunak S, Doré J, MetaHIT Consortium, Antolín M, Artiguenave F, Blottiere HM, Almeida M, Brechot C, Cara C, Chervaux C, Cultrone A, Delorme C, Denariaz G, Dervyn R, Foerstner KU, Friss C, van de Guchte M, Guedon E, Haimet F, Huber W, van Hylckama-Vlieg J, Jamet A, Juste C, Kaci G, Knol J, Lakhdari O, Layec S, Le Roux K, Maguin E, Mérieux A, Melo Minardi R, M'rini C, Muller J, Oozeer R, Parkhill J, Renault P, Rescigno M, Sanchez N, Sunagawa S, Torrejon A, Turner K, Vandemeulebrouck G, Varela E, Winogradsky Y, Zeller G, Weissenbach J, Ehrlich SD, Bork P. Enterotypes of the human gut microbiome. Nature. 2011;473(7346):174–80. doi: 10.1038/nature09944. Epub 2011 Apr 20.
4. Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, Sogin ML, Jones WJ, Roe BA, Affourtit JP, Egholm M, Henrissat B, Heath AC, Knight R, Gordon JI. A core gut microbiome in obese and lean twins. Nature. 2009;457(7228):480–4. doi:10.1038/nature07540. Epub 2008 Nov 30.
5. Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, Falony G, Almeida M, Arumugam M, Batto JM, Kennedy S, Leonard P, Li J, Burgdorf K, Grarup N, Jørgensen T, Brandslund I, Nielsen HB, Juncker AS, Bertalan M, Levenez F, Pons N, Rasmussen S, Sunagawa S, Tap J, Tims S, Zoetendal EG, Brunak S, Clément K, Doré J, Kleerebezem M, Kristiansen K, Renault P, Sicheritz-Ponten T, de Vos WM, Zucker JD, Raes J, Hansen T, MetaHIT Consortium, Bork P, Wang J, Ehrlich SD, Pedersen O. Richness of human gut microbiome correlates with metabolic markers. Nature. 2013;500(7464):541–6. doi:10.1038/nature12506.
6. De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, Collini S, Pieraccini G, Lionetti P. Impact of diet in shaping gut microbiota revealed by a comparative

study in children from Europe and rural Africa. Proc Natl Acad Sci U S A. 2010;107(33):14691–6. doi:10.1073/pnas.1005963107. Epub 2010 Aug 2.
7. Swidsinski A, Weber J, Loening-Baucke V, Hale LP, Lochs H. Spatial organization and composition of the mucosal flora in patients with inflammatory bowel disease. J Clin Microbiol. 2005;43(7):3380–9.
8. Joossens M, Huys G, Cnockaert M, De Preter V, Verbeke K, Rutgeerts P, Vandamme P, Vermeire S. Dysbiosis of the faecal microbiota in patients with Crohn's disease and their unaffected relatives. Gut. 2011;60(5):631–7. doi:10.1136/gut.2010.223263. Epub 2011 Jan 5.
9. Tilg H, Moschen AR. Microbiota and diabetes: an evolving relationship. Gut. 2014;63(9):1513–21. doi:10.1136/gutjnl-2014-306928. Epub 2014 May 15.
10. Vrieze A, Van Nood E, Holleman F, Salojärvi J, Kootte RS, Bartelsman JF, Dallinga-Thie GM, Ackermans MT, Serlie MJ, Oozeer R, Derrien M, Druesne A, Van Hylckama Vlieg JE, Bloks VW, Groen AK, Heilig HG, Zoetendal EG, Stroes ES, de Vos WM, Hoekstra JB, Nieuwdorp M. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology. 2012;143(4):913–6.e7. doi: 10.1053/j.gastro.2012.06.031. Epub 2012 Jun 20.
11. Ridaura VK, Faith JJ, Rey FE, Cheng J, Duncan AE, Kau AL, Griffin NW, Lombard V, Henrissat B, Bain JR, Muehlbauer MJ, Ilkayeva O, Semenkovich CF, Funai K, Hayashi DK, Lyle BJ, Martini MC, Ursell LK, Clemente JC, Van Treuren W, Walters WA, Knight R, Newgard CB, Heath AC, Gordon JI. Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science. 2013;341(6150):1241214. doi:10.1126/science.1241214.
12. Turnbaugh PJ, Ridaura VK, Faith JJ, Rey FE, Knight R, Gordon JI. The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. Sci Transl Med. 2009;1(6):6ra14. doi: 10.1126/scitranslmed.3000322.
13. Ley RE, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. Proc Natl Acad Sci U S A. 2005;102(31):11070–5. Epub 2005 Jul 20.
14. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. Nature. 2006;444(7122):1022–3.
15. Zhang H, DiBaise JK, Zuccolo A, Kudrna D, Braidotti M, Yu Y, Parameswaran P, Crowell MD, Wing R, Rittmann BE, Krajmalnik-Brown R. Human gut microbiota in obesity and after gastric bypass. Proc Natl Acad Sci U S A. 2009;106(7):2365–70. doi:10.1073/pnas.0812600106. Epub 2009 Jan 21.
16. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006; 444(7122):1027–31.
17. Schwiertz A, Taras D, Schäfer K, Beijer S, Bos NA, Donus C, Hardt PD. Microbiota and SCFA in lean and overweight healthy subjects. Obesity (Silver Spring). 2010;18(1):190–5. doi:10.1038/oby.2009.167. Epub 2009 Jun 4.
18. Zhang C, Zhang M, Pang X, Zhao Y, Wang L, Zhao L. Structural resilience of the gut microbiota in adult mice under high-fat dietary perturbations. ISME J. 2012;6(10):1848–57. doi:10.1038/ismej.2012.27. Epub 2012 Apr 12.
19. Zhang C, Zhang M, Wang S, Han R, Cao Y, Hua W, Mao Y, Zhang X, Pang X, Wei C, Zhao G, Chen Y, Zhao L. Interactions between gut microbiota, host genetics and diet relevant to development of metabolic syndromes in mice. ISME J. 2010;4(2):232–41. doi:10.1038/ismej.2009.112. Epub 2009 Oct 29.
20. Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, Liang S, Zhang W, Guan Y, Shen D, Peng Y, Zhang D, Jie Z, Wu W, Qin Y, Xue W, Li J, Han L, Lu D, Wu P, Dai Y, Sun X, Li Z, Tang A, Zhong S, Li X, Chen W, Xu R, Wang M, Feng Q, Gong M, Yu J, Zhang Y, Zhang M, Hansen T, Sanchez G, Raes J, Falony G, Okuda S, Almeida M, LeChatelier E, Renault P, Pons N, Batto JM, Zhang Z, Chen H, Yang R, Zheng W, Li S, Yang H, Wang J, Ehrlich SD, Nielsen R, Pedersen O, Kristiansen K, Wang J. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature. 2012;490(7418):55–60. doi:10.1038/nature11450. Epub 2012 Sep 26.

21. Karlsson FH, Tremaroli V, Nookaew I, Bergström G, Behre CJ, Fagerberg B, Nielsen J, Bäckhed F. Gut metagenome in European women with normal, impaired and diabetic glucose control. Nature. 2013;498(7452):99–103. doi: 10.1038/nature12198. Epub 2013 May 29.
22. Larsen N, Vogensen FK, van den Berg FW, Nielsen DS, Andreasen AS, Pedersen BK, Al-Soud WA, Sørensen SJ, Hansen LH, Jakobsen M. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. PLoS One. 2010;5:e9085. PMID: 20140211. Doi: 10.1371/journal.pone.0009085.
23. Festi D, Schiumerini R, Eusebi LH, Marasco G, Taddia M, Colecchia A. Gut microbiota and metabolic syndrome. World J Gastroenterol. 2014;20(43):16079–94.
24. Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, Neyrinck AM, Fava F, Tuohy KM, Chabo C, Waget A, Delmée E, Cousin B, Sulpice T, Chamontin B, Ferrières J, Tanti JF, Gibson GR, Casteilla L, Delzenne NM, Alessi MC, Burcelin R. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes. 2007;56:1761–72. PMID: 17456850. Doi: 10.2337/db06-1491.
25. Shi H, Kokoeva MV, Inouye K, Tzameli I, Yin H, Flier JS. TLR4 links innate immunity and fatty acid-induced insulin resistance. J Clin Invest. 2006;116:3015–25. PMID: 17053832. Doi: 10.1172/JCI28898.
26. Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM, Burcelin R. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. Diabetes. 2008;57(6):1470–81. doi:10.2337/db07-1403. Epub 2008 Feb 27.
27. Amar J, Burcelin R, Ruidavets JB, Cani PD, Fauvel J, Alessi MC, Chamontin B, Ferriéres J. Energy intake is associated, with endotoxemia in apparently healthy. Am J Clin Nutr. 2008;87:1219–23. PMID: 18469242.
28. Lassenius MI, Pietiläinen KH, Kaartinen K, Pussinen PJ, Syrjänen J, Forsblom C, Pörsti I, Rissanen A, Kaprio J, Mustonen J, Groop PH, Lehto M, FinnDiane Study Group. Bacterial endotoxin activity in human serum is associated with dyslipidemia, insulin resistance, obesity, and chronic inflammation. Diabetes Care. 2011;34:1809–15.
29. Serino M, Luche E, Gres S, Baylac A, Bergé M, Cenac C, Waget A, Klopp P, Iacovoni J, Klopp C, Mariette J, Bouchez O, Lluch J, Ouarné F, Monsan P, Valet P, Roques C, Amar J, Bouloumié A, Théodorou V, Burcelin R. Metabolic adaptation to a high-fat diet is associated with a change in the gut microbiota. Gut. 2012;61:543–53.
30. Lindberg AA, Weintraub A, Zähringer U, Rietschel ET. Structure-activity relationships in lipopolysaccharides of Bacteroides fragilis. Rev Infect Dis. 1990;12 Suppl 2:S133–41.
31. Hernández E, Bargiela R, Diez MS, Friedrichs A, Pérez-Cobas AE, Gosalbes MJ, Knecht H, Martínez-Martínez M, Seifert J, von Bergen M, Artacho A, Ruiz A, Campoy C, Latorre A, Ott SJ, Moya A, Suárez A, Martins dos Santos VA, Ferrer M. Functional consequences of microbial shifts in the human gastrointestinal tract linked to antibiotic treatment and obesity. Gut Microbes. 2013;4(4):306–15. doi:10.4161/gmic.25321. Epub 2013 Jun 12.
32. Zhao L. The gut microbiota and obesity: from correlation to causality. Nat Rev Microbiol. 2013;11(9):639–47. doi:10.1038/nrmicro3089. Epub 2013 Aug 5.
33. Weiss J. Bactericidal/permeability-increasing protein (BPI) and lipopolysaccharide-binding protein (LBP): structure, function and regulation in host defence against Gram-negative bacteria. Biochem Soc Trans. 2003;31(Pt 4):785–90.
34. Ruiz AG, Casafont F, Crespo J, Cayón A, Mayorga M, Estebanez A, Fernadez-Escalante JC, Pons-Romero F. Lipopolysaccharide-binding protein plasma levels and liver TNF-alpha gene expression in obese patients: evidence for the potential role of endotoxin in the pathogenesis of non-alcoholic steatohepatitis. Obes Surg. 2007;17(10):1374–80.
35. Creely SJ, McTernan PG, Kusminski CM, Fisher FM, Da Silva NF, Khanolkar M, Evans M, Harte AL, Kumar S. Lipopolysaccharide activates an innate immune system response in human adipose tissue in obesity and type 2 diabetes. Am J Physiol Endocrinol Metab. 2007;292(3):E740–7. Epub 2006 Nov 7.
36. Kong LC, Tap J, Aron-Wisnewsky J, Pelloux V, Basdevant A, Bouillot JL, Zucker JD, Doré J, Clément K. Gut microbiota after gastric bypass in human obesity: increased richness and asso-

ciations of bacterial genera with adipose tissue genes. Am J Clin Nutr. 2013;98(1):16–24. doi:10.3945/ajcn.113.058743. Epub 2013 May 29.
37. Graessler J, Qin Y, Zhong H, Zhang J, Licinio J, Wong ML, Xu A, Chavakis T, Bornstein AB, Ehrhart-Bornstein M, Lamounier-Zepter V, Lohmann T, Wolf T, Bornstein SR. Metagenomic sequencing of the human gut microbiome before and after bariatric surgery in obese patients with type 2 diabetes: correlation with inflammatory and metabolic parameters. Pharmacogenomics J. 2013;13(6):514–22. doi:10.1038/tpj.2012.43. Epub 2012 Oct 2.
38. Liou AP, Paziuk M, Luevano Jr JM, Machineni S, Turnbaugh PJ, Kaplan LM. Conserved shifts in the gut microbiota due to gastric bypass reduce host weight and adiposity. Sci Transl Med. 2013;5(178):178ra41. Doi: 10.1126/scitranslmed.3005687.
39. Monte SV, Caruana JA, Ghanim H, Sia CL, Korzeniewski K, Schentag JJ, Dandona P. Reduction in endotoxemia, oxidative and inflammatory stress, and insulin resistance after Roux-en-Y gastric bypass surgery in patients with morbid obesity and type 2 diabetes mellitus. Surgery. 2012;151(4):587–93. doi:10.1016/j.surg.2011.09.038. Epub 2011 Nov 16.
40. Glicksman C, Pournaras DJ, Wright M, Roberts R, Mahon D, Welbourn R, Sherwood R, Alaghband-Zadeh J, le Roux CW. Post-prandial plasma bile acid responses in normal weight and obese subjects. Ann Clin Biochem. 2010;47:482–4.
41. Werling M, Vincent RP, Cross GF, Marschall HU, Fändriks L, Lönroth H, Taylor DR, Alaghband-Zadeh J, Olbers T, Le Roux CW. Enhanced fasting and post-prandial plasma bile acid responses after Roux-en-Y gastric bypass surgery. Scand J Gastroenterol. 2013;48(11):1257–64. doi:10.3109/00365521.2013.833647. Epub 2013 Sep 18.
42. Simonen M, Dali-Youcef N, Kaminska D, Venesmaa S, Käkelä P, Pääkkönen M, Hallikainen M, Kolehmainen M, Uusitupa M, Moilanen L, Laakso M, Gylling H, Patti ME, Auwerx J, Pihlajamäki J. Conjugated bile acids associate with altered rates of glucose and lipid oxidation after Roux-en-Y gastric bypass. Obes Surg. 2012;22:1473–80.
43. Prawitt L, Staels B. Bile acid sequestrants: glucose-lowering mechanisms. Metab Syndr Relat Disord. 2010;8:3–8.
44. Angelin B, Björkhem I, Einarsson K, Ewerth S. Hepatic uptake of bile acids in man. Fasting and postprandial concentrations of individual bile acids in portal venous and systemic blood serum. J Clin Invest. 1982;70:724–31.
45. Song KH, Li T, Owsley E, Strom S, Chiang JY. Bile acids activate fibroblast growth factor 19 signaling in human hepatocytes to inhibit cholesterol 7alpha-hydroxylase gene expression. Hepatology. 2009;49(1):297–305. doi:10.1002/hep.22627.
46. Ryan KK, Tremaroli V, Clemmensen C, Kovatcheva-Datchary P, Myronovych A, Karns R, Wilson-Pérez HE, Sandoval DA, Kohli R, Bäckhed F, Seeley RJ. FXR is a molecular target for the effects of vertical sleeve gastrectomy. Nature. 2014;509(7499):183–8. doi:10.1038/nature13135. Epub 2014 Mar 26.
47. Flint HJ, Bayer EA, Rinco MT, Lamed R, White BA. Polysaccharide utilization by gut bacteria: potential for new insights from genomic analysis. Nat Rev Microbiol. 2008;6(2):121–31. doi:10.1038/nrmicro1817. Review.
48. Topping DL, Clifton PM. Short-chain fatty acids and human colonic function: roles of resistant starch and nonstarch polysaccharides. Physiol Rev. 2001;81(3):1031–64.
49. Brown AJ, Goldsworthy SM, Barnes AA, Eilert MM, Tcheang L, Daniels D, Muir AI, Wigglesworth MJ, Kinghorn I, Fraser NJ, Pike NB, Strum JC, Steplewski KM, Murdock PR, Holder JC, Marshall FH, Szekeres PG, Wilson S, Ignar DM, Foord SM, Wise A, Dowell SJ. The Orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. J Biol Chem. 2003;278(13):11312–9. Epub 2002 Dec 19.
50. Mortensen PB, Clausen MR. Short-chain fatty acids in the human colon: relation to gastrointestinal health and disease. Scand J Gastroenterol Suppl. 1996;216:132–48.
51. Al-Lahham SH, Roelofsen H, Priebe M, Weening D, Dijkstra M, Hoek A, Rezaee F, Venema K, Vonk RJ. Regulation of adipokine production in human adipose tissue by propionic acid. Eur J Clin Investig. 2010;40(5):401–7.
52. Udayappan SD, Hartstra AV, Dallinga-Thie GM, Nieuwdorp M. Intestinal microbiota and faecal transplantation as treatment modality for insulin resistance and type 2 diabetes mellitus. Clin Exp Immunol. 2014;177(1):24–9.

53. Sakakibara S, Yamauchi T, Oshima Y, Tsukamoto Y, Kadowaki T. Acetic acid activates hepatic AMPK and reduces hyperglycemia in diabetic KK-A(y) mice. Biochem Biophys Res Commun. 2006;344(2):597–604. Epub 2006 Apr 5.
54. Peng L, Li ZR, Green RS, Holzman IR, Lin J. Butyrate enhances the intestinal barrier by facilitating tight junction assembly via activation of AMP-activated protein kinase in Caco-2 cell monolayers. J Nutr. 2009;139(9):1619–25.
55. Säemann MD, Böhmig GA, Osterreicher CH, Burtscher H, Parolini O, Diakos C, Stöckl J, Hörl WH, Zlabinger GJ. Anti-inflammatory effects of sodium butyrate on human monocytes: potent inhibition of IL-12 and up-regulation of IL-10 production. FASEB J. 2000;14(15):2380–2.
56. Roelofsen H, Priebe MG, Vonk RJ. The interaction of short-chain fatty acids with adipose tissue: relevance for prevention of type 2 diabetes,". Benefic Microbes. 2010;1(4):433–7.
57. Maslowski KM, Vieira AT, Ng A, Kranich J, Sierro F, Yu D, Schilter HC, Rolph MS, Mackay F, Artis D, Xavier RJ, Teixeira MM, Mackay CR. Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. Nature. 2009;461(7268):1282–6. doi:10.1038/nature08530.
58. Kimura I, Ozawa K, Inoue D, Imamura T, Kimura K, Maeda T, Terasawa K, Kashihara D, Hirano K, Tani T, Takahashi T, Miyauchi S, Shioi G, Inoue H, Tsujimoto G. The gut microbiota suppresses insulin-mediated fat accumulation via the short-chain fatty acid receptor GPR43. Nat Commun. 2013;4:1829. doi:10.1038/ncomms2852.
59. De Vadder F, Kovatcheva-Datchary P, Goncalves D, Vinera J, Zitoun C, Duchampt A, Bäckhed F, Mithieux G. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. Cell. 2014;156(1–2):84–96. doi:10.1016/j.cell.2013.12.016. Epub 2014 Jan 9.

The History of Metabolic Surgery

7

Walter Pories

7.1 On the Shoulders of Giants

Either the history of metabolic surgery is an anomaly or what we were taught in school is just wrong. In our science classes, already burdened by the enforced emphasis on rote, we memorized the names of the great scientists who were sanctified by their singular inventions. We learned that Pasteur invented bacteriology, Kepler was the first to recognize planetary motion, and that Watson and Crick single-handedly discovered the binary structure and function of DNA.

The development of metabolic surgery, at the least, leads us to question the belief that science is shaped by one person who has a singular idea and the skills to bring it all to fruition. As Pasteur put it, "Fortune favors the prepared mind." In short, really, really study hard and you'll make a great invention. So we faithfully did our homework and looked forward to winning the Nobel Prize.

Sir Isaac Newton, however, got it right. With humility he recognized "If I have seen farther than others, it is because I was standing on the shoulders of giants." As one of the greatest thinkers in history, Newton impressed upon society the importance of our predecessors' accomplishments in relation to our own. There is no field of study that this philosophy rings more true than in the area of "metabolic surgery," no doubt one of the major advances of the last century.

Metabolic surgery reveals that at least in the development of this great scientific breakthrough, progression came in zig-zag steps made by ordinary, caring surgeons in response to challenging situations, often with the help of PhD colleagues who were also swept up in the excitement of a puzzling observation. Even changing the name of the field, once known as "bariatric" from the Greek (baros) to "metabolic" surgery came through multiple discussion and debates about the daring concept to name the

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new field for "the operative manipulation of a *normal* organ or organ system to achieve a biological result for a potential health gain," as defined by Varco and Buchwald [1].

This chapter therefore is a different type of history. It honors not individual "giants" but rather recognizes the struggles of the small band of surgeons who had the sensitivity to recognize that severe obesity was a disease. These surgeons, frustrated with the toll of this progressive illness, determined that the severely obese deserved better care and who, over the objections of their colleagues and society, managed not only to devise operations that led to durable loss of about one-third of the patients' original weights but also produced full and long-term remission of type 2 diabetes, hypertension, hyperlipidemias, polycystic ovary disease, and non-alcoholic steatotic hepatitis among others chronic diseases previously considered incurable. In addition, surprisingly, these operations also led to reductions not only in long-term mortality but even the prevalence of solid cancers within 5 years. Even more important, these pioneers provided a framework for basic science and the study of mechanisms that should lead to long term control with medications and without surgery.

Accordingly, instead of focusing on individuals, this review focuses on the growth of ideas and the evolution of concepts. There are far too many pioneers to mention individually. In addition, this history will also note the influence of concerns for patient safety, the impact of decisions by legal and insurance entities, the challenge of providing access to the surgery for those who need it and some thoughts about the future of this exciting field.

7.2 Obesity Is Not a New Phenomenon

Severe obesity is not a new entity. In fact, the Venus of Willendorf (Fig. 7.1), perhaps the oldest sculpture in the world, suggests that in what is now Lower Austria, this status was admired as long ago as 30,000 years ago.

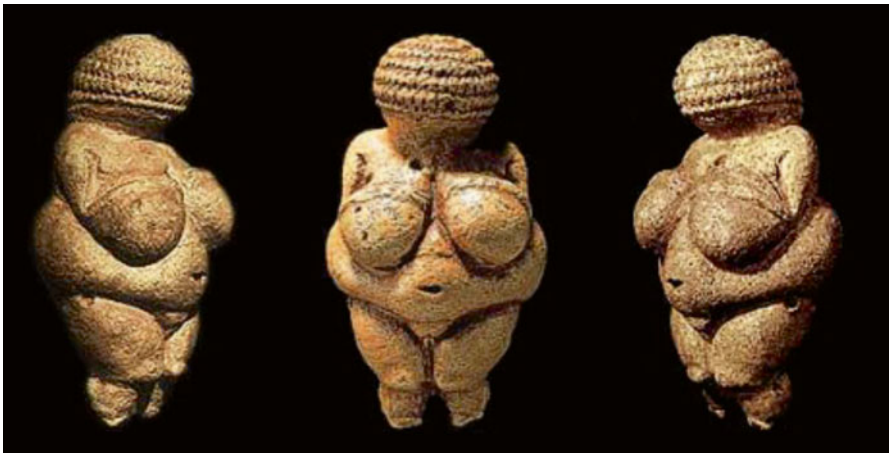

Fig. 7.1 The Venus of Willendorf

Even a few decades ago, it was still deemed desirable. Townsend et al. [2] nicely documented that "certain ethno-cultural groups associate large body sizes with marriageability, attractiveness, fertility, and generosity … traditionally, some Pacific Islanders associate power and status with large body sizes and that …. Pacific Islanders with higher Body Mass Indices (BMI = kg/m^2), compared to Whites with higher BMIs, were more likely to see themselves as either under or normal weight."

The concept that being large adds to a powerful image is not limited to the Polynesian islands. Winston Churchill, Nikita Khrushchev, Louis XVIII, and many other international leaders come to mind. It is only recently that obesity in a prominent person, such as Governor Christie, has become a disadvantage, enough to cause him to undergo the insertion of an adjustable gastric band.

7.3 No, Severe Obesity Is a Disease!

There were others, however, who recognized long ago that obesity was detrimental to health. Four hundred years before the birth of Christ, Hippocrates noted that "If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health." Shakespeare had Falstaff complain "Thou seest I have more flesh than another man, and therefore more frailty" and described Hamlet as "fat and scant of breath." Kintz [3] probably summarized our change of thought most concisely, "Obesity isn't as cool as it used to be, back in the earlier centuries. Before it was a reflection on your gross income, and now it's just gross."

Prior to the 1950s, what is currently known as bariatric surgery did not exist. In 1954 Kremen [4] and colleagues made the first critical step with the recognition that severe obesity is a disease and that diets, exercise and medications were ineffective in almost all of the patients. Led by their clinical observation that extensive resection of intestine could lead to severe weight loss, they pursued experiments in dogs that demonstrated that by excluding 50–70 % of the small intestine, they could produce profound weight loss.

This conceptual breakthrough was followed and the origins of bariatric surgery later applied to human subjects through the development of what is known as the jejunoileal bypass (JIB) (Fig. 7.2). Payne built upon the work done in the 1950s by Kremen and developed his version of the JIB which was actually a jejunocolic shunt and identified the associated metabolic changes 1963 [5]. Payne's original procedure involved the division of the small intestine 35–50 cm downstream from the ligament of Treitz. The proximal end was then anastomosed to the proximal transverse colon. Both the jejunoileal and jejunocolic bypasses achieved the goal of weight loss and lowered serum cholesterol due to the decreased absorption of dietary fats. The one black mark on the history of metabolic surgery is that over 30,000 of these operations were performed with multiple reports of severe malnutrition, mineral imbalances, diarrhea with 8–12 bowel movements/day, perianal excoriations, hepatic cirrhosis, hepatic failure, renal stones, severe dehydration, hypocalcemia, and poor vitamin absorption [6, 7] before Griffin, in a scathing editorial, demanded these procedures be abandoned.

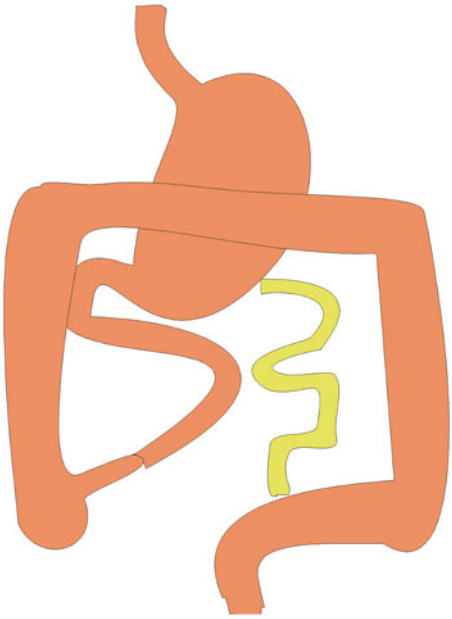

Fig. 7.2 Jejuno-ileal bypass

Even so, there were some successful cases and, for the first time, there was evidence that a surgical approach, if it was the right approach, could overcome severe obesity. That recognition and the drawbacks of the JIB procedure and its variations spurred innovative surgical options to safely achieve weight reduction in morbidly obese individuals. By the 1970s the jejunoileal bypass had been essentially abandoned and attention was being directed towards a different approach.

The finding by Buchwald [8] that exclusion of the terminal ileum could provide long-term control of hyperlipidemias needs to be noted as well as a sentinel signal that the metabolic effects of intestinal surgery deserved investigation.

7.4 The Currently Accepted Operations

The design of the current operations was led by Mason, appropriately often referred to as "the father of metabolic surgery" who documented, in a series of thoughtful and minutely recorded studies, that operations on the stomach and proximal small bowel, could achieve weight loss with far greater safety and better outcomes. In 1967 Mason and Ito [9] developed the original gastric bypass. Their configuration consisted of a horizontally oriented proximal gastric division with creation of a 12 mm loop gastrojejunostomy anastomosis. Issues related to marginal ulceration as well as significant bile reflux sparked many variations to the gastric bypass procedure culminating into the Roux Y configuration by Griffen [10] with a more vertically oriented pouch that represents the standard procedure that is performed today. Mason also developed the operations to limit intake with a small gastric

pouch and a small outlet, i.e. the vertical banded gastroplasty (VBG) that rose to prominence in the early 1980s. At that time it rivaled the Roux-en-Y gastric bypass; however it ultimately fell out of favor as many of the patients that underwent this procedure ultimately experienced significant weight regain. The VBG procedure consisted of the creation of a vertical pouch with use of a circular stapler to create a gastric window followed by a non-cutting linear stapler to form a small vertically oriented pouch. The pouch itself is formed on the lesser curve side of the stomach and a narrowed stoma is created between the pouch and the distal stomach after application of a silastic band. The VBG was a modification of the horizontal gastroplasty procedure as described by Printen and Mason [11].

In the meantime, in Italy, Scopinaro [12] pursued a series of detailed and rigorous studies that led to the development of the most effective metabolic operation, i.e., the biliopancreatic diversion (BPD) procedure, which he described in 1979. And, as Mason, he did far more than design an operation. He followed his patients with great care, conducted demanding clinical trials and reported his results with clarity and candor. The BPD still stands today as the most effective procedure in terms of weight loss and comorbidity resolution with remission rates of type 2 diabetes in the 92–95 % range. The concern is that the greater exclusion of gut from contact with food may be too radical with its harsh restrictive and malabsorptive characteristics [13]. The current version of his BPD consists of a horizontal gastrectomy, which leaves 200–500 mL of proximal stomach. The duodenal stump is then closed. A gastrojejunostomy with a 250 cm roux limb is subsequently created. The long biliopancreatic limb is then anastomosed to the roux limb at a distance of 50 cm proximal to the ileocecal valve. This operation although rarely performed in the USA is thought to be an appropriate procedure for the obese individuals with BMI's >60 kg/m^2.

Complications including a perceived higher incidence of protein calorie malnutrition, marginal ulceration and perforation provoked modification of Scopinaro's procedure and led Hess [14] and colleagues to add a duodenal switch procedure to Scopinaro's BPD. The duodenal switch procedure was initially described by Dr. DeMeester [15] as a potential treatment for severe duodenogastric reflux. Hess successfully theorized that by adding this modification to the original BPD, the beneficial aspects of the BPD could be retained while eliminating its unwanted complications.

The biliopancreatic diversion with duodenal switch (BDP-DS) has been performed in the USA over the last 27 years. Key differences as it relates to the BPD include a 100 cm common channel (as opposed to 50 cm) and a different type of partial gastrectomy. The gastrectomy is created by removing the greater curvature of the stomach (i.e., sleeve gastrectomy). It is commonly done over a 40–60 French bougie. The antrum, pylorus and proximal duodenum are preserved. This effectively provides a greater restrictive component by leaving a smaller gastric reservoir (150–200 mL) as compared to the original BDP. The duodenum is divided distal to the pylorus and a duodenojejunostomy is created between the proximal duodenum and a 150 cm roux limb. Both the BPD and BPD-DS are currently performed totally laparoscopically by highly skilled minimally invasive surgeons [16, 17].

Even so, that approach still led to more nutritional complications than the RYGB and is not widely used although there are champions who feel it is the best metabolic operation.

During the late 1990s the Roux-Y gastric bypass had become the most widely performed bariatric surgical procedure. RYGB is considered to be the "gold standard" of bariatric surgical procedures due to its effectiveness with weight loss and its acceptable complication profile [18]. The procedure involves proximal gastric pouch formation, roux limb formation, and performance of a gastrojejunostomy. Proximal pouch formation involves creating a 15–30 mL gastric pouch by transecting the stomach (usually with a stapling device). The Roux limb is created by transecting the jejunum at a point 15–75 cm distal to the ligament of Treitz. An end to side jejunojejunostomy is then made 70–150 cm down the roux limb. Long limb bypass with roux limb segments greater than 150 cm are performed by some surgeons which imparts a significant malabsorptive component to the operation [19]. The gastrojejunostomy is then fashioned by bringing the Roux limb alongside the gastric pouch without tension. This may be done in a retrocolic, antecolic, retrogastric, or antegastric configuration. The particular configuration chosen is largely surgeon dependent with conflicting data available regarding stricture and leak rates [20, 21]. Construction of the gastrojejunostomy anastomosis can be performed using one of several techniques. It can be created using a linear stapler, a circular stapler, or completely hand-sewn. There are studies available in the literature that support the use of each of the mentioned techniques [22].

Sleeve gastrectomy had its beginnings as a component of the BPD-DS operation [23]. It is now being performed with increasing frequency as a stand-alone procedure in the treatment of morbid obesity. The technique is relatively novel and therefore has not yet been standardized in all of its steps (bougie calibration size, staple line reinforcement method, and type of stapler used) [24]. The longitudinal gastrectomy typically begins with dissection in gastrocolic ligament along the greater curvature of the stomach. This is carried all the way up to the level of the angle of His. A calibration bougie is then placed and advance along the lesser curve through the pyloric channel. The stomach is then divided with sequential firings (4–6) of an endo-GIA stapling device alongside the bougie. The remnant stomach is then extracted from the largest port site which completes the procedure. Laparoscopic sleeve gastrectomy represents a relatively simplistic yet effective alternative for bariatric surgery candidates.

Gastric banding is a restrictive technique used to treat morbid obesity that was introduced into clinical practice in the 1980s. The current version of gastric banding was popularized by Dr. Kuzmak [25] and involves the placement of an adjustable silicone band around the upper portion of the stomach. This technique effectively creates a small gastric pouch with a narrow stoma. The stoma diameter is adjusted to its proper size by injecting saline into a subcutaneously placed port that is connected to the silicone band via a long silicone tube. This procedure is done laparoscopically and is considered the least extensive of the bariatric surgery procedures that are currently performed. The procedure consists of proximal stomach dissection through either a pars flaccida or perigastric technique to create

the pathway through which the band is passed and secured around the stomach. Most recently the perigastric technique has been largely abandoned because of higher posterior slippage rates [26].

Laparoscopy was first applied to metabolic surgery by Belachew with adjustable gastric banding [27]. This was shortly followed by Wittgrove with the game-changing demonstration that the complex Roux-en-Y gastric bypass (RYGB) could also be performed with this approach [28]. Subsequent to these developments many large series were published on the safety and efficacy of the laparoscopic approach to bariatric surgery [29].

The application of a robotic platform to assist in performing complex bariatric operations has gained some interest in recent years. Advocates of robotic bariatric surgery cite advantage when compared to laparoscopic surgery including (1) removal of counter-intuitive motion and instrument tremor, (2) decrease in the physical demands of the operating surgeon, (3) 3-dimensional visualization, and (4) increased flexibility and degree of movement is inherent in the robot arms [30]. To date all contemporary bariatric surgery operations have been successfully performed using robotic technology with comparable results to that of laparoscopy [31–34].

7.5 Measurement of Outcomes: Are the Claims Really True?

If the surgeons were startled by the unexpected result of metabolic surgery, their medical colleagues and, in fact, the public met the reports with disbelief. How could a simple intestinal operation cure diabetes, cut mortality by values as high as 80 % and even prevent solid cancers? It was just not possible! The reports were dismissed as just other previous surgical claims of miracles such as sympathectomy for peripheral vascular disease and removal of the carotid body for hypertension. The initial high mortality rates and epidemic of liability suits only confirmed the general impression that metabolic surgery was a hoax.

What was needed was at least a long rigorous clinical observational study of a large group of patients who had undergone a standardized operation. Our group at East Carolina University was well suited for such a study. The 29 counties we serve in the rural part of eastern North Carolina hold an underserved and impoverished population in the USA who tended not to leave the region and who were burdened with a prevalence of severe obesity four times higher than in the rest of the USA. In that setting, we pursued the study of a standardized "Greenville gastric bypass" with a 30 mL. gastric pouch, a 1.0 cm gastrojejunostomy and a retrocolic 60 cm alimentary limb. From 1980 to 1996, the study included 837 consecutive patients with a follow-up of 93 % with a mean of 9.2 years.

We could not duplicate that study today because the rules for human research have changed so sharply. In those years our approach was not only legal and appropriate but it also benefited the patients. We promised the participants (1) free care for their families, including their children, if the complied with follow-up. That action became illegal with congressional ruling that one could not charge the US

Government more than a private individual. Continuing that course would have made us ineligible to bill for Medicare. (It also stopped the time-honored practice of "professional courtesy," i.e., the practice of giving free care to ministers, nuns, nurses, and colleagues.) We also had (2) a driver who picked the participants up at home and drove them to the clinic in a university van. That practice, also appreciated by the patients, ceased with the university attorney's ruling that the legal liability was too great. Finally, (3) when we lost a patient to follow-up due to a change of name or address, we would seek the help of the sheriff who would provide location and transport. That approach would certainly violate the rules of HIPAA today but, in fact, the patients loved the free transportation and the officers were glad to perform duties that were not dangerous. This is not an argument against the protection of human subjects, which we support strongly, but rather an explanation on how we were able to achieve such results. The NIH study, i.e., the "Longitudinal Assessment of Bariatric Surgery (LABS)" shows that a 92 % follow-up over time is still possible but so expensive that the NIDDK had to cancel it after only 7 years.

The data from these studies extending over 16 years were invaluable in documenting that the gastric bypass produced durable weight loss of >100 lbs. with an 8 % regain over the following years and that at the point where the mean follow-up was 9.2 years, the remission rate of type 2 diabetes was 83 % (Fig. 7.3) [35]. In addition, we noted the reduction of other comorbidities of the metabolic syndrome including hypertension and hyperlipidemias. Finally, these studies documented a reduction in mortality of 78 % in the diabetic cohort.

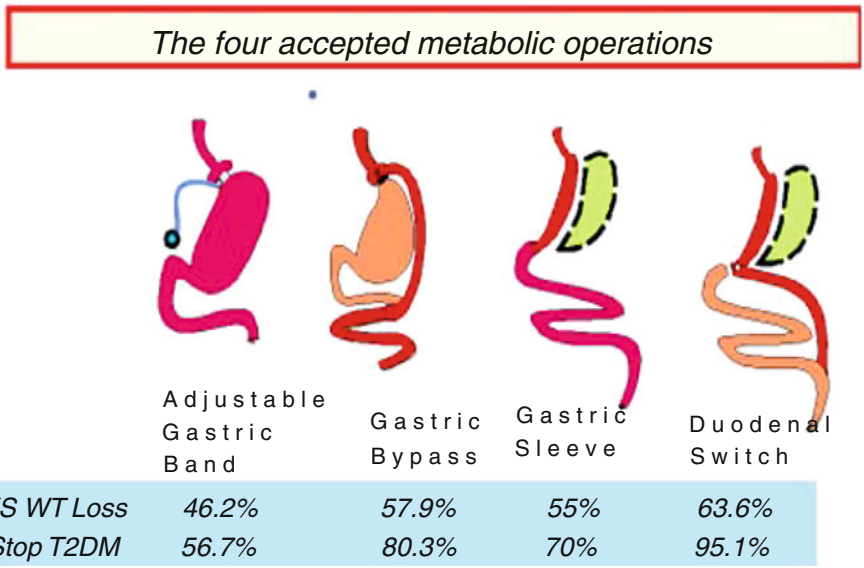

Fig. 7.3 Four accepted metabolic operations

Since then, there have been ample corroborations of these observations, especially by the Swedish Obesity Group, the NIDDK funded study, "Longitudinal Assessment of Bariatric Surgery (LABS), the Surgical Review Company's "BOLD" database, the NSQIP data base of the American College of Surgeons. There are variations in the data depending on the measures for full remission of diabetes, levels of blood pressure, duration of the disease, racial groups and differences in the operations but, overall, the data are all in accord in documenting the full and durable weight loss, remission of diabetes and comorbidities with a reduction in mortality. In addition, and still unexplained, is the reduction in the prevalence of solid cancer of about 65 % within 5 years [36].

7.6 Bariatric Surgery Centers of Excellence: The Pursuit of Safety

With the growing epidemic of obesity and diagrams depicting the surgical operations as just new variations of intestinal surgery, the procedures were quickly adopted by surgeons but too often with high morbidity and mortality rates.

The severely ill posed major technical challenges and the hospitals, the anesthesia services, the consulting medical colleagues and the support staff were not prepared for the difficulties involved in caring for these patients. Most were hypertensive, diabetic with limited pulmonary and cardiac reserve and, as in the development of cardiac surgery, the initial patients were also the sickest. Basic nursing equipment such as large wheel chairs, beds and adequate stretchers were frequently unavailable. Resources for imaging were not large or strong enough to address the problems of patients weighing over 400 lbs. Anesthesiologists had difficulties intubating these patients and calculating dosages for the anesthetic agents and fluids. Many surgeons were not familiar with operating and caring for patients of this size. Sometimes the available instruments were not long enough to reach the diaphragmatic hiatus in open operations. Most important, members of the nursing staff were not yet familiar with the lack of abnormal vital signs and the subtle warnings that were the first findings of an anastomotic leak in these immunoincompetent patients. And no one was prepared with the rapid deterioration of these patients who could progress from a mild discomfort to a fatal problem in a matter of hours. Accordingly there were major disparities in morbidity and mortality rates among institutions with mortality rates in some hospitals that exceeded ten percent. Intensive care units were strained with the care of complications due to anastomotic leaks and sepsis. Public skepticism concerning the safety of bariatric surgical procedures grew rapidly. Carriers refused to cover the operations, malpractice suits exploded, and liability insurance premiums became unaffordable. It became the "perfect storm" that led to widespread denial of the only effective life-saving therapy for the severely obese.

In 2003, it was evident that this crisis needed to be addressed. Accordingly, the officers of the American Society for Bariatric Surgery (Drs. Champion, Pories, and Wittgrove) founded the ASMBS Centers of Excellence program to recognize those hospitals with the best outcomes. With the nationwide support of the

bariatric surgeon, they not only required data with full reporting of outcomes but also set demanding criteria that included the requirement for the presence of experienced surgeons, reporting of all bariatric cases within 24 h of surgery, hospital facilities that were fully equipped to care for these challenging cases, availability of the full breadth of relevant consultants and a well-trained hospital staff (www.surgicalreview.org) [37]. In addition, a landmark conference was held at Georgetown University in 2005 where world leaders of bariatric surgery convened to help provide insight and consensus on what the standards of excellence should be. To assure quality control, the data were confirmed by site visits conducted by nurses experienced in the care of bariatric patients. Initially, the program was to be managed by the ASMBS but the Society was warned by counsel that such an arrangement would not have the credibility of an independent entity. Further, it would make the ASMBS vulnerable to legal actions by hospitals denied certification [38].

To avoid these concerns, the ASMBS founded the Surgical Review Corporation [38, 39] which, under the leadership of Gary Pratt, grew the program to include 425 hospitals and 22 countries. The goal of such a program would be to improve the outcomes of bariatric surgery and reduce the overall expense for bariatric surgery patients (including cost related to complications and comorbid conditions) [38]. To keep track of the data, the corporation developed a software program, the Bariatric Obesity Longitudinal Database (BOLD), a computer based entity that not only listed the presence or absence of a comorbidity but quantified these diseases. For example, the query on diabetes offered five possible answers: (1) no diabetes, (2) diabetes controlled by diet, (3) diabetes requiring the use of oral agents, (4) diabetes requiring the use of insulin, and (5) uncontrolled disease. Certification also required completion with each operation and visit within 24 h, affording access to data in real time. That approach allowed close tracking. For example, it became possible at the end of a day to determine how many patients had diabetes, how many were insured and the number of and reasons for readmissions.

This process was well received by the bariatric surgical community and subsequently implemented. The results were impressive. In a matter of just 2 years, the hospitals who would not commit the effort to become centers stopped providing metabolic surgery and the 90 days mortality dropped to 0.3 % throughout the USA. That figure comes into focus when compared to the mortality rates of other common operations: coronary artery bypass graft, 2–4 %; colectomy, 4–6 %; pancreatectomy, 6–10 %. The only common procedures that match bariatric surgery in safety are routine cholecystectomies and hip replacements. To emphasize the comparison even further, the 90-day mortality for normal deliveries in the USA is 0.1 %. These are remarkable figures given the fact that patients who undergo bariatric surgery are usually grade III anesthetic risks due to diabetes, hypertension, cardiopulmonary disease, immune-incompetence, and mental health challenges. Analyses of these data confirm that surgeons meeting centers of excellence requirements produce better outcomes than those who do not adhere to these standards [40–42].

Although the American College of Surgeons (ACS) participated in the founding of the SRC, appointing four ACS leaders to the 12 member Board of Directors, that organization became increasingly concerned about the evaluation of surgeons by an outside, uncontrolled organization, the inclusion of hospital performance as metric for surgical quality, disagreement about some of the requirements, and the use of the BOLD software instead of the NSQIP program that was in use by the College for other surgical specialties. Accordingly, the ACS developed its own Centers of Excellence program with differing requirements. By 2011, however, it became apparent that surgeons could not comply with two contradictory certification programs and the two programs merged to continue under the direction of the ACS. Over 450 facilities in the US are now certified as ACS Bariatric Surgery Centers of Excellence. A detailed description of the program, including the current requirements is available at https://www.facs.org/quality-programs/mbsaqip.

7.7 But How Does Metabolic Surgery Compare to the Best Medical Therapies?

Medical therapy for the treatment of morbid obesity has traditionally involved a combination of diet, behavior modification, medications, and exercise. According to a panel of experts at the National Institutes of Health [43] current medical models impart modest weight reduction that translates to a health benefit for the patient. The problem remains that weight loss by these means are relatively short-lived. The poor durability for weight loss when medical therapy alone is instituted is the force that has driven the development of surgical solutions to the obesity epidemic.

Even so, in spite of the excellent results reported in a number of clinical series, the medical community remained unimpressed. The meta-analyses of the world's literature published by Buchwald [8, 44] in addition to his reviews of the international bariatric surgical data documented the progress of the field better than that of any other specialty but even these vast databases were still not enough to convince the skeptics. What was really needed was a series of prospective, controlled, randomized trials that compare the surgical outcomes to those achieved by intensive medical therapy published in the best journals even though it was recognized that few patients in the USA actually reach ideal treatment.

That challenge has now been met as well. Other chapters in this book provide the details on the randomized clinical trials [45], funded by the NIH and reported by Schauer [46], by Mingrone [47], and by Ikrammudin [48] in the New England Journal of Medicine and JAMA. All of these trials, in addition to more recent ones reached the same conclusion, i.e., that surgical therapy was far superior to even the most intensive medical therapy in terms of control of weight, diabetes, and the associated comorbidities.

7.8 Changing Opinion: Acceptance of Metabolic Surgery as the Standard of Care

But Doctor, if bariatric surgery is the most effective treatment for my diabetes, why didn't you mention it?

Even though the rates obesity and diabetes have become our most costly diseases, metabolic surgery, the most effective therapy is still limited to less than 1 % of the population who could benefit. The data are sobering. The prevalence of obesity and diabetes has doubled in the last decade. Today over 70 % of US adults is overweight or obese [49]. One of every four adults over 65 is a diabetic. Finally the relationship of obesity to hypertension, hyperlipidemia, peripheral vascular disease and cancers are well known [50].

In spite of this national and growing epidemic to the point where obesity and its co-morbidities are our most costly diseases, insurance coverage for the most effective treatment has been a continuing and great challenge. In spite of the NIH Consensus Conference of 1991 that determined, based on rigorous long-term clinical trials, that metabolic surgery should be considered for the severely obese with a body mass index (BMI = kg/m^2) $\geq$ 40 or a BMI $\geq$ 35 with significant comorbidities, even 24 years later, securing coverage for the operations is a challenge due to demands by carriers that lack a scientific basis. Such requirements include a trial of diets for as long as 6 months, clearance by dieticians and psychiatrists—demands not expected of other abdominal procedures—as well as long delays. New and effective operations such as gastric sleeve procedures took years before they were approved in spite of excellent evidence that they were effective and safe.

Carriers often cite that they have provided ample support. By 2003 the number of bariatric operations in the USA increased from 16,000 to greater than 100,000 [51]. Today, over 200,000 Americans undergo metabolic procedures with over 350,000 performed annually throughout the world [52]. On closer examination, however, these numbers document that less than one percent of the American patients who could benefit from the surgery actually get the operations. Until Sugerman [53] convinced the administrators of Medicare in 2005 that metabolic surgery should be covered, carriers would barely listen but, at least, that hurdle has been overcome. Unfortunately, the uninsured and patients covered by Medicaid, those most likely to be burdened with the metabolic syndrome, still have great difficulties getting the surgery they need.

If there were a pill that, taken once, could produce a weight loss of 100 lbs. or more, achieve full remission of type 2 diabetes, hypertension, hyperlipidemia, and the other comorbidities and reduce mortality and even cut the chances for dying of cancer, the demand for such a medication would be overwhelming. And while there is no such pill, one of the safest abdominal operations can produce the same effect with an hour-long operation and 2 days in the hospital. It is amazing that so few have access to the surgery and even more amazing that their physicians do not recommend it.

The delays even in acceptance that obesity is harmful have been agonizing. It was not until 2013 that the American Medical Association classified obesity as a disease; however, there still are those who don't agree [54]. The AMA's criteria when defining obesity as a disease was as follows: an impairment of the normal functioning of some aspect of the body, characteristic signs or symptoms, and harm or morbidity (AMA House of Delegates 2013 resolution 420). Obesity easily fulfills each of these criteria. Impairment of normal function can readily be seen as the hormones associated with appetite control are often deranged in the obese [55]. These hormones include leptin, ghrelin, insulin, and polypeptide YY. Characteristic signs and symptoms associated with obesity are joint pain, sleep apnea, immobility, type 2 diabetes, and cardiovascular disease. Finally, a large analysis of over 50 prospective studies was performed and showed that all cause mortality increased by 30 % in obese compared to normal weight individuals [56]. Moreover, subjects that had a BMI >39 kg/m^2 were observed to have a median survival reduction of 10 years [14]. The AMA's stance on obesity has magnified the importance of producing an efficient therapy to combat this disease.

7.9 Providing a Voice: The Challenges of Educating the Public and Their Physicians

Even at this writing, most of the world remains unconvinced. Fortunately, through the leadership of Deitel, Sugerman, Buchwald, Scopinaro, Shikora, and Rosenthal, we now have three major publications with high impact values, "Surgery for Obesity and Allied Diseases" (SOARD), "Obesity Surgery" and "Bariatric Times" that offer reliable and trusted venues for reporting progress and offering quality articles that surgeons can send on to their colleagues.

7.9.1 Assuring Access

It would not be fair to assign the low application of metabolic surgery solely to the skepticism of colleagues and the resistance of carriers. Socioeconomic factors have also been shown to play a major role in determining why so few people that meet current medical eligibility requirements actually undergo a bariatric surgical procedure. In the USA, Martin and colleagues identified factors that drive this disparity and they include race, income, education level, gender, and insurance type [57].

In his study, he compared socioeconomic parameters of patients who by NIH criteria met eligibility requirements to undergo a bariatric procedure with individuals who did not. The results showed that patients who were eligible for surgery had lower family incomes, lower education levels, poor healthcare access, and were more likely to be non-white. Also, out of total 87,749 individuals who had a bariatric surgery procedure performed in the sample year 2006, most were white, with greater median incomes, and private insurance. By these results it seems as if the population that would be best served with surgery are the very individuals who may not have access to it. Perhaps removal of any discriminatory behavior by third party payers may be a step in the right direction.

There is also a supply and demand discrepancy in terms of how prevalent obesity has become. Global eradication of obesity is not feasible given the current health care and surgical resources available throughout the world. In the USA alone, it is estimated that it would take 5500 surgeons doing 400 cases per year, each for 10 years to treat the 22 million obese Americans [58]. The situation is even direr in developing nations. The response to this global crisis will indeed require both expanded surgical efforts as well as improved nonsurgical therapies to even begin to address the problem. Most would also agree that prevention of obesity through individual as well as societal philosophical changes on energy intake and expenditure is also key.

7.10 Opportunities for Basic Science: New Approaches to Study Mechanisms of Disease

In addition to providing the most effective therapies for our most costly and cruel chronic diseases, metabolic surgery has and continues to provide broad opportunities for basic research. Patients with diabetes can now be studied with the disease and then later without it. Access to tissues during surgery now provides ample specimens of blood, muscle, liver, skin and adipose tissues. Surgery has now provided a new window and, with luck and better understanding, we may be able to eradicate the metabolic syndrome much earlier and without operations.

7.11 Conclusions

The progress of metabolic surgery has been a remarkable achievement by a small group of surgeons, all active clinicians who have, in spite of great resistance and odds, offered a far better future for the severely obese and others burdened by the metabolic syndrome. We still have to exploit this great advance in medicine. As surgeons we must continue to focus on improving our craft and embrace the spirit of innovation which has allowed bariatric surgery to enjoy its current success. We must educate our non-bariatric colleagues that the surgery is effective and safe. We need to enlist their aid in the care of the bariatric patient who may present with a

complication unique to their modified gastrointestinal anatomy. Lastly we must challenge our community to allow the at risk population much needed access to life-saving surgical therapy.

References

1. Buchald H, Varco RL, editors. Metabolic surgery. New York: Grune and Stratton; 1978.
2. Townsend C, Takishama-Lacasa J, Latner J, Grandinetti, A, Kaholokula J. Ethnic and gender differences in ideal body size and related attitudes among Asians, Native Hawaiians, and Whites Hawaii. J Med Public Health. 2014;73(8):236–43.
3. Jarod Kintz. This Book is Not FOR SALE.
4. Kremen AJ, Linner JH, Nelson CH. An experimental evaluation of the nutritional importance of proximal and distal small intestine. Ann Surg. 1954;140(3):439–48. PMCID: PMC1609770.
5. Payne JH, DeWind LT, Commons RR. Metabolic observations in patients with jejunocolic shunts. Am J Surg. 1963;106:273–89.
6. Mir-Madjlessi SH, Mackenzie AH, Winkelman EI. Articular complications in obese patients after jejunocolic bypass. Cleve Clin Q. 1974;41(3):119–33.
7. Herbert C. Intestinal bypass for obesity. Can Fam Physician. 1975;21(7):56–9. PMCID: PMC2274667.
8. Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, Pories WJ, Bantle JP, Sledge I. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. Am J Med. 2009;122(3):248–56.e5.
9. Mason EE, Ito C. Gastric bypass in obesity. Surg Clin North Am. 1967;47(6):1345–51.
10. Griffen Jr WO. Bariatric surgery in the 1990s. Adv Surg. 1992;25:99–117.
11. Printen KJ, Mason EE. Gastric surgery for relief of morbid obesity. Arch Surg. 1973;106(4):428–31.
12. Scopinaro N, Gianetta E, Civalleri D, Bonalumi U, Bachi V. Bilio-pancreatic bypass for obesity: II. Initial experience in man. Br J Surg. 1979;66(9):618–20.
13. Buchwald H. Introduction and current status of bariatric procedures. Surg Obes Relat Dis. 2008;4(3 Suppl):S1–6. doi:10.1016/j.soard.2008.04.001.
14. Hess DS, Hess DW. Biliopancreatic diversion with a duodenal switch. Obes Surg. 1998;8(3):267–82.
15. DeMeester TR, Fuchs KH, Ball CS, Albertucci M, Smyrk TC, Marcus JN. Experimental and clinical results with proximal end-to-end duodenojejunostomy for pathologic duodenogastric reflux. Ann Surg. 1987;206(4):414–26. PMCID: PMC1493213.
16. Feng JJ, Gagner M. Laparoscopic biliopancreatic diversion with duodenal switch. Semin Laparosc Surg. 2002;9(2):125–9.
17. Paiva D, Bernardes L, Suretti L. Laparoscopic biliopancreatic diversion: technique and initial results. Obes Surg. 2002;12(3):358–61.
18. Christou NV, Sampalis JS, Liberman M, Look D, Auger S, McLean AP, MacLean LD. Surgery decreases long-term mortality, morbidity, and health care use in morbidly obese patients. Ann Surg. 2004;240(3):416–23. discussion 423–4.
19. Brolin RE. Long limb Roux en Y gastric bypass revisited. Surg Clin North Am. 2005;85(4):807–17.
20. Edwards MA, Jones DB, Ellsmere J, Grinbaum R, Schneider BE. Anastomotic leak following antecolic versus retrocolic laparoscopic Roux-en-Y gastric bypass for morbid obesity. Obes Surg. 2007;17(3):292–7.
21. Bertucci W, Yadegar J, Takahashi A, Alzahrani A, Frickel D, Tobin K, Kapur K, Namdari B, Dutson E, Gracia C, Mehran A. Antecolic laparoscopic Roux-en-Y gastric bypass is not associated with higher complication rates. Am Surg. 2005;71(9):735–7.

22. Abdel-Galil E, Sabry AA. Laparoscopic Roux-en-Y gastric bypass – evaluation of three different techniques. Obes Surg. 2002;12(5):639–42.
23. Marceau P, Biron S, Marceau S, Hould FS, Lebel S, Lescelleur O, Biertho L, Kral JG. Biliopancreatic diversion-duodenal switch: independent contributions of sleeve resection and duodenal exclusion. Obes Surg. 2014;24(11):1843–9.
24. Dhahri A, Verhaeghe P, Hajji H, Fuks D, Badaoui R, Deguines JB, Regimbeau JM. Sleeve gastrectomy: technique and results. J Visc Surg. 2010;147(5 Suppl):e39–46.
25. Kuzmak LI, Yap IS, McGuire L, Dixon JS, Young MP. Surgery for morbid obesity. Using an inflatable gastric band. AORN J. 1990;51(5):1307–24. Erratum in: AORN J 1990;51(6):1573.
26. Khoursheed M, Al-Bader I, Mohammad AI, Soliman MO, Dashti H. Slippage after adjustable gastric banding according to the pars flaccida and the perigastric approach. Med Princ Pract. 2007;16(2):110–3.
27. Belachew M, Legrand MJ, Defechereux TH, Burtheret MP, Jacquet N. Laparoscopic adjustable silicone gastric banding in the treatment of morbid obesity. A preliminary report. Surg Endosc. 1994;8(11):1354–6.
28. Wittgrove AC, Clark GW, Tremblay LJ. Laparoscopic gastric bypass, Roux-en-Y: preliminary report of five cases. Obes Surg. 1994;4(4):353–7.
29. Schauer PR, Ikramuddin S, Gourash W, Ramanathan R, Luketich J. Outcomes after laparoscopic Roux-en-Y gastric bypass for morbid obesity. Ann Surg. 2000;232(4):515–29. PMCID: PMC1421184.
30. Wilson EB, Sudan R. The evolution of robotic bariatric surgery. World J Surg. 2013;37(12):2756–60. doi:10.1007/s00268-013-2125-3.
31. Edelson PK, Dumon KR, Sonnad SS, Shafi BM, Williams NN. Robotic vs. conventional laparoscopic gastric banding: a comparison of 407 cases. Surg Endosc. 2011;25(5):1402–8.
32. Diamantis T, Alexandrou A, Nikiteas N, Giannopoulos A, Papalambros E. Initial experience with robotic sleeve gastrectomy for morbid obesity. Obes Surg. 2011;21(8):1172–9.
33. Sanchez BR, Mohr CJ, Morton JM, Safadi BY, Alami RS, Curet MJ. Comparison of totally robotic laparoscopic Roux-en-Y gastric bypass and traditional laparoscopic Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2005;1(6):549–54.
34. Sudan R, Bennett KM, Jacobs DO, Sudan DL. Multifactorial analysis of the learning curve for robot-assisted laparoscopic biliopancreatic diversion with duodenal switch. Ann Surg. 2012;255(5):940–5.
35. Pories WJ, Swanson MS, MacDonald KG, Long SB, Morris PG, Brown BM, Barakat HA, deRamon RA, Israel G, Dolezal JM, et al. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. Ann Surg. 1995;222(3):339–50. PMCID: PMC1234815.
36. Adams TD, Hunt SC. Cancer and obesity: effect of bariatric surgery. World J Surg. 2009;33(10):2028–33.
37. Pratt GM, McLees B, Pories WJ. The ASBS Bariatric Surgery Centers of Excellence program: a blueprint for quality improvement. Surg Obes Relat Dis. 2006;2(5):497–503.
38. Bradley DW, Sharma BK. Centers of Excellence in Bariatric Surgery: design, implementation, and one-year outcomes. Surg Obes Relat Dis. 2006;2(5):513–7.
39. Pories W. Surgical Review Corporation: centers of excellence. Surg Obes Relat Dis. 2004.
40. Pratt GM, Learn CA, Hughes GD, Clark BL, Warthen M, Pories W. Demographics and outcomes at American Society for Metabolic and Bariatric Surgery Centers of Excellence. Surg Endosc. 2009;23(4):795–9.
41. Dixon J. Survival advantage with bariatric surgery: report from the 10th international congress on obesity. Surg Obes Relat Dis. 2006;2(6):585–6.
42. Finkelstein EA, Ruhm CJ, Kosa KM. Economic causes and consequences of obesity. Annu Rev Public Health. 2005;26:239–57.
43. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Expert panel on the identification, evaluation, and treatment of

overweight in adults. Am J Clin Nutr. 1998;68(4):899–917.
44. Buchwald H, Buchwald JN, McGlennon TW. Systematic review and meta-analysis of medium-term outcomes after banded Roux-en-Y gastric bypass. Obes Surg. 2014;24(9):1536–51.
45. Gloy VL, Briel M, Bhatt DL, Kashyap SR, Schauer PR, Mingrone G, Bucher HC, Nordmann AJ. Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomized controlled trials. BMJ. 2013;347:f5934.
46. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Brethauer SA, Navaneethan SD, Aminian A, Pothier CE, Kim ES, Nissen SE, Kashyap SR, STAMPEDE Investigators. Bariatric surgery versus intensive medical therapy for diabetes – 3-year outcomes. N Engl J Med. 2014;370(21):2002–13.
47. Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Leccesi L, Nanni G, Pomp A, Castagneto M, Ghirlanda G, Rubino F. Bariatric surgery versus conventional medical therapy for type 2 diabetes. N Engl J Med. 2012;366(17):1577–85.
48. Ikramuddin S, Korner J, Lee WJ, Connett JE, Inabnet WB, Billington CJ, Thomas AJ, Leslie DB, Chong K, Jeffery RW, Ahmed L, Vella A, Chuang LM, Bessler M, Sarr MG, Swain JM, Laqua P, Jensen MD, Bantle JP. Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia: the Diabetes Surgery Study randomized clinical trial. JAMA. 2013;309(21):2240–9.
49. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. JAMA. 2012;307(5):491–7.
50. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003; 348(17):1625–38.
51. Steinbrook R. Surgery for severe obesity. N Engl J Med. 2004;350(11):1075–9.
52. Dumon KR, Murayama KM. Bariatric surgery outcomes. Surg Clin North Am. 2011;91(6):1313–38.
53. Kral JG, Christou NV, Flum DR, Wolfe BM, Schauer PR, Gagner M, Ren C, Stiles S, Wadden TA, Tanner S, Stratiff R, Pories WJ, Sugerman HJ. Medicare and bariatric surgery. Surg Obes Relat Dis. 2005;1(1):35–63.
54. Allison DB, Downey M, Atkinson RL, Billington CJ, Bray GA, Eckel RH, Finkelstein EA, Jensen MD, Tremblay A. Obesity as a disease: a white paper on evidence and arguments commissioned by the Council of the Obesity Society. Obesity (Silver Spring). 2008;16(6):1161–77.
55. Sumithran P, Prendergast LA, Delbridge E, Purcell K, Shulkes A, Kriketos A, Proietto J. Long-term persistence of hormonal adaptations to weight loss. N Engl J Med. 2011;365(17): 1597–604.
56. Prospective Studies Collaboration, Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, Qizilbash N, Collins R, Peto R. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009;373(9669):1083–96. PMCID: PMC2662372.
57. Martin M, Beekley A, Kjorstad R, Sebesta J. Socioeconomic disparities in eligibility and access to bariatric surgery: a national population-based analysis. Surg Obes Relat Dis. 2010;6(1):8–15.
58. Richards NG, Beekley AC, Tichansky DS. The economic costs of obesity and the impact of bariatric surgery. Surg Clin North Am. 2011;91(6):1173–80.
59. Browning D. To show our humanness–relational and communicative competence in pediatric palliative care. Bioethics Forum. 2002;18(3/4):23–8.
60. Harrold LR, Andrade SE. Medication adherence of patients with selected rheumatic conditions: a systematic review of the literature. Semin Arthritis Rheum. 2009;38(5):396–402.
61. Nicassio PM, Kay MA, Custodio MK, Irwin MR, Olmstead R, Weisman MH. An evaluation of a biopsychosocial framework for health-related quality of life and disability in rheumatoid arthritis. J Psychosom Res. 2011;71(2):79–85.
62. Nicassio PM, Schuman C, Radojevic V, Weisnman MH. Helplessness as a mediator of health status in fibromyalgia. Cognit Ther Res. 1999;23(2):181–96.

Part II

What We Know About Mechanisms of Weight Loss Surgery

Obesity and Cancer

8

Robert W. O'Rourke

8.1 Introduction

Obesity is a strong risk factor for multiple types of cancer. The mechanisms underlying this association are multiple and include increased systemic inflammation, increased alterations in the systemic hormonal milieu, and direct paracrine tumor-promoting effects of adipose tissue, adipose tissue stem cells, and mature adipocytes. These complex mechanisms generate a carcinogenic milieu in multiple tissues in obesity.

8.2 Epidemiology

The risk ratios for the incidence of and mortality from multiple cancers increase with increasing body mass index (BMI). Endometrial cancer demonstrates the strongest association with obesity, with a mortality risk ratio of 1.5 for overweight women (BMI 25–30), 2.5 for class 1 obesity (BMI 30–35), and over 6 in class 3 obesity (BMI > 40). Other cancers that are strongly associated with obesity include colon, renal, pancreatic, and esophageal adenocarcinomas. Overall, obesity is estimated to be a dominant causative factor in up to 20 % of all cases of cancer [1, 2].

Exceptions exist to the positive correlation between obesity and cancer, including lung cancer, squamous cell cancer of the esophagus, cancers of the head and neck [1–3], prostate cancer [4, 5], and premenopausal breast cancer [2], all of which demonstrate no clear correlation with obesity, or in some cases, a

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negative correlation. Body weight-independent risk factors such as hormonal status and smoking may explain these exceptions to the otherwise strong association between obesity and cancer. Obesity not only affects cancer incidence and long-term mortality, but also influences treatment outcomes. For example, despite conflicting data regarding obesity's effects on prostate cancer incidence, data clearly demonstrate decreased survival among obese patients compared to lean patients who develop prostate cancer [6]. Obese patients with colon cancer, lymphoma, and breast cancer also suffer worse treatment outcomes compared with lean patients with similar cancers matched for stage. The effects of obesity on treatment efficacy may underlie some of these observations, including underdosing of chemotherapy, reduced delivery of radiation therapy, and technical challenges associated with extirpative surgery. Biologic effects of adipose tissue may also interfere with cancer therapy; increased aromatase activity from adipose tissue may interfere with aromatase inhibitor therapy in obese breast cancer patients [7], for example.

In contrast to these data, in some cases obesity appears to exert a beneficial effect on survival in patients already diagnosed with cancer, a phenomenon termed the "obesity paradox." While a strong risk factor for developing renal cell cancer, obesity predicts extended survival in those with a diagnosis of renal cell carcinoma, even after controlling for tumor stage [8]; similar albeit conflicting data exist in endometrial, head and neck, rectal, and esophageal cancers. The mechanisms underlying such protective effects are poorly defined and the associated epidemiologic data are complex and debated. Some argue that increased adipose tissue stores provide a protective "nutrient buffer" for obese patients undergoing cancer treatment. Along these lines, obesity appears to be associated with decreased chemo- and radiation-therapy toxicities which may contribute to increased treatment efficacy [9]. Alternatively, artifact may underlie observations that support the obesity paradox; for example, limitations in BMI as a metric of obesity, which most studies utilize, may mask the effects of increased adiposity on cancer in older patients (who generally have higher levels of adiposity at lower BMI due to decreased muscle mass) or the disproportionate effect of visceral adipose tissue on cancer pathogenesis; alternative measures of obesity such as waist circumference or more sophisticated measures of body fat may reveal hidden associations with cancer. Selection bias and other statistical confounders have also been suggested as explanations for the obesity paradox [10]. The obesity paradox therefore remains controversial.

The relationship between obesity and cancer risk is complex and multiple variables impact on this association. Multiple factors indirectly related to obesity, including gender, ethnicity, dietary factors, the presence of metabolic diseases including diabetes, and differences in body habitus, including subcutaneous and visceral adiposity, all contribute to cancer risk independent of BMI and confound epidemiologic analyses. Nonetheless, despite these complexities, obesity is clearly a dominant independent risk factor for cancer.

8.3 Inflammation

Inflammation is a dominant mechanism underlying the pathogenesis of cancer. Inflammatory bowel disease, hepatitis, and pancreatitis among others are all associated with an increased risk of cancer in involved tissues independent of body weight. Immune leukocytes elaborate multiple cytotoxic molecules to carry out immune responses, all of which have potentially mutagenic effects; these include reactive oxygen species, free radicals, antibodies, and cytolytic proteins. Cytokine expression is also a fundamental component of immune and inflammatory responses; cytokines potentiate leukocyte activation and proliferation, propagating inflammatory responses via autocrine and paracrine effects. Cytokines exert multiple effects on nonimmune cells as well, including controlling endothelial cell function, angiogenesis, and proliferation and apoptosis in multiple cell types. Conceptually, the combination of increased elaboration of mutagenic inflammatory weapons combined with increased expression of pro-proliferative cytokines creates an environment predisposed to carcinogenesis.

Obesity is associated with a state of chronic systemic low-grade inflammation that has its genesis in adipose tissue and afflicts all tissues. This inflammatory state is a direct consequence of failure of adipocyte nutrient buffering in the obese state. With progressive obesity, adipocyte nutrient storage capacity is overwhelmed. Adipocytes increase in size to a diameter beyond 100 μm, the diffusion distance of oxygen, which is thought to establish a state of cellular hypoxia within adipose tissue. This hypoxic state, in parallel with direct, hypoxia-independent effects of nutrient toxicity, triggers a series of cell stress responses in adipocytes, including endoplasmic reticulum and oxidative stresses, which in turn lead to adipocyte apoptosis and necrosis. These events generate an inflammatory response designed to scavenge apoptotic and necrotic cells. This inflammatory response is characterized by a diverse leukocyte infiltrate that includes macrophages, T-cells, B-cells, NK cells, eosinophils, and other immune cell subtypes, within which adipose tissue macrophages play a central role, mediating local (adipose tissue-based) and systemic insulin resistance and elaborating multiple pro-inflammatory cytokines. Adipose tissue inflammation is further amplified as a result of direct effects of excess nutrients on leukocytes. Free fatty acids, glucose, and downstream metabolites such as diacyglycerol, ceramides, and advanced glycation end-products, directly trigger inflammation by binding and activating Toll-like receptors (TLR) and receptors for advanced glycation end-products (RAGE) expressed by leukocytes, creating a positive feedback loop that perpetuates adipose tissue inflammation. TLR and RAGE ligands thus represent direct molecular links between metabolism and inflammation.

Early in the development of obesity, adipocyte hypertrophy is modest and nutrient excess, cell stress, and inflammation remain confined to adipose tissue. With progressive obesity, however, adipocyte hypertrophic limits and nutrient storage capacity are exceeded, adipose tissue dysfunction progresses, and excess nutrients and metabolites overflow from adipose tissue into the systemic circulation. As other tissues not as well adapted to nutrient processing and storage as adipose tissue are

exposed to excess nutrients and metabolites, the same cell stress processes that initially unfold in adipose tissue "metastasize" to other organs, establishing a low-grade inflammatory state in all tissues that underlies the pathogenesis of malignant and nonmalignant metabolic disease. Adipose tissue overflow and involvement of non-adipose tissues in inflammatory and cell stress processes form the basis of systemic metabolic disease.

Cytokines are central mediators of the inflammatory state in obesity and dominant effectors of carcinogenesis on the context of overweight and obesity. TNF-α was one of the first cytokines implicated in obesity. Bruce Spiegelman's laboratory demonstrated in 1993 that adipose tissue in obesity was a primary source of TNF-α, and furthermore, that TNF-α played a central role in mediating insulin resistance in the context of obesity [11]. This discovery was one of the first demonstrations of an immunoregulatory role for adipose tissue and a mechanistic link between inflammation and metabolism. While other cytokines have been implicated in obesity-related inflammation, TNF-α remains a central player. TNF-α levels are elevated in adipose tissue and in serum in obese mice and humans. Independent of obesity, TNF-α also plays an important role in the pathogenesis of multiple types of cancer. TNF-α has been implicated in cancers of the skin, liver and lymphoid system in murine models; TNF-α knockout mice are protected from chemically induced skin and colon cancers [12, 13]. Similar murine models implicate other inflammatory cytokines including IL-1, IL-6, and IL-8 in carcinogenesis, and expression of these cytokines is also elevated in obesity. Human data confirms a role for cytokines in cancer pathogenesis: for example, IL-6 and IL-8 gene polymorphisms are linked to gastric, colorectal, and esophageal cancers [14, 15]. Adipose tissue macrophages are a dominant source of inflammatory cytokines in obesity, although other cells within adipose tissue, including T-cells, B-cells, and adipocytes, also express inflammatory cytokines.

The specific mechanisms by which inflammatory cytokines contribute to carcinogenesis are multiple. Cytokines activate inducible nitric oxide synthase, and the resultant increase in nitric oxide levels has been shown to promote tumor proliferation, metastasis, and angiogenesis in multiple models [16]. Cytokines trigger NFκB signaling, a central cell signaling pathway in carcinogenesis that promotes inflammation and regulates cancer cell proliferation and apoptosis to provide a growth advantage to cancer cells [17, 18]. Cytokines are also tropic factors, promoting cell proliferation in most non-transformed and transformed cells via multiple signaling pathways that include not only NFkB, but JAK/Stat, Akt, AMPK, and mTOR signaling. For example, TNF-α promotes proliferation of stromal and endothelial cells, potentiating fibrosis and angiogenesis within the tumor microenvironment. IL-1 is similarly required for angiogenesis and tumorigenesis in multiple animal models [19, 20]. IL-6 and IL-8, also increased in expression in obesity, demonstrate a pro-proliferative action on a broad range of cell types. Finally, virtually all cytokines play important roles in cell adhesion, chemotaxis, and migration, which along with other inflammatory chemokines, may contribute to tumor metastasis.

Type II diabetes spans the interface between metabolism, inflammation, and carcinogenesis, and is an independent risk factor for multiple cancers, with the highest

risk ratios associated with pancreatic and liver cancers. Inflammation is a major contributor to the pathogenesis of diabetes independent of cancer. Aspirin, a potent anti-inflammatory agent, was shown to ameliorate diabetes as early as 1901 [21], and modern anti-inflammatory drugs such as salsalate, a salicylate-derivative, as well as anti-TNF-α and anti-IL-1 antibodies are currently in clinical trials as therapy for diabetes [22–24]. Parallel data demonstrate that long-term therapy with aspirin and non-steroidal anti-inflammatory drugs reduce cancer risk [25, 26]. These observations demonstrate that inflammation, metabolism, and carcinogenesis are intertwined, and that inflammation-based therapy for metabolic disease has potential as cancer therapy.

8.4 Endocrine Causes of Obesity-Related Cancer

Nutrient excess induces marked alterations in the systemic hormonal milieu characterized by increased expression of multiple anabolic growth factors, including insulin, IGF, steroid hormones, adipokines, and gut hormones. This hormonal environment promotes proliferation of pre-neoplastic and neoplastic cells.

Insulin plays a dominant role in promoting a carcinogenic hormonal milieu in obesity. As adipose tissue buffering capacity is exceeded, free fatty acids spill into the systemic circulation, inducing systemic lipotoxicity in peripheral tissues. Skeletal muscle and the liver are primary targets. These tissues respond to excess lipids by shifting energy utilization from glucose to fatty acid oxidation. This shift in cellular energy homeostasis is the result of a transcriptional program that involves decreased expression of insulin receptors, glucose transporters, and insulin signaling molecules and increased expression of enzymes involved in fatty acid catabolism. These changes underlie skeletal muscle insulin resistance and lead to systemic hyperglycemia, to which pancreatic islet beta cells respond with a compensatory increase in insulin secretion. As diabetes progresses, pancreatic beta cell exhaustion eventually occurs as a result of chronic over-secretion of insulin, leading to end-stage insulin-dependent diabetes. Prior to this, however, cells throughout the body are exposed to elevated insulin levels. These responses underlie the development of peripheral insulin resistance and hyperinsulinemia, central metabolic features of obesity.

Hyperinsulinemia in obesity has broad effects beyond glucose homeostasis. Insulin is a potent growth factor that promotes proliferation and inhibits apoptosis in virtually all benign and malignant cells. Insulin has also been shown to induce tumorigenesis in multiple in vitro and in vivo models. Increased insulin levels in humans are independently associated with multiple cancers, including those most strongly associated with obesity, such as colon, endometrial, pancreas, and breast [27–29]. Insulin receptor expression is increased in multiple cancers, including breast, prostate, hepatocellular, and leukemic cancers [30, 31]. Insulin also promotes the expression of insulin-like growth factor-1 (IGF-1), a hormone secreted by the liver that stimulates the growth of numerous cancers. IGF-1 mediates its tropic effects by binding its own receptor as well as the insulin receptor, both of which are

over-expressed in many tumors [30]. IGF-1 also induces angiogenesis which has been linked to cancer progression [32]. Serum IGF-1 levels are increased in many cancers in humans, and murine studies demonstrate a growth-promoting effect of IGF-1 on the growth of multiple types of cancer [27, 29].

Steroid hormones also contribute to obesity-related cancer. Steroid hormones are important contributing agents in multiple cancers independent of obesity, including breast, endometrial, and ovarian cancers, and serum levels of steroid hormone levels correlate directly with the risk of these cancers in humans [33, 34], while numerous in vitro and in vivo experimental models support a role for steroid hormones in tumor progression. A number of distinct mechanisms contribute to increased steroid hormone levels in obesity. Estrogen levels are increased as a result of increased adipose tissue mass, a site of conversion of androgens to estradiol by aromatase which is expressed in white adipose tissue. In postmenopausal women, adipose tissue becomes a dominant source of estrogen as ovarian estrogen secretion diminishes; in obese premenopausal women, adipose tissue may also represent a dominant source of estrogen. Increased adipose tissue mass leads to increased expression of TNF-α, IL-6, and leptin, all adipose tissue products, and these cytokines and adipokines induce aromatase expression by adipocytes, exacerbating adipose tissue steroidogenesis [35]. Furthermore, insulin, IGF-1, and glucose, all increased in obesity, inhibit expression of sex hormone-binding globulin in the liver, increasing systemic steroid bioavailability [36]. Finally insulin induces ovarian and adrenal androgen synthesis, increasing androgen levels as well as estradiol levels by providing androgen substrate for adipose tissue aromatase. Serum levels of steroid hormones correlate positively with BMI [37], and are decreased with weight loss, with a reduction in cancer risk [38, 39]. Induction of obesity with high-fat diet in animals is associated with increased incidence and growth of steroid hormone-sensitive tumors. Steroid-sensitive breast cancer is strongly associated with obesity, which is more often associated with estrogen receptor $(ER)^+$ breast cancers [40, 41]. Furthermore, while ER^+ breast cancers generally have a more favorable prognosis than ER^- tumors, this may not be true in the obese, as mortality associated with ER^+ tumors is substantially higher in obese patients compared with lean patients [42], suggesting that elevated circulating estrogen in obesity may stimulate ER^+ breast cancer growth.

Dysregulated adipokine expression and activity contributes to the procarcinogenic state in obesity. Leptin, secreted primarily by adipocytes, and adiponectin, secreted by both adipocytes and adipose tissue stromal cells, are dominant adipokines with pleiotropic and opposing effects. Leptin expression is increased in obesity, and while conflicting functional data exist, for the most part leptin appears to promote metabolic disease, insulin resistance, and inflammation. Adiponectin in contrast is expressed at lower levels in obesity compared to lean states, and manifests effects that oppose leptin, attenuating metabolic disease, insulin resistance, and inflammation. Leptin and adiponectin manifest similar opposing effects on neoplastic growth, as serum levels of leptin correlate directly, and adiponectin levels correlate indirectly, with the risk of multiple cancers, including breast, colon, prostate, endometrial, gastric, colorectal, and leukemic cancers [43–46]. In vitro and

in vivo models are also consistent with this dichotomy, with leptin promoting and adiponectin inhibiting proliferation, growth, angiogenesis, and invasion of multiple types of cancer cells and tumors in in vitro and in vivo models. Cancer cells mutate to take advantage of the effects of adipokines on tumorigenesis: hepatocellular and breast cancers up-regulate expression of the leptin receptor, a phenomenon that associated with worse prognosis [47]. Numerous adipokines in addition to leptin and adiponectin are dysregulated in obesity, contribute to metabolic disease, and are implicated in cancer pathogenesis, including visfatin, resistin, and apelin. This family of proteins regulates diverse aspects of physiology that contribute to cancer progression, and targeting adipokine signaling holds promise as cancer therapy. Leptin antagonist peptides and adiponectin agonists are under study in preclinical models as potential therapeutic agents for breast endometrial and cancers [48, 49].

8.5 Adipocyte-Tumor Cross Talk

Emerging data demonstrate that adipose tissue, adipose tissue stem cells, and mature adipocytes directly promote cancer initiation and progression. Histologic data from human cancers support a role for adipocytes in cancer progression: steatosis in the liver and the pancreas has been linked to hepatocellular and pancreatic cancers, while adipocyte infiltration of pancreas and breast tissues is associated with increased disease progression and aggressiveness of cancers in these organs [50–52]. Data from in vitro cell culture models as well as in vivo murine models of cancer demonstrate that adipocytes potentiate proliferative and invasive capacities and in vivo progression and metastasis of multiple cancers [53–56].

The anatomic basis of adipocyte-tumor cross talk is complex, and adipocytes and other adipose tissue components influence pre-neoplastic and neoplastic cells via multiple endocrine and paracrine mechanisms. Adipokines and steroid hormones secreted directly from canonical adipose tissue depots, as well as secondary endocrine effects of increased adipose tissue mass (e.g., hyperinsulinemia), exert tropic endocrine effects on multiple target tissues and have been implicated in carcinogenesis. Many tumors associated with obesity reside near anatomic adipose tissue depots, including renal, pancreatic, hepatic, and colon, and are thus also subject to paracrine effects of adipokines and other adipocyte products. Renal and pancreatic cancers arise in tissues surrounded by retroperitoneal and visceral fat and demonstrate strong correlations with BMI. In addition to the endocrine effects of formal anatomic adipose tissue depots on remote tissues, adipocytes are central components of the stromal microenvironment of multiple tissues in which tumors arise, and thus exert paracrine pre-neoplastic and neoplastic cells. Finally, provocative data demonstrate that adipose tissue stem cells are recruited to tumor tissues from remote sites, and migrate to tumors in response to tumor-secreted chemotactic factors and differentiate into adipocytes, fibroblasts, and endothelial cells that contribute to the tumor stromal microenvironment [57].

Nutrient delivery is an important mechanism by which adipocytes promote carcinogenesis. Tumor cells and adipocytes participate in cross talk which reprograms

adipocyte metabolism to enhance metabolic energy substrate shuttling from adipocytes to cancer cells: ovarian cancer cells, for example, inhibit lipogenesis and induce lipolysis in adipocytes, promoting free fatty acid transfer to tumor cells [58]; breast cancer cells similarly induce a dedifferentiated, fibrotic, glycolytic phenotype in adipocytes that predisposes peritumoral adipocytes to increased energy substrate transfer to tumor cells [59], while adipocytes provide glutamine to leukemia cells, contributing to chemoresistance [60].

8.6 Other Contributors

Excess nutrients directly regulate tumor cell growth independent of adipocytes, inflammatory leukocytes, or other accessory cells. Saturated free fatty acids promote cancer cell proliferation, while unsaturated free fatty acids promote apoptosis [61, 62], effects mediated in part via regulation of mTOR signaling [63]. Similar data demonstrate tumor-promoting effects of advanced glycation end products [64]. Obesity is also associated multiple micronutrient deficiencies that are implicated in cancer pathogenesis, including deficiencies of vitamin D, selenium, and magnesium. These observations have sparked study of dietary modification and micronutrient supplementation for cancer prevention and treatment in the context of both obese and lean states.

Alterations in the microbiome in obese animals and humans have garnered significant recent attention, and have also been implicated in cancer pathogenesis in the context of obesity [65]. Stool transfer from obese animals induces obesity in lean animals. Microbiome changes observed in obese humans include a shift in major bacterial archaea with an increase in gram-negative gut bacteria which is thought to contribute to increased absorption of lipopolysaccharide from the gut, exacerbating the inflammatory state associated with obesity. A host of other systemic physiologic effects have been linked to obesity-related aberrations in the microbiome, including alterations in bile acid metabolism that may contribute to oxidative damage and mutagenesis. While a nascent field, research into the role of the microbiome in obesity and cancer is rapidly evolving.

8.7 Cell Signaling Pathways Linking Energy Homeostasis and Carcinogenesis

Cellular metabolism is tightly linked to cell survival, which is in turn determined by the balance between proliferation and apoptosis thresholds, which are regulated in response to nutrient delivery. Nonmalignant cells proliferate when nutrients are plentiful, but shift to a catabolic, non-proliferative, apoptosis-prone state when nutrients are scarce. In cancer, however, proliferation and apoptosis are uncoupled from nutrient status, allowing malignant cells to proliferate regardless of nutrient availability. This central feature of cancer cell metabolism provides tumor cells with a growth advantage and distinguishes malignant cells from nonneoplastic cells.

Akt is a dominant signaling mediator that links metabolism and proliferation in all cells. Akt is activated by insulin and regulates cellular glucose and lipid metabolism. Akt in parallel promotes proliferation and inhibits apoptosis via activation of the downstream signaling mediator mammalian target of rapamycin (mTOR), thus linking nutrient status to cell proliferation. AMP-activated protein kinase (AMPK), in contrast, is a central cell signaling mediator that is activated when nutrient stores are low. AMPK induces cellular catabolism by inhibiting Akt, and down-regulates proliferation by inhibiting mTOR, acting as a brake on cell proliferation when nutrients are scarce. Akt and AMPK thus act as opposing forces that link cellular energy homeostasis with cell growth in response to nutrient availability. Levels of the adipokine adiponectin, which are decreased in obesity, activate AMPK; the adipokine milieu in obesity thus predisposes cells towards an anabolic, proliferative state. Furthermore, multiple cancers exploit Akt-AMPK signaling to generate a growth advantage over non-neoplastic cells. Mutations in Akt and AMPK pathways are among the most common in all cancers and contribute to the decoupling of cancer cell proliferation from nutrient status. Activating mutations in Akt are present in 20–100 % of human all tumors. Downstream regulatory genes that interact with Akt and AMPK to modify their functions are also commonly mutated in cancer, most notably PTEN and LKB1, tumor suppressor genes associated with multiple hereditary and sporadic cancers. Oncogenic mutations in PTEN and LKB1 increase Akt activity and inhibit AMPK activity regardless of nutrient availability, further contributing to the uncoupling cell proliferation from nutrient status commonly observed in malignant cells.

While debated, data suggest that long-term treatment with the diabetic agent metformin attenuates cancer risk [66]. One of a number of proposed mechanisms for this effect is activation of AMPK activity. Similar data attribute a cancer-protective effect to the diabetic drugs thiazolidinediones. These observations have generated interest in the use of current and next-generation metabolic drugs as treatment for cancer. Research exploring agents that regulate Akt and AMPK activity as cancer therapeutics are in progress. Agents targeting cell metabolism hold significant promise for cancer prevention and therapeutics.

8.8 Future Directions

Diet- and bariatric surgery-induced weight loss reduces the risk of obesity-related cancer [67, 68], and is associated with reductions in inflammatory mediators, anabolic hormones including insulin, IGF, and steroids, and serum adipokine levels. Surgical and non-surgical interventions appear to have qualitatively different mechanisms of action with respect to carcinogenesis. Bariatric surgery, but not diet-induced weight loss, may be associated with increased metabolic rate with a concomitant shift in cellular energy homeostasis towards catabolic AMPK-dominated signaling, suggesting that surgery influences energy homeostasis at the cellular level. These findings reinforce the concept of cancer as a disorder of metabolism and suggest a role for bariatric and metabolic surgery in cancer

prevention. Pharmacologic therapy for cancer based on inflammatory mediators, metabolic modulating drugs such as metformin and AMPK agonists, and adipokine-based drugs are also areas of active research. An understanding of the molecular and cellular mechanisms that underlie the processes that mediate the link between obesity, metabolism, and carcinogenesis will lead to novel metabolism-based cancer therapy.

References

1. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003;348(17):1625–38.
2. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008;371(9612):569–78.
3. Leung CC, Lam TH, Yew WW, Chan WM, Law WS, Tam CM. Lower lung cancer mortality in obesity. Int J Epidemiol. 2011;40:174–82.
4. Giovannucci E, Rimm EB, Liu Y, et al. Body mass index and risk of prostate cancer in U.S. health professionals. J Natl Cancer Inst. 2003;95:1240–4.
5. Engeland A, Tretli S, Bjorge T. Height, body mass index, and prostate cancer: a follow-up of 950,000 Norwegian men. Br J Cancer. 2003;89:1237–42.
6. MacInnis RJ, English DR. Body size and composition and prostate cancer risk: systematic review and meta-regression analysis. Cancer Causes Control. 2006;17(8):989–1003.
7. Pfeiler G, Königsberg R, Hadji P, Fitzal F, Maroske M, Dressel-Ban G, Zellinger J, Exner R, Seifert M, Singer C, Gnant M, Dubsky P. Impact of body mass index on estradiol depletion by aromatase inhibitors in postmenopausal women with early breast cancer. Br J Cancer. 2013;109(6):1522–7.
8. Choi Y, Park B, Jeong BC, et al. Body mass index and survival in patients with renal cell carcinoma: a clinical-based cohort and meta-analysis. Int J Cancer. 2013;132(3):625–34.
9. Wang J, Myles B, Wei C, Chang JY, Hofstetter WL, Ajani JA, Swisher SG, Cox JD, Komaki R, Liao Z, Lin SH. Obesity and outcomes in patients treated with chemoradiotherapy for esophageal carcinoma. Dis Esophagus. 2014;27(2):168–75.
10. Renehan AG. The "obesity paradox" and survival after colorectal cancer: true or false? Cancer Causes Control. 2014;25(10):1419–22.
11. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science. 1993;259(5091):87–91.
12. Lind MH, Rozell B, Wallin RP, van Hogerlinden M, Ljunggren HG, Toftgard R, et al. Tumor necrosis factor receptor 1-mediated signaling is required for skin cancer development induced by NF-kappaB inhibition. Proc Natl Acad Sci U S A. 2004;101(14):4972–7.
13. Kitakata H, Nemoto-Sasaki Y, Takahashi Y, Kondo T, Mai M, Mukaida N. Essential roles of tumor necrosis factor receptor p55 in liver metastasis of intrasplenic administration of colon 26 cells. Cancer Res. 2002;62(22):6682–7.
14. Camp NJ, Slattery ML. Classification tree analysis: a statistical tool to investigate risk factor interactions with an example for colon cancer (United States). Cancer Causes Control. 2002;13:813–23.
15. Savage SA, Abnet CC, Mark SD, Qiao YL, Dong ZW, Dawsey SM, et al. Variants of the IL8 and IL8RB genes and risk for gastric cardia adenocarcinoma and esophageal squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev. 2004;13(12):2251–7.
16. Cheng H, Wang L, Mollica M, Re AT, Wu S, Zuo L. Nitric oxide in cancer metastasis. Cancer Lett. 2014. pii: S0304-3835(14)00351-6. doi: 10.1016/j.canlet.2014.07.014. [Epub ahead of print].

17. Biswas DK, Shi Q, Baily S, Strickland I, Ghosh S, Pardee AB, et al. NF-kappa B activation in human breast cancer specimens and its role in cell proliferation and apoptosis. Proc Natl Acad Sci U S A. 2004;101(27):10137–42.
18. Duffey DC, Chen Z, Dong G, Ondrey FG, Wolf JS, Brown K, et al. Expression of a dominant-negative mutant inhibitor kappa B alpha of nuclear factor-kappaB in human head and neck squamous cell carcinoma inhibits survival, proinflammatory cytokine expression, and tumor growth in vivo. Cancer Res. 1999;59(14):3468–74.
19. Saijo Y, Tanaka M, Miki M, et al. Proinflammatory cytokine IL-1 β promotes tumor growth of Lewis lung carcinoma by induction of angiogenic factors: in vivo analysis of tumor-stromal interaction. J Immunol. 2002;169:469–75.
20. Voronov E, Shouval DS, Krelin Y, et al. IL-1 is required for tumor invasiveness and angiogenesis. Proc Natl Acad Sci U S A. 2003;100:2645–50.
21. Williamson RT. On the treatment of glycosuria and diabetes mellitus with sodium salicylate. Br Med J. 1901;1(2100):760–2.
22. Faghihimani E, Aminorroaya A, Rezvanian H, Adibi P, Ismail-Beigi F, Amini M. Salsalate improves glycemic control in patients with newly diagnosed type 2 diabetes. Acta Diabetol. 2013;50(4):537–43.
23. Larsen CM, Faulenbach M, Vaag A, Vølund A, Ehses JA, Seifert B, Mandrup-Poulsen T, Donath MY. Interleukin-1 receptor antagonist in type 2 diabetes mellitus. N Engl J Med. 2007;356:1517–26.
24. Ursini F, Naty S, Grembiale RD. Infliximab and insulin resistance. Autoimmun Rev. 2010;9(8):536–9.
25. Bertagnolli MM, Eagle CJ, Zauber AG, et al. Celecoxib for the prevention of sporadic colorectal adenomas. N Engl J Med. 2006;355:873–84.
26. Arber N, Eagle CJ, Spicak J, et al. Celecoxib for the prevention of colorectal adenomatous polyps. N Engl J Med. 2006;355:885–95.
27. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer. 2004;4(8):579–91.
28. Schoen RE, et al. Increased blood glucose and insulin, body size, and incident colorectal cancer. J Natl Cancer Inst. 1999;91:1147–54.
29. Lukanova A, Zeleniuch-Jacquotte A, Lundin E, Micheli A, Arslan AA, Rinaldi S, Muti P, Lenner P, Koenig KL, Biessy C, Krogh V, Riboli E, Shore RE, Stattin P, Berrino F, Hallmans G, Toniolo P, Kaaks R. Prediagnostic levels of C-peptide, IGF-I, IGFBP-1-2 and-3 and risk of endometrial cancer. Int J Cancer. 2004;108:262–8.
30. Frasca F, Pandini G, Sciacca L, et al. The role of insulin receptors and IGF-I receptors in cancer and other diseases. Arch Phys Biochem. 2008;114(1):23–37.
31. Cox ME, Gleave ME, Zakikhani M, et al. Insulin receptor expression by human prostate cancers. Prostate. 2009;69(1):33–40.
32. Wu Y, Yakar S, Zhao L, Hennighausen L, LeRoith D. Circulating insulin-like growth factor-I levels regulate colon cancer growth and metastasis. Cancer Res. 2002;62(4):1030–5.
33. Missmer SA, Eliassen AH, Barbieri RL, Hankinson SE. Endogenous estrogen, androgen, and progesterone concentrations and breast cancer risk among postmenopausal women. J Natl Cancer Inst. 2004;96:1856–65.
34. Allen NE, Key TJ, Dossus L, Rinaldi S, Cust A, Lukanova A, Peeters PH, Onland-Moret NC, Lahmann PH, Berrino F, Panico S, Larrañaga N, Pera G, Tormo MJ, Sánchez MJ, Ramón Quirós J, Ardanaz E, Tjønneland A, Olsen A, Chang-Claude J, Linseisen J, Schulz M, Boeing H, Lundin E, Palli D, Overvad K, Clavel-Chapelon F, Boutron-Ruault MC, Bingham S, Khaw KT, Bueno-de-Mesquita HB, Trichopoulou A, Trichopoulos D, Naska A, Tumino R, Riboli E, Kaaks R. Endogenous sex hormones and endometrial cancer risk in women in the European Prospective Investigation into Cancer and Nutrition (EPIC). Endocr Relat Cancer. 2008;15(2):485–97.
35. Purohit A, Newman SP, Reed MJ. The role of cytokines in regulating estrogen synthesis: implications for the etiology of breast cancer. Breast Cancer Res. 2002;4:65–9.

36. Pugeat M, Nader N, Hogeveen K, Raverot G, Déchaud H, Grenot C. Sex hormone-binding globulin gene expression in the liver: drugs and the metabolic syndrome. Mol Cell Endocrinol. 2010;316(1):53–9.
37. Key TJ, Appleby PN, Reeves GK, Roddam A, Dorgan JF, Longcope C, Stanczyk FZ, Stephenson Jr HE, Falk RT, Miller R, Schatzkin A, Allen DS, Fentiman IS, Key TJ, Wang DY, Dowsett M, Thomas HV, Hankinson SE, Toniolo P, Akhmedkhanov A, Koenig K, Shore RE, Zeleniuch-Jacquotte A, Berrino F, Muti P, Micheli A, Krogh V, Sieri S, Pala V, Venturelli E, Secreto G, Barrett-Connor E, Laughlin GA, Kabuto M, Akiba S, Stevens RG, Neriishi K, Land CE, Cauley JA, Kuller LH, Cummings SR, Helzlsouer KJ, Alberg AJ, Bush TL, Comstock GW, Gordon GB, Miller SR, Longcope C, Endogenous Hormones Breast Cancer Collaborative Group. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. J Natl Cancer Inst. 2003;95(16):1218–26.
38. Tchernof A, Nolan A, Sites CK, Ades PA, Poehlman ET. Weight loss reduces C-reactive protein levels in obese postmenopausal women. Circulation. 2002;105:564–9.
39. Christou NV, Lieberman M, Sampalis F, Sampalis JS. Bariatric surgery reduces cancer risk in morbidly obese patients. Surg Obes Relat Dis. 2008;4:691–5.
40. Ahn J, Schatzkin A, Lacey Jr JA, Albanes D, Ballard-Barbash R, Adams KF, Kipnis V, Mouw T, Hollenbeck AR, Leitzmann MF. Adiposity, adult weight change, and postmenopausal breast cancer risk. Arch Intern Med. 2008;167:2091–100.
41. Rose DP, Komninou D, Stephenson GD. Obesity, adipocytokines, and insulin resistance in breast cancer. Obes Rev. 2004;5:153–65.
42. Maehle BO, Tretli S. Pre-morbid body mass index in breast cancer: reversed effect on survival in hormone receptor negative patients. Breast Cancer Res Treat. 1996;41:123–30.
43. Dallal CM, Brinton LA, Bauer DC, Buist DS, Cauley JA, Hue TF, Lacroix A, Tice JA, Chia VM, Falk R, Pfeiffer R, Pollak M, Veenstra TD, Xu X, Lacey Jr JV, B ~ FIT Research Group. Obesity-related hormones and endometrial cancer among postmenopausal women: a nested case-control study within the B ~ FIT cohort. Endocr Relat Cancer. 2013;20(1):151–60.
44. Tworoger SS, Eliassen AH, Kelesidis T, et al. Plasma adiponectin concentrations and risk of incident breast cancer. J Clin Endo Metab. 2007;92(4):1510–6.
45. Cust AE, Kaaks R, Friedenreich C, et al. Plasma adiponectin levels and endometrial cancer risk in pre- and post-menopausal women. J Clin Endo Met. 2007;92(1):255–63.
46. Wei EK, Giovannucci E, Fuchs CS, Willett WC, Mantzoros CS. Low plasma adiponectin levels and risk of colorectal cancer in men: a prospective study. J Natl Cancer Inst. 2005;97(22): 1688–94.
47. Ribatti D, Belloni AS, Nico B, Di Comite M, Crivellato E, Vacca A. Leptin–leptin receptor are involved in angiogenesis in human hepatocellular carcinoma. Peptides. 2008;29:1596–602.
48. Gonzalez RR, Leavis PC. A peptide derived from the human leptin molecule is a potent inhibitor of the leptin receptor function in rabbit endometrial cells. Endocrine. 2003;21(2):185.
49. Surmacz E. Leptin and adiponectin: emerging therapeutic targets in breast cancer. J Mammary Gland Biol Neoplasia. 2013;18(3-4):321–32.
50. Mathur A, Zyromski NJ, Pitt HA, Al-Azzawi H, Walker JJ, Saxena R, Lillemoe KD. Pancreatic steatosis promotes dissemination and lethality of pancreatic cancer. J Am Coll Surg. 2009;208(5):989–94.
51. Yamaguchi J, et al. Prognostic impact of marginal adipose tissue invasion in ductal carcinoma of the breast. Am J Clin Pathol. 2008;130:382–8.
52. Rio MC. The role of cancer-associated adipocytes (CAA) in the dynamic interaction between the tumor and the host. In: Mueller MM, Fusenig NE, editors. Tumor-associated fibroblasts and their matrix, vol. 4. Netherlands: Springer; 2011. p. 111–23.
53. Manabe Y, et al. Mature adipocytes, but not preadipocytes, promote the growth of breast carcinoma cells in collagen gel matrix culture through cancer-stromal cell interactions. J Pathol. 2003;201(2):221–8.
54. Amemori S, et al. Adipocytes and preadipocytes promote the proliferation of colon cancer cells in vitro. Am J Physiol Gastro Liver Physiol. 2007;292(3):G923–9.

55. White PB, True EM, Ziegler KM, Wang SS, Swartz-Basile DA, Pitt HA, Zyromski NJ. Insulin, leptin, and tumoral adipocytes promote murine pancreatic cancer growth. J Gastrointest Surg. 2010;12:1888–93.
56. Tokuda Y, Satoh Y, Fujiyama C, Toda S, Sugihara H, Masaki Z. Prostate cancer cell growth is modulated by adipocyte-cancer cell interaction. BJU Int. 2003;91(7):716–20.
57. Zhang Y, Daquinag A, Traktuev DO, Amaya-Manzanares F, Simmons PJ, March KL, Pasqualini R, Arap W, Kolonin MG. White adipose tissue cells are recruited by experimental tumors and promote cancer progression in mouse models. Cancer Res. 2009;69(12):5259–66.
58. Nieman KM, Kenny HA, Penicka CV, Ladanyi A, Buell-Gutbrod R, Zillhardt MR, Romero IL, Carey MS, et al. Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth. Nat Med. 2011;17(11):1498–503.
59. Bochet L, Lehuédé C, Dauvillier S, Wang YY, Dirat B, Laurent V, Dray C, Guiet R, et al. Adipocyte-derived fibroblasts promote tumor progression and contribute to the desmoplastic reaction in breast cancer. Cancer Res. 2013;73(18):5657–68.
60. Ehsanipour EA, Sheng X, Behan JW, Wang X, Butturini A, Avramis VI, Mittelman SD. Adipocytes cause leukemia cell resistance to L-asparaginase via release of glutamine. Cancer Res. 2013;73(10):2998–3006.
61. Sheng H, Li P, Chen X, Liu B, Zhu Z, Cao W. Omega-3 PUFAs induce apoptosis of gastric cancer cells via ADORA1. Front Biosci (Landmark Ed). 2014;19:854–61.
62. Xu Y, Qian SY. Anti-cancer activities of ω-6 polyunsaturated fatty acids. Biomed J. 2014;37(3):112–9.
63. Zheng H, Tang H, Liu M, He M, Lai P, Dong H, Lin J, Jia C, Zhong M, Dai Y, Bai X, Wang L. Inhibition of endometrial cancer by n-3 polyunsaturated fatty acids in preclinical models. Cancer Prev Res (Phila). 2014;7(8):824–34.
64. Takino J, Yamagishi S, Takeuchi M. Cancer malignancy is enhanced by glyceraldehyde-derived advanced glycation end-products. J Oncol. 2010;2010:739852.
65. Ley RE. Obesity and the human microbiome. Curr Opin Gastroenterol. 2010;26(1):5–11.
66. Thakkar B, Aronis KN, Vamvini MT, Shields K, Mantzoros CS. Metformin and sulfonylureas in relation to cancer risk in type II diabetes patients: a meta-analysis using primary data of published studies. Metabolism. 2013;62(7):922–34.
67. Sjostrom L, Narbro K, Sjostrom CD, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med. 2007;357:741–52.
68. Birks S, Peeters A, Backholer K, O'Brien P, Brown W. A systematic review of the impact of weight loss on cancer incidence and mortality. Obes Rev. 2012;13(10):868–91.

Effect of Bariatric Surgery on Incretin Function

9

Blandine Laferrère

9.1 Introduction

Incidence of individuals classified as obese and overweight is on the rise, with a total of 2.1 billion individuals affected worldwide [1]. The association of obesity with comorbidities such as type 2 diabetes (T2DM), cardiovascular diseases, cancer, fatty liver, lung disease, and osteoarthritis makes it a major public health problem. Although the treatment of obesity by diet and exercise tackles the two sides of the energy balance equation, changes in behavior are rarely sustained overtime and the resulting weight loss is often limited (4–10 %) and transient (a few months) [2]. On the contrary, bariatric surgery results in weight loss of large magnitude (up to 45 % total weight loss) [3], generally sustained up to 20 years after surgery [4]. Surgical weight loss is accompanied by the resolution and or improvement of most obesity associated comorbidities, particularly type 2 diabetes, as shown in observational studies [3, 5] and in randomized controlled trials [6–9]. Bariatric surgeries were initially classified based on their presumed mechanism of action, i.e., gastric volume restriction, and reconfiguration of the small intestine to create malabsorption. Among bariatric surgeries currently performed, biliopancreatic diversion (BPD) and Roux-en-Y gastric bypass (RYGBP) include an element of restriction and malabsorption, while vertical sleeve gastrectomy (VSG), and adjustable gastric banding (AGB) are described as purely restrictive procedures. Currently, RYGBP and VSG are the two most common bariatric surgical procedures performed in the USA [10]. RYGBP results in a small gastric pouch and the shunting of the gastric fundus, the pylorus, the duodenum, and the upper jejunum from ingested nutrients. In VSG, the great curvature and the gastric fundus are removed, but the

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continuity of the intestine is untouched. Interestingly, although the reconstructed anatomy of RYGBP and VSG is vastly different, their effects on weight loss and diabetes remission are comparable, at least in the first 1–2 years after the surgery [11]. Although restriction and malabsorption may play a role after RYGBP and VSG, other mechanisms, not yet fully elucidated, such as gut hormones, seem to be involved in weight loss and remission of diabetes.

9.2 RYGBP and Diabetes Remission

Meta-analyses, observational studies, and more recently, randomized controlled trials, show high rates of diabetes remission, from 40 to 80 %, after bariatric surgery [3–9]. The rate of remission depends on the type of surgery, the amount of weight loss, as well as patient characteristics pre-surgery [7, 12–14]. Shorter diabetes duration, better diabetes control, fewer oral medications and/or not being on insulin, undergoing a bypass type of surgery (BPD, RYGBP) rather than a purely restrictive one (AGB), the amount of weight loss, are all determinants of diabetes remission [12, 13, 15]. Weight loss, by either calorie restriction [16, 17] or by bariatric surgery [18, 19] improves insulin sensitivity and fasting blood glucose. In fact, both methods of weight loss improve glucose levels similarly if the amount of weight loss is matched [20]. The improvement of blood glucose is directly proportional to the amount of weight loss after AGB [13]. Caloric restriction corrects glucose and lipid toxicity [21]. Calorie intake decreases after bariatric surgery [22]. Decreased caloric intake and weight loss, together with beta cell reserve, are likely the major determinants of long-term glucose control after bariatric surgery. However, the effect of RYGBP or of VSG on glucose control is very rapid and in part independent of weight loss. Not only do a significant amount of patients leave the hospital without any medications and with greatly improved glucose levels [12], but the surgery improves diabetes in patients less or not obese [23, 24]. The rapid improvement in glucose levels prior to large weight loss after RYGBP suggests that factors independent of weight loss may be responsible for the rapid and high rate of diabetes remission after this surgery [7, 6, 13, 14, 25]. Signals coming from the remodeling of the gut anatomy have been prime candidates. Past studies have focused on hormonal gut signals and neuronal gut-brain pathways, and more specifically, on the incretin hormone glucagon like peptide 1 (GLP-1). GLP-1 physiological effects include potentiation of glucose stimulated insulin release in the postprandial setting, suppression of glucagon, slowing of gastric emptying, decrease of body weight by central mechanisms, and favorable cardiovascular protection [26]. Because of the consistent and robust effect of RYGBP on GLP-1, GLP-1 has long been singled out as the prime candidate for mediating the effects of RYGBP surgery on satiety and glucose control. For the interest of this review, and because most data collected on the incretin effect were in patients undergoing RYGBP, this review will focus on RYGBP.

9.3 Importance of the Incretin Effect in Physiology

The incretin effect is the greater insulin response to oral glucose compared to an isoglycemic intravenous glucose load. Two gut hormones, GLP-1 and glucose-dependent insulinotropic peptide (GIP), secreted by the gut endocrine cells in response to the ingestion of nutrients, are responsible for the incretin effect, i.e., the enhancement of glucose stimulated insulin secretion [27, 28]. In the 1930s, La Barre [29] and Heller [30] identified the glucose lowering properties of duodenal extracts administered intravenously, and La Barre named it "incretin." Thirty years later, McIntyre showed that a rapid infusion of 60 g of glucose in the jejunum resulted in a much greater insulin response compared to the IV administration of an equivalent glucose load, and this in spite of lower glycemic levels [31]. The incretin effect was later quantified with a ~40 % greater insulin release after oral compared to a matched IV glucose load in healthy normal weight and obese subjects [27]. About 30 years after the term incretin was invented, GIP was identified as another main incretin [32]. Its original name, gastric inhibitory peptide, refers to the pharmacological role of the peptide to decrease acid secretion and was later changed to glucose-dependent insulinotropic peptide, to reflect its physiological incretin effect. About 10 years later, GLP-1 was isolated and recognized as a key incretin [33]. The incretin effect, the augmented response of insulin after oral glucose compared to matched IV glucose, or the enhancement of glucose-stimulated insulin secretion (GSIS), is mediated by the two incretin hormones GLP-1 and GIP, released from gut endocrine cells in response to meals and acting on the beta cell to stimulate insulin secretion [34]. The release of the incretins GIP and GLP-1 is proportional to the nutrient caloric load with fat and carbohydrate being the main stimulants [35–37] and is responsible for maintaining euglycemia in spite of highly variable oral loads. The concentration of circulating incretins is in the range of 10–30 ng/ml for GLP-1 and 100–150 ng/ml for GIP. The concentration of circulating incretins is often not different between lean, obese with normal glucose tolerance (NGT) and individuals with T2DM [38], but may be altered with hyperglycemia [39, 40]. The incretin effect on insulin secretion is blunted in patients with T2DM [36, 41]. The administration of exogenous pharmacological doses of GLP-1 or GLP-1 analogs restores insulin secretion and lowers blood glucose in diabetes, and the GIP effect can be restored after lowering glycemia [42]. Both GLP-1 and GIP have a trophic effect on the beta cell, in vitro, and in vivo in rodents [43–46]. This effect has not been demonstrated in humans. GLP-1 has other important physiological effects. It inhibits glucagon, slows gastric emptying, decreases food intake and reduces body weight [47], and all of these effects make it an interesting tool for the treatment of overweight and obese individuals with T2DM. The half-life of GLP-1 and GIP is only a few minutes. Both hormones are rapidly degraded by the enzyme dipeptidyl peptidase 4 (DPP-4). DPP-4 inhibitors and long acting GLP-1 analogs are now used in clinical practice to treat T2DM, and GLP-1 analogs were recently approved for by the FDA for weight loss.

9.4 Gastric Bypass Surgery Alters Gut Physiology

RYGBP results in a smaller gastric pouch (~30 ml), shunting the larger part of the stomach, pylorus, duodenum, and upper jejunum from ingested food. The emptying of the gastric pouch through the gastrojejunal anastomosis to the distal part of the jejunum is rapid for liquids [48]. Ingested nutrients travel rapidly through the alimentary limb to mix with secretions from the gastric remnant, gall bladder and exocrine pancreas in the common limb, distal to the jejuno-jejunal anastomosis. The acceleration of nutrient transit and the exposure of the various segments of the lower intestine to undigested nutrients is one of the main effects of RYGBP and triggers a greater release of most satiety and incretin gut peptides [49–51]. The chronic effect of RYGBP include remodeling of the gut with development of gut hypertrophy and increased intestinal metabolic activity [52], with an increased expression of glucose transporters sodium glucose co-transporter 1 (SGLT1) and glucose transporter 2 (GLUT2) [53], of GLP-1, peptide YY (PYY), and glucagon like peptide 2 (GLP-2) [54–56]. Although bile acids stimulate GLP-1 release in vitro and in vivo [57], the temporal change in bile acid metabolism after RYGBP is unlikely to explain the rise of GLP-1 release [58].

9.5 Change of Incretins After RYGBP

With the availability of commercial kits for measuring GIP and GLP-1, publications reporting incretin levels after RYGBP abound (Table 9.1). Circulating concentrations of GLP-1 and GIP increase after mixed meals/oral glucose loads, respectively by a factor 10 and 1.5, to reach peak levels of ~100 and 300 pM, respectively after

Table 9.1 Change of nutrient stimulated GLP-1 and GIP after bariatric surgery

Reference	Surgery	Obese/T2DM	Stimulus	GLP-1	GIP
Sarson et al. [76, 77]	RYGBP	OB	Meal		↓
Halverson et al. [78]	RYGBP	OB	OGTT		↑
Sirinek et al. [79]	RYGBP	OB	OGTT		↓
Naslund et al. [80]	JIB	OB	Meal	↑	↑
Verdich et al. [81]	Diet	19 OB/12 lean	Meal	↑	↓
Valverde et al. [82]	BPD/VBG		OGTT	↑	
Korner et al. [83]	RYGBP	OB/lean	Meal	↑	↓
Borg et al. [84]	RYGBP	OB	Meal	↑	
Morinigo et al. [49]	RYGBP	OB	Meal	↑	
Laferrère et al. [61]	RYGBP	OB/T2DM	OGTT	↑	↑
Jorgensen et al. [85]	RYGBP	OB/T2DM/NGT	Meal	↑	–
Jacobsen et al. [65]	RYGBP	OB	OGTT	↑	–
Romero et al. [86]	VSG/RYGBP	OB/T2DM	Meal	↑	↑
Mallipedhi et al. [87]	VSG/BPD	IGT/T2DM	OGTT	↑	↓
Plourde et al. [88]	BPD	T2DM/NGT	Meal	↑	↓
Kim et al. [64]	RYGBP	Lean T2DM	OGTT	↑	↓

RYGBP. The effect of GBP on GLP-1 is robust [59] and reported in all studies (Table 9.1). In our laboratory, we have studied over 100 patients post RYGBP, and observed 100 % as "responders," with a large increase in GLP-1 after either a meal test or a glucose tolerance test. The enhancement of GLP-1 is sustained for many years after the surgery, although the magnitude of GLP-1 release may vary overtime [60]. The effect of RYGBP on GIP is less consistent. GIP was shown to either increase [61], not change, or decrease [62–64], depending on the study. This difference may be related to variation in surgical techniques with different lengths of the biliopancreatic limb or to diabetes status. Both active and total GLP-1 levels are elevated after RYGBP, and the ratio of active-to-total GLP-1 decreases after surgery RYGBP [61, 65]. The interpretation of this change in the ratio of active-to-total GLP-1 is unclear [66]. In fact, circulating DPP-4 activity decreases after RYGBP [67], but not after weight loss by diet; however, circulating DPP-4 activity does not correlate with change in circulating incretins or of the incretin effect [67]. The incretin effect, measured by comparing insulin secretion after an oral glucose load and an isoglycemic glucose clamp, blunted in patients with T2DM [41], increases to levels of normal glucose tolerant individuals one month after surgery in patients with T2DM who go into remission [61], but did not increase significantly in patients matched for body weight who underwent the same 10 % weight loss by calorie restriction [20]. The release of incretins GLP-1 and GIP and the recovery of the incretin effect persist years after the surgery in patients in diabetes remission (Laferrère, unpublished). So interestingly, levels of incretins are very high after RYGBP and the corresponding incretin effect on insulin secretion is restored to the level of controls. This raises the possible question of decreased beta cell sensitivity to incretins after the surgery. Yet the insulinotropic effect of GIP and GLP-1 is preserved in patients with normal glucose tolerance after RYGBP [68]. Whether this is also true in patients with diabetes is unknown. The mechanism responsible for the enhanced release of GLP-1 after RYGBP is the rapid emptying of the gastric pouch. Gastric emptying of liquid is accelerated after RYGBP [48, 69–71] and GLP-1 peak levels correlate positively with measures of gastric pouch emptying [49]. In a recent study, we administered a 600 kcal liquid meal with 1500 mg of acetaminophen to individuals before and after RYGBP. One year after the surgery, the mean body mass index decreased from 47.4 ± 6.6 to 29.6 ± 6.1 kg/m^2. The acetaminophen curve was shifted to the left and the time-to-peak decreased (Fig. 9.1a). Peak GLP-1 during the meal was strongly correlated with peak acetaminophen ($r^2 = 0.356$, $p < 0.01$) (Fig. 9.1b). The enhanced GLP-1 release after RYGBP, observed after oral administration of a test meal, is entirely abolished if the meal is administered in the gastric remnant [72, 73], or delivered at a very slow rate of 4 kcal/min in the jejunal alimentary limb [53]. These elegant experiments demonstrate the importance of the mode and rate of delivery of nutrients to the distal intestine. Restoring a more physiological rate of gastric emptying by either infusing the meal in the gastric remnant with a functioning pylorus [72, 73], or by slowing the rate of the infusion [53], blunts the exaggerated GLP-1 release to pre-RYGBP levels or to levels observed in non-operated controls. GLP-1 has a trophic effect on the pancreas [43–46]. Whether the chronic and sustained elevation of postprandial GLP-1 after RYGBP has a

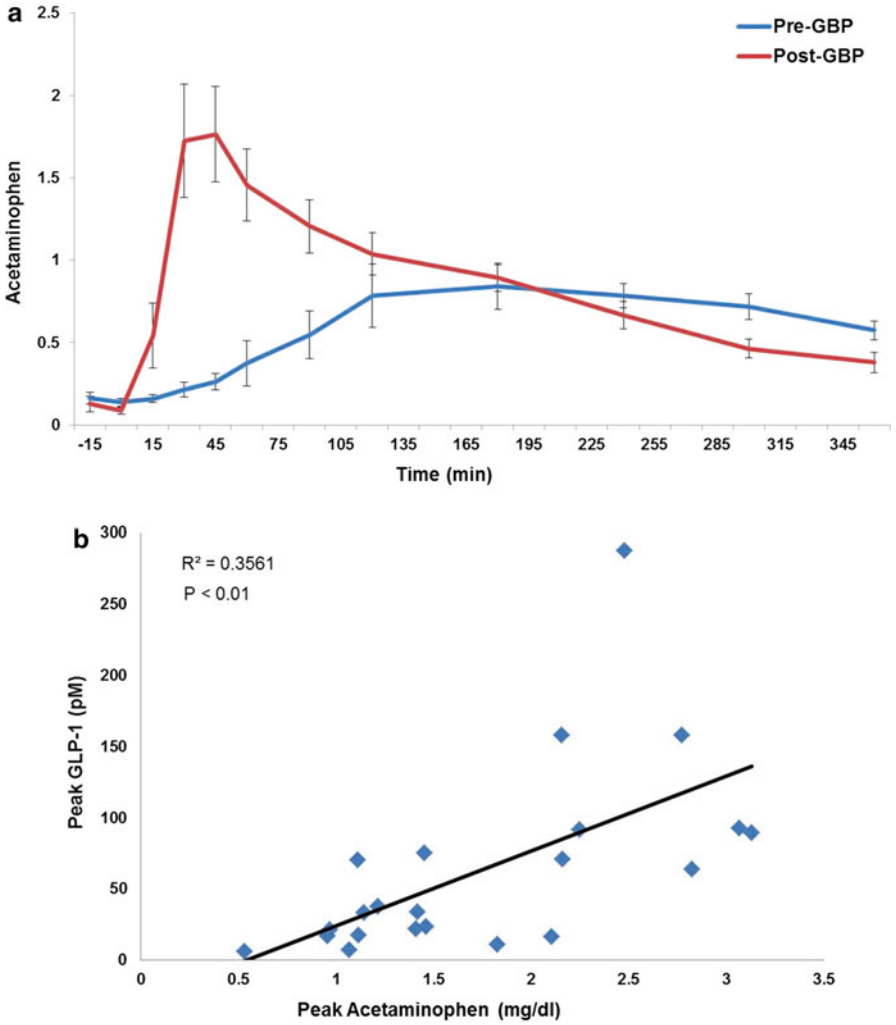

Fig. 9.1 Accelerate gastric pouch emptying after RYGBP. (**a**) Acetaminophen levels during a 600 kcal liquid meal given before or 1 year after RYGBP surgery; (**b**) Strong relationship between gastric pouch emptying and GLP-1 release during a 600 kcal meal

long-term trophic effect on the beta cell is unknown in humans. Rare cases of nesidioblastosis have been shown in patients with neuroglycopenia after RYGBP [74]. An interesting study in pigs showed increased islet number and beta cell proliferation after RYGBP, in parallel with rise in GLP-1, demonstrating the effect of RYGBP on the plasticity of the endocrine pancreas in this animal model [75].

9.6 Lessons from Rodent Models

Although data in humans and pigs support a role for GLP-1 in controlling glucose after RYGBP, experiments with knock out (KO) animal models challenge the role of GLP-1 in the control of body weight and glucose after RYGBP or VSG. Berthoud et al. [89] showed that chronic brain infusion of exendin-9-39 into the lateral cerebral ventricle similarly increased food intake and body weight in both RYGBP and sham-operated rats, suggesting that, while contributing to the physiological control of food intake and body weight, central GLP-1 receptor signaling tone is not the critical mechanism uniquely responsible for the body weight-lowering effects of RYGBP. In a separate experiment, the same authors showed that obese GLP-1R-deficient mice lost the same amount of body weight and fat mass and maintained similarly lower body weight compared with wild-type mice after a RYGBP-like procedure [89]. GLP-1 levels are also enhanced after VSG in humans [90] and rodents [91], and are thought to be a mediator of diabetes remission after this surgery [92]. However, VSG-operated GLP-1 receptor-deficient mice respond similarly to wild-type controls in terms of body weight loss, improved glucose tolerance, food intake reduction, and altered food selection [93]. These data demonstrate that GLP-1 receptor activity is not necessary for the metabolic improvements induced by VSG or RYGBP surgery in these animal models. The relevance of these KO experiments to clinical observations is unclear.

9.7 Effect of RYGBP on the Incretins: Does It Matter for Beta Cell Function?

The main effect of theincretins is enhancement of glucose stimulated-insulin secretion. In order to single out the incretin effect from the weight loss effect of the surgery, we have used two approaches. One is to compare the effect of an oral glucose challenge to that of an isoglycemic IV glucose clamp on beta cell function, to quantify the incretin effect. Presumably, the change in beta cell response to oral glucose after RYGBP would engage neural and hormonal gut mechanisms, while the response to IV glucose would only be a function of the change in glycemia related to weight loss. The other approach is to block the effect of the endogenous incretins. Although there is no available GIP receptor inhibitor for human use, the specific GLP-1 receptor inhibitor exendin 9-39 has been used in four cross sectional [94–97] studies and one longitudinal short term [98] study in post-RYGBP patients. Exendin 9-39 administration has little to no effect prior to surgery, but completely blunts the recovery of beta cell glucose sensitivity (BCGS), or the insulin secretin rate in response to incremental changes in blood glucose during a glucose challenge, observed 1 week and 3 months after RYGBP [98]. The administration of Exendin 9-39 worsens postprandial glucose tolerance, although only minimally [97]. Exendin 9-39 suppresses insulin secretion in response to a meal by 50 % [94, 97]

and corrects the profound reactive hypoglycemia in patients with severe neuroglycopenia [94]. So clearly the exaggerated GLP-1 response to ingestion of food or glucose plays a key role in postprandial insulin secretion and glycemic control after RYGBP. To assess beta cell function, we measured BCGS and the disposition index (DI), i.e. the relationship between insulin secretion and insulin sensitivity. Both measures were calculated using data from an oral glucose load and from a matched isoglycemic IV glucose load, collected on separate days, in patients with T2DM and severe obesity, before and at 1 month, then yearly for 3 years after RYGBP surgery. Prior to surgery, BCGS after either an oral or IV isoglycemic glucose challenge, was, as expected, significantly impaired in patients with T2DM compared to lean controls, and to obese controls with normal glucose tolerance (NGT), matched for BMI. After RYGBP, all patients were in diabetes remission (HbA1C < 6.5 %, fasting glucose <126 mg/dl, on no diabetes medications). The BCGS and DI measured using parameters derived from the oral glucose test improved rapidly at 1 month and normalized to the levels of the lean and the obese NGT controls at 1 year. However, BCGS and DI measured after IV glucose administration improved only minimally and remained much impaired compared to that of the lean and obese NGT non-operated controls [99]. This experiment highlights the role of the incretins and other gut-mediated factors in the amelioration of beta cell response to oral nutrients after RYGBP. It also clearly shows a persistent beta cell defect that cannot be rescued with an IV glucose challenge, 3 years after the surgery, even in persons who are in clinical diabetes remission. In humans, there is no evidence to date for a full recovery of beta cell function to IV stimuli in patients in diabetes remission [99].

In order to distinguish between a caloric restriction/weight loss effect and an effect independent of weight loss, we compared individuals studied before and after RYGBP to individuals studied before and after an equivalent 10 % weight loss by caloric restriction with or without AGB. BCGS and DI after IV glucose stimulus improved significantly and similarly after the two modes of weight loss. After the oral glucose challenge, beta cell function improved significantly more after RYGBP than after diet. Results from this experiment underscore the importance of the engagement of the gut and the incretin effect, rather than weight loss, in the metabolic response to nutrient stimulation after RYGBP [100].

9.8 Conclusions

Bariatric surgery and its associated weight loss result in diabetes remission. The effect of the incretins hormones on postprandial insulin secretion and glucose control is amplified after RYGBP, as a result of the accelerated passage of nutrients. The enhanced incretin effect rescues beta cell function, independent of weight loss. This effect, observed only during meals, may not play a predominant part in diabetes remission after RYGBP.

References

1. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC, Biryukov S, Abbafati C, Abera SF, Abraham JP, Abu-Rmeileh NM, Achoki T, AlBuhairan FS, Alemu ZA, Alfonso R, Ali MK, Ali R, Guzman NA, Ammar W, Anwari P, Banerjee A, Barquera S, Basu S, Bennett DA, Bhutta Z, Blore J, Cabral N, Nonato IC, Chang JC, Chowdhury R, Courville KJ, Criqui MH, Cundiff DK, Dabhadkar KC, Dandona L, Davis A, Dayama A, Dharmaratne SD, Ding EL, Durrani AM, Esteghamati A, Farzadfar F, Fay DF, Feigin VL, Flaxman A, Forouzanfar MH, Goto A, Green MA, Gupta R, Hafezi-Nejad N, Hankey GJ, Harewood HC, Havmoeller R, Hay S, Hernandez L, Husseini A, Idrisov BT, Ikeda N, Islami F, Jahangir E, Jassal SK, Jee SH, Jeffreys M, Jonas JB, Kabagambe EK, Khalifa SE, Kengne AP, Khader YS, Khang YH, Kim D, Kimokoti RW, Kinge JM, Kokubo Y, Kosen S, Kwan G, Lai T, Leinsalu M, Li Y, Liang X, Liu S, Logroscino G, Lotufo PA, Lu Y, Ma J, Mainoo NK, Mensah GA, Merriman TR, Mokdad AH, Moschandreas J, Naghavi M, Naheed A, Nand D, Narayan KM, Nelson EL, Neuhouser ML, Nisar MI, Ohkubo T, Oti SO, Pedroza A, Prabhakaran D, Roy N, Sampson U, Seo H, Sepanlou SG, Shibuya K, Shiri R, Shiue I, Singh GM, Singh JA, Skirbekk V, Stapelberg NJ, Sturua L, Sykes BL, Tobias M, Tran BX, Trasande L, Toyoshima H, van de Vijver S, Vasankari TJ, Veerman JL, Velasquez-Melendez G, Vlassov VV, Vollset SE, Vos T, Wang C, Wang X, Weiderpass E, Werdecker A, Wright JL, Yang YC, Yatsuya H, Yoon J, Yoon SJ, Zhao Y, Zhou M, Zhu S, Lopez AD, Murray CJ, Gakidou E. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384(9945):766–81. doi: 10.1016/S0140-6736(14)60460-8.
2. Unick JL, Beavers D, Bond DS, Clark JM, Jakicic JM, Kitabchi AE, Knowler WC, Wadden TA, Wagenknecht LE, Wing RR, Look ARG. The long-term effectiveness of a lifestyle intervention in severely obese individuals. Am J Med. 2013;126(3):236–42. doi:10.1016/j.amjmed.2012.10.010. 242e.1–2.
3. Courcoulas AP, Christian NJ, Belle SH, Berk PD, Flum DR, Garcia L, Horlick M, Kalarchian MA, King WC, Mitchell JE, Patterson EJ, Pender JR, Pomp A, Pories WJ, Thirlby RC, Yanovski SZ, Wolfe BM, Longitudinal Assessment of Bariatric Surgery Consortium. Weight change and health outcomes at 3 years after bariatric surgery among individuals with severe obesity. JAMA. 2013;310(22):2416–25. doi:10.1001/jama.2013.280928.
4. Sjostrom L, Peltonen M, Jacobson P, Sjostrom CD, Karason K, Wedel H, Ahlin S, Anveden A, Bengtsson C, Bergmark G, Bouchard C, Carlsson B, Dahlgren S, Karlsson J, Lindroos AK, Lonroth H, Narbro K, Naslund I, Olbers T, Svensson PA, Carlsson LM. Bariatric surgery and long-term cardiovascular events. JAMA. 2012;307(1):56–65. doi:10.1001/jama.2011.1914.
5. Pories WJ, Swanson MS, MacDonald KG, Long SB, Morris PG, Brown BM, Barakat HA, deRamon RA, Israel G, Dolezal JM, et al. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. Ann Surg. 1995;222(3):339–50. discussion 350–332.
6. Schauer PR, Kashyap SR, Wolski K, Brethauer SA, Kirwan JP, Pothier CE, Thomas S, Abood B, Nissen SE, Bhatt DL. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med. 2012;366(17):1567–76. doi:10.1056/NEJMoa1200225.
7. Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Leccesi L, Nanni G, Pomp A, Castagneto M, Ghirlanda G, Rubino F. Bariatric surgery versus conventional medical therapy for type 2 diabetes. N Engl J Med. 2012;366(17):1577–85. doi:10.1056/NEJMoa1200111.
8. Lee WJ, Chong K, Ser KH, Lee YC, Chen SC, Chen JC, Tsai MH, Chuang LM. Gastric bypass vs sleeve gastrectomy for type 2 diabetes mellitus: a randomized controlled trial. Arch Surg. 2011;146(2):143–8. doi:10.1001/archsurg.2010.326.
9. Ikramuddin S, Korner J, Lee WJ, Connett JE, Inabnet WB, Billington CJ, Thomas AJ, Leslie DB, Chong K, Jeffery RW, Ahmed L, Vella A, Chuang LM, Bessler M, Sarr MG, Swain JM,

Laqua P, Jensen MD, Bantle JP. Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia: the Diabetes Surgery Study randomized clinical trial. JAMA. 2013;309(21):2240–9. doi:10.1001/jama.2013.5835.
10. Lo Menzo E, Szomstein S, Rosenthal RJ. Changing trends in bariatric surgery. Scand J Surg. 2014. doi:10.1177/1457496914552344.
11. Kashyap SR, Bhatt DL, Wolski K, Watanabe RM, Abdul-Ghani M, Abood B, Pothier CE, Brethauer S, Nissen S, Gupta M, Kirwan JP, Schauer PR. Metabolic effects of bariatric surgery in patients with moderate obesity and type 2 diabetes: analysis of a randomized control trial comparing surgery with intensive medical treatment. Diabetes Care. 2013;36(8):2175–82. doi:10.2337/dc12-1596.
12. Schauer PR, Burguera B, Ikramuddin S, Cottam D, Gourash W, Hamad G, Eid GM, Mattar S, Ramanathan R, Barinas-Mitchel E, Rao RH, Kuller L, Kelley D. Effect of laparoscopic Roux-en Y gastric bypass on type 2 diabetes mellitus. Ann Surg. 2003;238(4):467–84. doi:10.1097/01.sla.0000089851.41115.1b. discussion 484–465.
13. Dixon JB, O'Brien PE, Playfair J, Chapman L, Schachter LM, Skinner S, Proietto J, Bailey M, Anderson M. Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. JAMA. 2008;299(3):316–23. doi:10.1001/jama.299.3.316.
14. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, Schoelles K. Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004;292(14):1724–37. doi:10.1001/jama.292.14.1724.
15. Arterburn DE, Bogart A, Sherwood NE, Sidney S, Coleman KJ, Haneuse S, O'Connor PJ, Theis MK, Campos GM, McCulloch D, Selby J. A multisite study of long-term remission and relapse of type 2 diabetes mellitus following gastric bypass. Obes Surg. 2013;23(1):93–102. doi:10.1007/s11695-012-0802-1.
16. Guldstrand M, Ahren B, Adamson U. Improved beta-cell function after standardized weight reduction in severely obese subjects. Am J Physiol Endocrinol Metab. 2003;284(3):E557–65. doi:10.1152/ajpendo.00325.2002.
17. Villareal DT, Banks MR, Patterson BW, Polonsky KS, Klein S. Weight loss therapy improves pancreatic endocrine function in obese older adults. Obesity. 2008;16(6):1349–54. doi:10.1038/oby.2008.226.
18. Campos GM, Rabl C, Peeva S, Ciovica R, Rao M, Schwarz JM, Havel P, Schambelan M, Mulligan K. Improvement in peripheral glucose uptake after gastric bypass surgery is observed only after substantial weight loss has occurred and correlates with the magnitude of weight lost. J Gastrointest Surg. 2010;14(1):15–23. doi:10.1007/s11605-009-1060-y.
19. Bradley D, Conte C, Mittendorfer B, Eagon JC, Varela JE, Fabbrini E, Gastaldelli A, Chambers KT, Su X, Okunade A, Patterson BW, Klein S. Gastric bypass and banding equally improve insulin sensitivity and beta cell function. J Clin Invest. 2012;122(12):4667–74. doi:10.1172/JCI64895.
20. Laferrère B, Teixeira J, McGinty J, Tran H, Egger JR, Colarusso A, Kovack B, Bawa B, Koshy N, Lee H, Yapp K, Olivan B. Effect of weight loss by gastric bypass surgery versus hypocaloric diet on glucose and incretin levels in patients with type 2 diabetes. J Clin Endocrinol Metab. 2008;93(7):2479–85. doi:10.1210/jc.2007-2851.
21. Henry RR, Wiest-Kent TA, Scheaffer L, Kolterman OG, Olefsky JM. Metabolic consequences of very-low-calorie diet therapy in obese non-insulin-dependent diabetic and nondiabetic subjects. Diabetes. 1986;35(2):155–64.
22. Warde-Kamar J, Rogers M, Flancbaum L, Laferrère B. Calorie intake and meal patterns up to 4 years after Roux-en-Y gastric bypass surgery. Obes Surg. 2004;14(8):1070–9. doi:10.1381/0960892041975668.
23. Cohen RV, Pinheiro JC, Schiavon CA, Salles JE, Wajchenberg BL, Cummings DE. Effects of gastric bypass surgery in patients with type 2 diabetes and only mild obesity. Diabetes Care. 2012;35(7):1420–8. doi:10.2337/dc11-2289.
24. Shah SS, Todkar JS, Shah PS, Cummings DE. Diabetes remission and reduced cardiovascular risk after gastric bypass in Asian Indians with body mass index <35 kg/m(2). Surg Obes Relat Dis. 2010;6(4):332–8. doi:10.1016/j.soard.2009.08.009.

25. Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, Pories WJ, Bantle JP, Sledge I. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. Am J Med. 2009;122(3):248–56. doi:10.1016/j.amjmed.2008.09.041. e245.
26. Campbell JE, Drucker DJ. Pharmacology, physiology, and mechanisms of incretin hormone action. Cell Metab. 2013;17(6):819–37. doi:10.1016/j.cmet.2013.04.008.
27. Perley MJ, Kipnis DM. Plasma insulin responses to oral and intravenous glucose: studies in normal and diabetic subjects. J Clin Invest. 1967;46(12):1954–62. doi:10.1172/JCI105685.
28. Creutzfeldt W, Nauck M. Gut hormones and diabetes mellitus. Diabetes Metab Rev. 1992;8(2):149–77.
29. Zunz E, La Barre J. Contributions à l'étude des variations physiologiques de la sécrétion interne du pancréas: relations entre les sécretions externe et interne du pancréas. Arch Int Physiol Biochim. 1929;31:20–44.
30. Heller H. The state in the blood and the excretion by the kidney of the antidiuretic principle of posterior pituitary extracts. J Physiol. 1937;89(1):81–95.
31. McIntyre N, Holdsworth CD, Turner DS. Intestinal factors in the control of insulin secretion. J Clin Endocrinol Metab. 1965;25(10):1317–24. doi:10.1210/jcem-25-10-1317.
32. Dupre J, Ross SA, Watson D, Brown JC. Stimulation of insulin secretion by gastric inhibitory polypeptide in man. J Clin Endocrinol Metab. 1973;37(5):826–8. doi:10.1210/jcem-37-5-826.
33. Bell GI, Santerre RF, Mullenbach GT. Hamster preproglucagon contains the sequence of glucagon and two related peptides. Nature. 1983;302(5910):716–8.
34. Nauck MA, Homberger E, Siegel EG, Allen RC, Eaton RP, Ebert R, Creutzfeldt W. Incretin effects of increasing glucose loads in man calculated from venous insulin and C-peptide responses. J Clin Endocrinol Metab. 1986;63(2):492–8. doi:10.1210/jcem-63-2-492.
35. Lindgren O, Carr RD, Holst JJ, Deacon CF, Ahren B. Dissociated incretin hormone response to protein versus fat ingestion in obese subjects. Diabetes Obes Metab. 2011;13(9):863–5. doi:10.1111/j.1463-1326.2011.01420.x.
36. Bagger JI, Knop FK, Lund A, Vestergaard H, Holst JJ, Vilsboll T. Impaired regulation of the incretin effect in patients with type 2 diabetes. J Clin Endocrinol Metab. 2011;96(3):737–45. doi:10.1210/jc.2010-2435.
37. Mari A, Bagger JI, Ferrannini E, Holst JJ, Knop FK, Vilsboll T. Mechanisms of the incretin effect in subjects with normal glucose tolerance and patients with type 2 diabetes. PLoS One. 2013;8(9):e73154. doi:10.1371/journal.pone.0073154.
38. Nauck MA, Vardarli I, Deacon CF, Holst JJ, Meier JJ. Secretion of glucagon-like peptide-1 (GLP-1) in type 2 diabetes: what is up, what is down? Diabetologia. 2011;54(1):10–8. doi:10.1007/s00125-010-1896-4.
39. Calanna S, Christensen M, Holst JJ, Laferrère B, Gluud LL, Vilsboll T, Knop FK. Secretion of glucose-dependent insulinotropic polypeptide in patients with type 2 diabetes: systematic review and meta-analysis of clinical studies. Diabetes Care. 2013;36(10):3346–52. doi:10.2337/dc13-0465.
40. Calanna S, Christensen M, Holst JJ, Laferrère B, Gluud LL, Vilsboll T, Knop FK. Secretion of glucagon-like peptide-1 in patients with type 2 diabetes mellitus: systematic review and meta-analyses of clinical studies. Diabetologia. 2013;56(5):965–72. doi:10.1007/s00125-013-2841-0.
41. Nauck M, Stockmann F, Ebert R, Creutzfeldt W. Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. Diabetologia. 1986;29(1):46–52.
42. Hojberg PV, Vilsboll T, Rabol R, Knop FK, Bache M, Krarup T, Holst JJ, Madsbad S. Four weeks of near-normalisation of blood glucose improves the insulin response to glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide in patients with type 2 diabetes. Diabetologia. 2009;52(2):199–207. doi:10.1007/s00125-008-1195-5.
43. Ma X, Hui H, Liu Z, He G, Hu J, Meng J, Guan L, Luo X. Poly-GLP-1, a novel long-lasting glucagon-like peptide-1 polymer, ameliorates hyperglycaemia by improving insulin sensitivity and increasing pancreatic beta-cell proliferation. Diabetes Obes Metab. 2009;11(10):953–65. doi:10.1111/j.1463-1326.2009.01070.x.

44. Farilla L, Bulotta A, Hirshberg B, Li Calzi S, Khoury N, Noushmehr H, Bertolotto C, Di Mario U, Harlan DM, Perfetti R. Glucagon-like peptide 1 inhibits cell apoptosis and improves glucose responsiveness of freshly isolated human islets. Endocrinology. 2003;144(12):5149–58. doi:10.1210/en.2003-0323.
45. Wang Q, Brubaker PL. Glucagon-like peptide-1 treatment delays the onset of diabetes in 8 week-old db/db mice. Diabetologia. 2002;45(9):1263–73. doi:10.1007/s00125-002-0828-3.
46. De Leon DD, Deng S, Madani R, Ahima RS, Drucker DJ, Stoffers DA. Role of endogenous glucagon-like peptide-1 in islet regeneration after partial pancreatectomy. Diabetes. 2003;52(2):365–71.
47. Holst JJ. The physiology of glucagon-like peptide 1. Physiol Rev. 2007;87(4):1409–39. doi:10.1152/physrev.00034.2006.
48. Wang G, Agenor K, Pizot J, Kotler DP, Harel Y, Van Der Schueren BJ, Quercia I, McGinty J, Laferrère B. Accelerated gastric emptying but no carbohydrate malabsorption 1 year after gastric bypass surgery (GBP). Obes Surg. 2012;22(8):1263–7. doi:10.1007/s11695-012-0656-6.
49. Morinigo R, Moize V, Musri M, Lacy AM, Navarro S, Marin JL, Delgado S, Casamitjana R, Vidal J. Glucagon-like peptide-1, peptide YY, hunger, and satiety after gastric bypass surgery in morbidly obese subjects. J Clin Endocrinol Metab. 2006;91(5):1735–40. doi:10.1210/jc.2005-0904.
50. Olivan B, Teixeira J, Bose M, Bawa B, Chang T, Summe H, Lee H, Laferrère B. Effect of weight loss by diet or gastric bypass surgery on peptide YY3-36 levels. Ann Surg. 2009;249(6):948–53. doi:10.1097/SLA.0b013e3181a6cdb0.
51. Laferrère B, Swerdlow N, Bawa B, Arias S, Bose M, Olivan B, Teixeira J, McGinty J, Rother KI. Rise of oxyntomodulin in response to oral glucose after gastric bypass surgery in patients with type 2 diabetes. J Clin Endocrinol Metab. 2010;95(8):4072–6. doi:10.1210/jc.2009-2767.
52. Saeidi N, Meoli L, Nestoridi E, Gupta NK, Kvas S, Kucharczyk J, Bonab AA, Fischman AJ, Yarmush ML, Stylopoulos N. Reprogramming of intestinal glucose metabolism and glycemic control in rats after gastric bypass. Science. 2013;341(6144):406–10. doi:10.1126/science.1235103.
53. Nguyen NQ, Debreceni TL, Bambrick JE, Chia B, Deane AM, Wittert G, Rayner CK, Horowitz M, Young RL. Upregulation of intestinal glucose transporters after Roux-en-Y gastric bypass to prevent carbohydrate malabsorption. Obesity. 2014;22(10):2164–71. doi:10.1002/oby.20829.
54. Mumphrey MB, Patterson LM, Zheng H, Berthoud HR. Roux-en-Y gastric bypass surgery increases number but not density of CCK-, GLP-1-, 5-HT-, and neurotensin-expressing enteroendocrine cells in rats. Neurogastroenterol Motil. 2013;25(1):e70–9. doi:10.1111/nmo.12034.
55. Le Roux CW, Borg C, Wallis K, Vincent RP, Bueter M, Goodlad R, Ghatei MA, Patel A, Bloom SR, Aylwin SJ. Gut hypertrophy after gastric bypass is associated with increased glucagon-like peptide 2 and intestinal crypt cell proliferation. Ann Surg. 2010;252(1):50–6. doi:10.1097/SLA.0b013e3181d3d21f.
56. Hansen CF, Bueter M, Theis N, Lutz T, Paulsen S, Dalboge LS, Vrang N, Jelsing J. Hypertrophy dependent doubling of L-cells in Roux-en-Y gastric bypass operated rats. PLoS One. 2013;8(6):e65696. doi:10.1371/journal.pone.0065696.
57. Thomas C, Gioiello A, Noriega L, Strehle A, Oury J, Rizzo G, Macchiarulo A, Yamamoto H, Mataki C, Pruzanski M, Pellicciari R, Auwerx J, Schoonjans K. TGR5-mediated bile acid sensing controls glucose homeostasis. Cell Metab. 2009;10(3):167–77. doi:10.1016/j.cmet.2009.08.001.
58. Dutia R, Embrey M, O'Brien C, Haeusler RA, Agénor KK, Homel P, McGinty J, Vincent R, Alaghband-Zadeh J, Staels B, le Roux C, Yu J, Laferrère B. Temporal changes in bile acid levels and 12α-hydroxylation after Roux-en-Y gastric bypass surgery in type 2 diabetes. Int J Obes (Lond). 2015 May;39(5):806–13. doi: 10.1038/ijo.2015.1. Epub 2015 Jan 20.

59. Laferrère B. Effect of gastric bypass surgery on the incretins. Diabetes Metab. 2009;35(6 Pt 2):513–7. doi:10.1016/S1262-3636(09)73458-5.
60. Van der Schueren BJ, Homel P, Alam M, Agenor K, Wang G, Reilly D, Laferrère B. Magnitude and variability of the glucagon-like peptide-1 response in patients with type 2 diabetes up to 2 years following gastric bypass surgery. Diabetes Care. 2012;35(1):42–6. doi:10.2337/dc11-1472.
61. Laferrère B, Heshka S, Wang K, Khan Y, McGinty J, Teixeira J, Hart AB, Olivan B. Incretin levels and effect are markedly enhanced 1 month after Roux-en-Y gastric bypass surgery in obese patients with type 2 diabetes. Diabetes Care. 2007;30(7):1709–16. doi:10.2337/dc06-1549.
62. Korner J, Bessler M, Inabnet W, Taveras C, Holst JJ. Exaggerated glucagon-like peptide-1 and blunted glucose-dependent insulinotropic peptide secretion are associated with Roux-en-Y gastric bypass but not adjustable gastric banding. Surg Obes Relat Dis. 2007;3(6):597–601. doi:10.1016/j.soard.2007.08.004.
63. Wu Q, Xiao Z, Cheng Z, Tian H. Changes of blood glucose and gastrointestinal hormones 4 months after Roux-en-Y gastric bypass surgery in Chinese obese type 2 diabetes patients with lower body mass index. J Diabetes Investig. 2013;4(2):214–21. doi:10.1111/jdi.12005.
64. Kim MJ, Park HK, Byun DW, Suh KI, Hur KY. Incretin levels 1 month after laparoscopic single anastomosis gastric bypass surgery in non-morbid obese type 2 diabetes patients. Asian J Surg. 2014;37(3):130–7. doi:10.1016/j.asjsur.2013.09.008.
65. Jacobsen SH, Olesen SC, Dirksen C, Jorgensen NB, Bojsen-Moller KN, Kielgast U, Worm D, Almdal T, Naver LS, Hvolris LE, Rehfeld JF, Wulff BS, Clausen TR, Hansen DL, Holst JJ, Madsbad S. Changes in gastrointestinal hormone responses, insulin sensitivity, and beta-cell function within 2 weeks after gastric bypass in non-diabetic subjects. Obes Surg. 2012;22(7):1084–96. doi:10.1007/s11695-012-0621-4.
66. Bak MJ, Wewer Albrechtsen NJ, Pedersen J, Knop FK, Vilsboll T, Jorgensen NB, Hartmann B, Deacon CF, Dragsted LO, Holst JJ. Specificity and sensitivity of commercially available assays for glucagon-like peptide-1 (GLP-1): implications for GLP-1 measurements in clinical studies. Diabetes Obes Metab. 2014;16(11):1155–64. doi: 10.1111/dom.12352.
67. Alam ML, Van der Schueren BJ, Ahren B, Wang GC, Swerdlow NJ, Arias S, Bose M, Gorroochurn P, Teixeira J, McGinty J, Laferrère B. Gastric bypass surgery, but not caloric restriction, decreases dipeptidyl peptidase-4 activity in obese patients with type 2 diabetes. Diabetes Obes Metab. 2011;13(4):378–81. doi:10.1111/j.1463-1326.2011.01358.x.
68. Dirksen C, Bojsen-Moller KN, Jorgensen NB, Jacobsen SH, Kristiansen VB, Naver LS, Hansen DL, Worm D, Holst JJ, Madsbad S. Exaggerated release and preserved insulinotropic action of glucagon-like peptide-1 underlie insulin hypersecretion in glucose-tolerant individuals after Roux-en-Y gastric bypass. Diabetologia. 2013;56(12):2679–87. doi:10.1007/s00125-013-3055-1.
69. Horowitz M, Cook DJ, Collins PJ, Harding PE, Hooper MJ, Walsh JF, Shearman DJ. Measurement of gastric emptying after gastric bypass surgery using radionuclides. Br J Surg. 1982;69(11):655–7.
70. Naslund I, Beckman KW. Gastric emptying rate after gastric bypass and gastroplasty. Scand J Gastroenterol. 1987;22(2):193–201.
71. Morinigo R, Lacy AM, Casamitjana R, Delgado S, Gomis R, Vidal J. GLP-1 and changes in glucose tolerance following gastric bypass surgery in morbidly obese subjects. Obes Surg. 2006;16(12):1594–601. doi:10.1381/096089206779319338.
72. Pournaras DJ, Aasheim ET, Bueter M, Ahmed AR, Welbourn R, Olbers T, le Roux CW. Effect of bypassing the proximal gut on gut hormones involved with glycemic control and weight loss. Surg Obes Relat Dis. 2012;8(4):371–4. doi:10.1016/j.soard.2012.01.021.
73. McLaughlin T, Peck M, Holst J, Deacon C. Reversible hyperinsulinemic hypoglycemia after gastric bypass: a consequence of altered nutrient delivery. J Clin Endocrinol Metab. 2010;95(4):1851–5. doi:10.1210/jc.2009-1628.

74. Service GJ, Thompson GB, Service FJ, Andrews JC, Collazo-Clavell ML, Lloyd RV. Hyperinsulinemic hypoglycemia with nesidioblastosis after gastric-bypass surgery. N Engl J Med. 2005;353(3):249–54. doi:10.1056/NEJMoa043690.
75. Lindqvist A, Spegel P, Ekelund M, Garcia Vaz E, Pierzynowski S, Gomez MF, Mulder H, Hedenbro J, Groop L, Wierup N. Gastric bypass improves beta-cell function and increases beta-cell mass in a porcine model. Diabetes. 2014;63(5):1665–71. doi:10.2337/db13-0969.
76. Sarson DL, Besterman HS, Bloom SR. Radioimmunoassay of gastric inhibitory polypeptide and its release in morbid obesity and after jejuno-ileal bypass [proceedings]. J Endocrinol. 1979;81(2):155P–6.
77. Sarson DL, Scopinaro N, Bloom SR. Gut hormone changes after jejunoileal (JIB) or biliopancreatic (BPB) bypass surgery for morbid obesity. Int J Obes. 1981;5(5):471–80.
78. Halverson JD, Kramer J, Cave A, Permutt A, Santiago J. Altered glucose tolerance, insulin response, and insulin sensitivity after massive weight reduction subsequent to gastric bypass. Surgery. 1982;92(2):235–40.
79. Sirinek KR, O'Dorisio TM, Hill D, McFee AS. Hyperinsulinism, glucose-dependent insulinotropic polypeptide, and the enteroinsular axis in morbidly obese patients before and after gastric bypass. Surgery. 1986;100(4):781–7.
80. Naslund E, Backman L, Holst JJ, Theodorsson E, Hellstrom PM. Importance of small bowel peptides for the improved glucose metabolism 20 years after jejunoileal bypass for obesity. Obes Surg. 1998;8(3):253–60.
81. Verdich C, Flint A, Gutzwiller JP, Naslund E, Beglinger C, Hellstrom PM, Long SJ, Morgan LM, Holst JJ, Astrup A. A meta-analysis of the effect of glucagon-like peptide-1 (7-36) amide on ad libitum energy intake in humans. J Clin Endocrinol Metab. 2001;86(9):4382–9. doi:10.1210/jcem.86.9.7877.
82. Valverde I, Puente J, Martin-Duce A, Molina L, Lozano O, Sancho V, Malaisse WJ, Villanueva-Penacarrillo ML. Changes in glucagon-like peptide-1 (GLP-1) secretion after biliopancreatic diversion or vertical banded gastroplasty in obese subjects. Obes Surg. 2005;15(3):387–97. doi:10.1381/0960892053576613.
83. Korner J, Bessler M, Cirilo LJ, Conwell IM, Daud A, Restuccia NL, Wardlaw SL. Effects of Roux-en-Y gastric bypass surgery on fasting and postprandial concentrations of plasma ghrelin, peptide YY, and insulin. J Clin Endocrinol Metab. 2005;90(1):359–65. doi:10.1210/jc.2004-1076.
84. Borg CM, le Roux CW, Ghatei MA, Bloom SR, Patel AG, Aylwin SJ. Progressive rise in gut hormone levels after Roux-en-Y gastric bypass suggests gut adaptation and explains altered satiety. Br J Surg. 2006;93(2):210–5. doi:10.1002/bjs.5227.
85. Jorgensen NB, Jacobsen SH, Dirksen C, Bojsen-Moller KN, Naver L, Hvolris L, Clausen TR, Wulff BS, Worm D, Lindqvist Hansen D, Madsbad S, Holst JJ. Acute and long-term effects of Roux-en-Y gastric bypass on glucose metabolism in subjects with Type 2 diabetes and normal glucose tolerance. Am J Physiol Endocrinol Metab. 2012;303(1):E122–31. doi:10.1152/ajpendo.00073.2012.
86. Romero F, Nicolau J, Flores L, Casamitjana R, Ibarzabal A, Lacy A, Vidal J. Comparable early changes in gastrointestinal hormones after sleeve gastrectomy and Roux-En-Y gastric bypass surgery for morbidly obese type 2 diabetic subjects. Surg Endosc. 2012;26(8):2231–9. doi:10.1007/s00464-012-2166-y.
87. Mallipedhi A, Prior SL, Barry JD, Caplin S, Baxter JN, Stephens JW. Temporal changes in glucose homeostasis and incretin hormone response at 1 and 6 months after laparoscopic sleeve gastrectomy. Surg Obes Relat Dis. 2014;10(5):860–9. doi:10.1016/j.soard.2014.02.038.
88. Plourde CE, Grenier-Larouche T, Caron-Dorval D, Biron S, Marceau S, Lebel S, Biertho L, Tchernof A, Richard D, Carpentier AC. Biliopancreatic diversion with duodenal switch improves insulin sensitivity and secretion through caloric restriction. Obesity. 2014;22(8):1838–46. doi:10.1002/oby.20771.
89. Ye J, Hao Z, Mumphrey MB, Townsend RL, Patterson LM, Stylopoulos N, Munzberg H, Morrison CD, Drucker DJ, Berthoud HR. GLP-1 receptor signaling is not required for

reduced body weight after RYGB in rodents. Am J Physiol Regul Integr Comp Physiol. 2014;306(5):R352–62. doi:10.1152/ajpregu.00491.2013.
90. Jimenez A, Mari A, Casamitjana R, Lacy A, Ferrannini E, Vidal J. GLP-1 and glucose tolerance after sleeve gastrectomy in morbidly obese subjects with type 2 diabetes. Diabetes. 2014;63(10):3372–7. doi:10.2337/db14-0357.
91. Chambers AP, Smith EP, Begg DP, Grayson BE, Sisley S, Greer T, Sorrell J, Lemmen L, LaSance K, Woods SC, Seeley RJ, D'Alessio DA, Sandoval DA. Regulation of gastric emptying rate and its role in nutrient-induced GLP-1 secretion in rats after vertical sleeve gastrectomy. Am J Physiol Endocrinol Metab. 2014;306(4):E424–32. doi:10.1152/ajpendo.00469.2013.
92. Madsbad S, Holst JJ. GLP-1 as a mediator in the remission of type 2 diabetes after gastric bypass and sleeve gastrectomy surgery. Diabetes. 2014;63(10):3172–4. doi:10.2337/db14-0935.
93. Wilson-Perez HE, Chambers AP, Ryan KK, Li B, Sandoval DA, Stoffers D, Drucker DJ, Perez-Tilve D, Seeley RJ. Vertical sleeve gastrectomy is effective in two genetic mouse models of glucagon-like Peptide 1 receptor deficiency. Diabetes. 2013;62(7):2380–5. doi:10.2337/db12-1498.
94. Salehi M, Gastaldelli A, D'Alessio DA. Blockade of glucagon-like peptide 1 receptor corrects postprandial hypoglycemia after gastric bypass. Gastroenterology. 2014;146(3):669–80. doi:10.1053/j.gastro.2013.11.044. e662.
95. Sathananthan M, Farrugia LP, Miles JM, Piccinini F, Dalla Man C, Zinsmeister AR, Cobelli C, Rizza RA, Vella A. Direct effects of exendin-(9,39) and GLP-1-(9,36)amide on insulin action, beta-cell function, and glucose metabolism in nondiabetic subjects. Diabetes. 2013;62(8):2752–6. doi: 10.2337/Db13-0140.
96. Vetter ML, Wadden TA, Teff KL, Khan Z, Carvajal R, Ritter S, Moore RH, Chittams JL, Iagnocco A, Murayama K, Korus G, Williams NN, Rickels MR. GLP-1 plays a limited role in improved glycemia shortly after Roux-en-Y gastric bypass: a comparison to intensive lifestyle modification. Diabetes. 2014. doi:10.2337/db14-0558.
97. Jimenez A, Casamitjana R, Viaplana-Masclans J, Lacy A, Vidal J. GLP-1 action and glucose tolerance in subjects with remission of type 2 diabetes after gastric bypass surgery. Diabetes Care. 2013;36(7):2062–9. doi: dc12-1535 [pii] 10.2337/dc12-1535.
98. Jorgensen NB, Dirksen C, Bojsen-Moller KN, Jacobsen SH, Worm D, Hansen DL, Kristiansen VB, Naver L, Madsbad S, Holst JJ. Exaggerated glucagon-like peptide 1 response is important for improved beta-cell function and glucose tolerance after Roux-en-Y gastric bypass in patients with type 2 diabetes. Diabetes. 2013;62(9):3044–52. doi:10.2337/db13-0022.
99. Dutia R, Brakoniecki K, Bunker P, Paultre F, Homel P, Carpentier AC, McGinty J, Laferrère B. Limited recovery of beta-cell function after gastric bypass despite clinical diabetes remission. Diabetes. 2014;63(4):1214–23. doi:10.2337/db13-1176.
100. Dutia R, Brakoniecki K, Wang G, Mogul S, Agenor K, McGinty J, Belsley SJ, Rosen DJ, Laferrère B. Greater improvement in β-cell function after gastric bypass is independent of weight loss. Diabetes. 2013;1825.

Effect of Bariatric Surgery on Insulin Secretion

10

Kim T. Nguyen and Judith Korner

10.1 Introduction

Increase in obesity has led to higher prevalence of type 2 DM (T2DM), a chronic and progressive disease marked by insulin resistance and the eventual loss of insulin secretion. While weight loss improves glucose tolerance in obese patients with T2DM, conventional medical management often fails to achieve sustained weight loss and glycemic control in severely obese patients [1–3]. Multiple studies have documented the efficacy of bariatric surgery in attaining substantial weight loss as well as long-term improvement in diabetes and its associated comorbidities [4–10].

The effect of bariatric surgery on insulin sensitivity and secretion differs depending on the type of surgery, with the greatest effect observed following malabsorptive procedures [4, 5, 11]. Metabolic improvement after restrictive procedures such as gastric banding (LAGB) appears to be driven mostly by weight loss [12]. Greater insulin sensitivity and insulin secretion after malabsorptive procedures such as Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion (BPD) are driven not only by greater weight loss but also by anatomical changes that alter gut hormone secretion and nutrient transport. Sleeve gastrectomy (SG), initially thought to be mostly restrictive, also alters gut hormone secretion and leads to improvements in insulin sensitivity more comparable to RYGB than LAGB [13, 14].

The mechanisms by which bariatric surgery improves glucose homeostasis in obese patients with T2DM have yet to be fully elucidated, and likely encompass both weight loss dependent and weight independent mechanisms. In the immediate postoperative period, before notable weight loss has even occurred, there is a rapid

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decrease in fasting insulin and fasting glucose that reflects increased hepatic insulin sensitivity [15, 16]. Following significant weight loss several months after surgery, peripheral insulin sensitivity also improves, in parallel with the amount of weight loss. However, RYGB and SG are also associated with increased β-cell function and altered secretion of the incretin, glucagon-like peptide-1 (GLP-1), which occurs early and persists postoperatively.

This chapter discusses altered insulin sensitivity and insulin secretion after bariatric surgery, focusing on the factors contributing to increased insulin secretion particularly after RYGB.

10.2 Insulin Sensitivity

In obese diabetic patients, weight loss is accompanied by a corresponding increase in insulin sensitivity and increase in β-cell activity [17, 18]. It is also well established that significant caloric restriction improves glucose tolerance in diabetic patients [19]. Altered insulin sensitivity after bariatric surgery reflects the impact of both caloric restriction and weight loss.

Profound improvements in fasting glucose concentration and insulin action have been noted early after bariatric surgery, often before significant weight loss has even occurred [20–22]. Caloric restriction, which occurs immediately after all surgical interventions, likely plays an important role in the favorable metabolic changes observed, particularly in the early postoperative period [19, 22]. For example, after losing an equivalent amount of weight over about 3 weeks through RYGB or a 500 kcal per day diet, obese diabetic patients exhibited similar improvements in insulin sensitivity, acute insulin response, and β-cell function as assessed by an intravenous glucose challenge [23]. This early improvement reflects mostly improved hepatic insulin sensitivity from caloric restriction, as the profound negative calorie balance leads to decreased liver fat and increased insulin sensitivity [24], reduced basal glucose production, and increased liver clearance of insulin [25, 26].

Subsequent change in peripheral insulin sensitivity varies by surgical procedure. After LAGB, further improvement in peripheral insulin sensitivity occurs more gradually and is in proportion to the amount of weight loss [12]. In contrast, RYGB leads to profound changes in insulin sensitivity and insulin action much more rapidly [27–32]. Moreover, several studies have noted greater improvement in T2DM and greater increase in insulin sensitivity after RYGB over time, even after equivalent weight loss by dietary or restrictive interventions, suggesting weight-independent mechanisms [27, 28, 33]; however, these studies did not necessarily control for equivalent daily caloric intake. Others observe that the increased insulin sensitivity after RYGB occurs in proportion to weight loss, which is greater after malabsorptive surgery [34, 35].

Improved peripheral insulin sensitivity is greater after BPD than after other procedures and occurs as early as 2 weeks postoperatively [6, 36, 37]. As noted by Mari *et al.*, BPD increases insulin sensitivity regardless of the baseline glucose tolerance, and leads to a significant decrease in insulin hypersecretion. Insulin sensitivity after

BPD has even been observed to exceed that of obese patients with normal glucose tolerance [37]. Neither weight loss nor GLP-1 secretion after oral glucose or meals appears to correlate with improved insulin sensitivity after BPD [36]. The factors contributing to improved insulin sensitivity remain unclear, although insulin sensitivity after BPD is greater after an oral than an intravenous challenge, consistent with a mechanism linked to bypass of the duodenum and jejunum [38]. In addition, the diversion of bile acid to the ileum leads to decreased lipid absorption and increased bile acid reabsorption, which may affect glucose metabolism through increased binding of bile acids to farnesoid X receptor (FXR) [39, 40]. Increased activation of FXR in the ileum activates fibroblast growth factor-19 (FGF-19), which then binds to the fibroblast growth factor receptor-4 (FGFR-4) and suppresses hepatic gluconeogenesis [40]. This mechanism is also likely to contribute to improved insulin sensitivity after RYGB and SG.

While the long-term effects of SG on weight loss and glycemic control need further study, SG has demonstrated metabolic effects beyond that of purely restrictive procedures such as LAGB. Changes in insulin sensitivity after SG are thought to be similar to RYGB, although results have been discrepant between studies [41–44]. Abbatini et al. compared LAGB, SG, and RYGB and observed that T2DM improved similarly for RYGB and SG. Sleeve gastrectomy actually led to greater improvement in insulin sensitivity than RYGB when assessed by a euglycemic hyperinsulinemic clamp in the absence of any hypoglycemic medication [43]. Another study that assessed insulin sensitivity by applying a mathematical model to data from a mixed meal tolerance test found greater improvement in insulin sensitivity after RYGB than SG [41]. Differences in study population and mechanistic studies may account for the discordant results, but further research into the impact of sleeve gastrectomy on glucose homeostasis is needed.

In summary, insulin sensitivity improves after bariatric surgery and weight loss. Initial improvement occurs largely due to caloric restriction and primarily reflects improved hepatic insulin sensitivity, while subsequent improvement in peripheral insulin sensitivity occurs secondary to weight loss and possibly due to mechanisms specific to the surgical technique.

10.3 β-Cell Function and Insulin Secretion

Assessment of β-cell function is complicated because β-cells adapt to chronic stimuli with a standard set point of secretory capacity, but must also be able to respond to acute challenges such as feeding by promptly releasing sufficient insulin to control glycemia. Bariatric surgery leads to greater insulin sensitivity and insulin action which relieves secretory pressure on the β-cell and leads to a decrease in total insulin secretion; it also improves β-cell response to dynamic changes.

Basal β-cell function is reflected in fasting insulin and total insulin secretion. β-cell responsiveness to dynamic change is assessed using parameters such as the insulinogenic index (change in insulin relative to change in glucose over an interval of time), acute insulin response (AIR) to intravenous glucose, and β-cell glucose

sensitivity (measured as the slope of the insulin secretion to plasma glucose dose-response relationship) [45, 46]. Disposition index (DI) is an overall measure of β-cell function that combines both insulin sensitivity and insulin secretion [15]. Comparison of insulin secretion patterns and changes in peripheral insulin and glucose levels should take into account the altered dynamics of accelerated transit and absorption of nutrients after procedures such as RYGB, SG, and BPD.

After LAGB, the insulin curve is characterized by a parallel downward shift in concentration, consistent with increased insulin sensitivity [47, 48]. Early and dynamic insulin secretion is not necessarily improved, but DI increases after at least moderate weight loss [30, 33, 47]. Overall peripheral insulin levels decrease in proportion to the degree of weight loss and are more consistent with increased hepatic clearance than reduced insulin secretion [12].

Insulin secretion after oral ingestion of nutrients is singularly altered after RYGB, with an earlier and exaggerated rise in insulin concentration followed by rapid decline [28, 35, 48–53]. Intrinsic β-cell function recovers early on after RYGB, with several studies reporting an improved acute insulin response [18, 26, 31, 35, 47, 52, 54, 55], although residual glucose intolerance persists [35, 49, 53]. Fasting insulin and total insulin output decrease after RYGB [31, 35, 48]. Insulinogenic index also increases after RYGB [31, 49, 53, 56]. In contrast to LAGB, β-cell glucose sensitivity increases early after RYGB in response to an oral glucose challenge, although responsiveness to intravenous glucose is most notable several months after surgery, in parallel with weight loss [25, 35, 47]. Dutia et al. found that β-cell glucose sensitivity, DI, and insulin secretion rapidly and markedly improved after an oral glucose tolerance test but these early changes were less apparent after an intravenous glucose tolerance test, highlighting the importance of the oral route and gastrointestinal factors in the improvement of β-cell function after RYGB.

Further evidence of the impact of altered nutrient transport and glucose absorption after RYGB on β-cell function and insulin action is provided by the rare cases of severe postprandial hypoglycemia that arise only after RYGB but not LAGB [57–59]. Islet cell hypertrophy may be involved based on surgical specimens from symptomatic patients treated with partial pancreatectomy, but this has been disputed by later studies [58–60]. While the pathogenesis of this syndrome remains unclear, the condition is characterized by excessive insulin response despite improved insulin sensitivity [57, 61]. Given the exaggerated GLP-1 response following RYGB, it has been hypothesized that enhanced GLP-1 secretion contributes to excessive insulin response, and affected patients have been found to have greater insulin and GLP-1 response to meal tests relative to other postsurgical patients without postprandial hypoglycemia [57, 61–63]. One study suggested that postprandial hypoglycemia could be successfully treated with a GLP-1 receptor antagonist, which avoided postprandial hypoglycemia by decreasing the exaggerated release of GLP-1 and insulin [63].

In contrast to the exaggerated insulin response after RYGB, the major effect of BPD is a rapid and significant decrease in insulin resistance [37]. Total insulin secretion decreases in parallel with the increase in insulin sensitivity in all patients after BPD, regardless of baseline glucose tolerance [36, 64]. Improvement in

insulin sensitivity and β-cell glucose sensitivity, as well as acute insulin response and DI, occurs as early as 1 week after BPD, before significant weight loss has occurred [36–38, 64]. The early increase in insulin sensitivity and greater insulin response after oral glucose challenge but not to intravenous glucose challenge implicate early and rapid delivery of unabsorbed nutrients to the distal small intestine as a mechanism for improvement in T2DM [38].

Sleeve gastrectomy, like RYGB, leads not only to improved insulin sensitivity but improved insulin secretion and an exaggerated postprandial increase in GLP-1 [42, 43, 65, 66]. Insulin sensitivity improves rapidly and markedly after SG and fasting insulin decreases similarly to RYGB [7, 42, 67]. While further studies are needed, an increase in the insulinogenic index and early insulin response after SG correlates with baseline C-peptide levels, suggesting that SG similarly increases β-cell function [67].

In summary, β-cell function progressively increases over time according to weight loss after restrictive procedures, leading to lower fasting insulin and total insulin secretion. RYGB and BPD also improve the dynamic responsiveness of the β-cell often before significant weight loss has even occurred. While altered nutrient transit and glucose absorption may partly explain the changes in acute insulin response and β-cell glucose sensitivity, concurrent changes in gut hormone secretion also influence further adaptation of β-cell function.

10.4 Mechanisms for Changes in Insulin Action and β-Cell Function

Caloric restriction and weight loss clearly play a significant role in the improvement of insulin resistance and β-cell dysfunction after bariatric surgery. However, early and profound improvement in insulin sensitivity and insulin action, before significant weight loss has even occurred, as well as the magnitude of improvement after surgeries such as RYGB and BPD, suggests that mechanisms independent of weight loss and specific to the surgical intervention may also account for the sustained and marked improvement of T2DM.

10.4.1 Gut Hormone Secretion

Altered nutrient transit after RYGB, SG, and BPD lead to changes in glucose absorption as well as the secretion of gut-derived hormones from enteroendocrine cells. The incretin effect, which is the greater insulin response after oral glucose compared with an equivalent intravenous glucose dose, is diminished in T2DM [68]. GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) are the two incretins responsible for one-half to two-thirds of insulin secretion. GLP-1 is secreted mostly from ileal L cells while GIP is secreted from duodenal K cells, and both are rapidly inactivated by the enzyme dipeptidyl peptidase IV (DPP-IV). GLP-1 analogues and DPP-IV inhibitors have been developed as

antidiabetic medications, stressing the importance of GLP-1 in glucose regulation [69, 70].

Multiple studies have observed that postprandial secretion of GLP-1 is substantially and durably increased after RYGB, but not after LAGB or diet-induced weight loss [27, 28, 32, 48, 52, 62, 71]. The increase in GLP-1 occurs early after RYGB, before significant weight loss has occurred, and is clearly related to the more rapid delivery of nutrients to the distal small intestine [27, 71–73]. Recovery of the incretin effect has been associated with exaggerated GLP-1 secretion even after equivalent weight loss [71], although the insulinotropic effect of GLP-1 on β-cell function may be smaller than previously thought. Pharmacologic blockade of GLP-1 receptors with exendin (9-39) only minimally decreases β-cell glucose sensitivity, glucagon suppression, and insulin secretion [74–76]. Interindividual variability in GLP-1 receptor response to GLP-1 may also play a role in the variable weight loss and range of glucose control achieved after RYGB [77].

Postprandial changes in GIP after RYGB have been inconsistent, likely reflecting variability in surgical technique, test meal composition, and timing of blood sample collections [28, 29, 48, 78]. BPD leads to decreased fasting and stimulated GIP, while GLP-1 is increased but to a smaller extent than seen after RYGB [36]. Decreased GIP activity, as in GIP-receptor knockout mice, has been shown to cause hyperglycemia and impaired insulin secretion after oral administration of glucose, suggesting a role for GIP in the acute insulin response [79]. GIP infusion has been shown to mildly increase insulin secretion and decrease glucagon [80]. Decreased GIP secretion after bariatric surgery may reflect restoration of the insulinotropic effect of GIP, which is impaired in T2DM [68, 81]. Although GIP may not mediate early recovery of β-cell function or insulin secretion, decreased GIP may contribute to decreased glucagon postoperatively and further potentiate incretin response by decreasing glucotoxicity and secretory pressure on the β-cell.

Decreased ghrelin, an orexigenic peptide produced in the fundus and body of the stomach, is thought to decrease hunger and may also lead to lower HbA1c after RYGB and VSG [66, 82, 83]. Ghrelin increases after diet-induced weight loss and LAGB, where it correlated with insulin levels and hepatic insulin clearance but not insulin sensitivity [32, 84, 85]. Reports of ghrelin levels after RYGB have been inconsistent, with some groups reporting a decrease while others have noted lack of change or an increase [50, 52, 86–88]. Differences between studies such as varying degrees of weight loss, postoperative intervals, study time points, and the use of assays measuring “active” octanoylated isoform versus total ghrelin likely account for the discrepant results. SG, through its resection of the fundus as well as a greater part of the stomach body, leads to decreased fasting and postprandial ghrelin [66]. While decreased ghrelin may attenuate hunger and contribute to further weight loss and thereby affect insulin sensitivity, it does not appear to influence insulin secretion or insulin sensitivity directly.

10.4.2 Altered Nutrient Flow

Early and rapid delivery of unabsorbed nutrients to the distal small intestine may activate the "ileal brake" that potentiates the secretion of GLP-1 and Peptide YY, an anorexigenic hormone also elevated after RYGB that is known to slow intestinal transit time, increase satiety, and delay gastric emptying. Exaggerated GLP-1 secretion helps to improve insulin secretion and insulin sensitivity while PYY facilitates maintenance of glycemic control by decreasing food consumption. Consistent with this hypothesis is the observation that the procedures most consistently leading to improved T2DM shorten the route of nutrient flow from the stomach to the intestine and increase the rate of transport of ingested nutrients [5, 7, 13, 30, 66].

Rodent models of ileal interposition (IT), a surgical procedure whereby a segment of the ileum is inserted into the proximal intestine so that there is no gastric restriction or duodenal bypass, provide further evidence for the role of the distal ileum in improving glucose tolerance. IT in different rodent models resulted in elevated levels of GLP-1 and PYY and improvements in glucose tolerance, insulin sensitivity, and β-cell function [89–93]. Improvement in oral glucose tolerance after IT was reversed by inhibition of GLP-1 receptors with exendin (9-39), reinforcing the hypothesis that early and increased GLP-1 receptor activation contributes to improved insulin action after RYGB [93].

Bypass of the proximal small intestine and exclusion of nutrient transit through the duodenum and jejunum has also been hypothesized to contribute to improvement in T2DM. Duodenal-jejunal bypass (DJB) without gastric restriction in animal studies of both nonobese and diet-induced obese diabetic rats led to improvement in hyperglycemia independent of food intake and weight reduction [78, 94, 95]. Intestinal glucoregulatory hormones and vagal innervation may contribute to alleviation of hyperglycemia in this DJB model [95]. In humans, DJB had only a moderate effect with improvement in HbA1c that mildly deteriorated by 12 months after surgery [96]. It is unclear if the glycemic impact of DJB lies in its alteration of the intestinal site of nutrient delivery or in its moderate weight loss.

Further evidence that exclusion of the proximal small intestine may affect glucose homeostasis through unknown mechanisms can be derived from more recent studies of endoluminal sleeves (ELS) that allow nutrients to flow from the pylorus to the jejunum without contacting duodenal mucosa. Aguirre et al. demonstrated that despite less weight loss than similar rats that had undergone RYGB, rats treated with ELS attained similar improvement in glycemic control. Studies in humans have also demonstrated reduced HbA1c after various endoluminal duodenal-jejunal bypass sleeves, although investigation into safety, efficacy, and long-term outcomes are ongoing [97, 98].

10.4.3 Bile Acids

Increased bile acid reabsorption has been proposed as a potential mechanism for improved insulin sensitivity after RYGB and BPD, but not LAGB [39, 40, 99–104].

After RYGB, increased bile acids were two-fold higher and positively correlated with peak GLP-1 and adiponectin, and inversely correlated with 2-hour postprandial glucose and thyroid stimulating hormone (TSH), implicating altered bile acid concentrations as a mechanism in glucose and lipid metabolism. Bile acids may affect insulin action through binding to the TGR5 receptor on L-cells, which release GLP-1 [100, 101]. Gerhard et al. also showed that diabetic patients achieving remission after RYGB had larger increases in fasting bile acids than non-diabetics or diabetics who did not go into remission[[99].

Altered enterohepatic recycling of bile acids and consequent increase in serum bile acids induced by IT in rats also suggest a mechanism for improved glycemia after BPD. Increased bile acids bind to FXR and stimulate secretion of FGF19, which subsequently inhibits hepatic glucose production and improves insulin sensitivity [39, 40]. Whole body FXR knock-out mice have been shown to be refractory to the metabolic improvements seen in wild-type mice after SG [104]. In prospective human and animal studies, Pournaras et al. concluded that RYGB but not LAGB causes more rapid delivery of bile acids to the terminal ileum and therefore higher total bile acid levels, plasma GLP-1, PYY, and FGF19 [102]. Other studies have similarly found increases in plasma bile acids and FGF19 after RYGB, but Kohli et al observed that surgery-induced increase in bile acids did not correlate with postprandial insulin secretion or insulin sensitivity [100, 105].

10.4.4 Microbiota

Data from mouse studies and humans have provided evidence that gut microbiota may play an important role in energy storage and possibly the development of obesity and associated complications, although it remains unclear whether changes in the gut microbiome are a consequence or cause of obesity [106]. Bariatric surgery, though inducing anatomic, systemic, and environmental changes, may impact the composition of gut microbiota. Several studies have suggested that bariatric surgery shifts bacterial flora in obese patients toward profiles more similar to that of lean patients. Altered anatomy may play a key role in the changes in microbiota, as differences in microbial ecology were most notable distal to the site of surgical manipulation in rat models [106–109]. Transfer of gut microbiota from RYGB treated mice to non-operated, aseptic mice has been shown to be sufficient to cause decreased weight and adiposity, possibly due to altered microbial synthesis of short-chain fatty acids [107]. Whether changes in microbiota affect insulin sensitivity or insulin secretion directly is unknown.

10.4.5 Insulin Clearance

Early improvement in hepatic gluconeogenesis and hepatic insulin sensitivity may account for the rapid decrease in fasting glucose and fasting insulin after RYGB. Bojsen-Moller et al. found that fasting hepatic insulin clearance increased

as early as 1 week and further at 3 months for both diabetic and normoglycemic patients after RYGB. Postprandial insulin clearance increased only in the T2DM patients, in whom the increased insulin clearance occurred as early as 1 week following surgery and persisted at 3 months and after 1 year [25]. Based on this study and others who have noted rapid improvement in fasting glucose and fasting insulin before significant weight loss, it becomes plausible that nonenteral factors such as increased hepatic insulin sensitivity and insulin clearance account for some of the early improvement following caloric restriction [25, 110]. Early postoperative increases in plasma free fatty acids are followed by increased suppression consistent with improved peripheral insulin sensitivity with progressive weight loss, as demonstrated during clamp studies in T2DM patients 1 year after RYGB [25].

10.4.6 Other Mechanisms

G-protein coupled taste receptors detect gut luminal contents and transmit signals that regulate nutrient transporter expression and nutrient uptake, as well as the release of gut hormones and neurotransmitters involved in the regulation of energy and glucose homeostasis. Sweet taste receptors are dysregulated in T2DM and may increase postprandial hyperglycemia by increasing glucose absorption. In rodent models, DJB has modulated sweet taste receptor expression and decreased glucose transport. Accelerated delivery of undigested nutrients to the lower small intestine after RYGB may also affect the regulation of taste receptors or glucose transporters on L cells, leading to increased PYY and GLP-1 secretion. The precise impact of altered gut hormone secretion due to altered taste receptor perception after bariatric surgery, and its consequences for insulin secretion and sensitivity, remains to be seen [111].

Obesity and T2DM are known to alter circulating concentrations of many metabolites [112–114]. Metabolite profiling in diabetic patients has shown that weight loss after RYGB, but not diet-induced weight loss, leads to a decrease in fasting plasma concentrations of branched chain amino acids and their C3 and C5 acylcarnitine metabolites and correlates negatively with insulin sensitivity [115]. Similar alterations in metabolites have been observed after LAGB or RYGB in a nondiabetic group following equivalent weight loss [116]. It is unclear whether changes in amino acid metabolism and possibly transport are unique to RYGB or a consequence of improved insulin action.

10.5 Conclusion

Improvement in T2DM after bariatric surgery is marked by profound changes in insulin sensitivity and insulin secretion due to weight loss associated and weight loss independent mechanisms. Caloric restriction and the amount of weight loss achieved by bariatric surgery significantly account for improvements in insulin sensitivity and action. Hepatic insulin sensitivity occurs early in response to caloric

restriction and peripheral insulin sensitivity improves further in parallel with weight loss. However, altered nutrient transport and glucose absorption leading to changes in gut hormone secretion also impact insulin sensitivity and β-cell function, with recovery of both basal and dynamic insulin secretion. The contribution of changes in bile acid reabsorption, microbiota, amino acid metabolism, and intestinal nutrient sensing and carbohydrate metabolism to β-cell function and glucose homeostasis are additional areas for ongoing research. Further understanding of how β-cell function and insulin sensitivity are altered by bariatric surgery has provided tremendous insight into the multiple endocrine functions of the gastrointestinal tract, and has highlighted potential therapeutic targets for the treatment of T2DM and obesity.

References

1. Ali MK, Bullard KM, Gregg EW. Achievement of goals in U.S. Diabetes Care, 1999–2010. N Engl J Med. 2013;369(3):287–8.
2. Stark Casagrande S, et al. The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988-2010. Diabetes Care. 2013;36(8):2271–9.
3. Pi-Sunyer FX, Becker DM, Bouchard C, Carleton RA, Colditz GA, Dietz WH, Foreyt JP, Garrison RJ, Grunday SM, Hansen BC, Higgins M, Hill JO, Howard BV, Klesges RC, Kuczmarski RJ, Kumanyika S, Legako RD, Prewitt TE, Rocchini AP, Smith PL, Snetselaar LG, Sowers JR, Weintraub M, Williamson DF, Wilson GT. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults – the evidence report. National Institutes of Health. Obes Res. 1998;6(Suppl 2):51S–209S.
4. Buchwald H, et al. Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004;292(14):1724–37.
5. Buchwald H, et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. Am J Med. 2009;122(3):248–56. e5.
6. Mingrone G, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. N Engl J Med. 2012;366(17):1577–85.
7. Schauer PR, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med. 2012;366(17):1567–76.
8. Sjostrom L. Review of the key results from the Swedish Obese Subjects (SOS) trial—a prospective controlled intervention study of bariatric surgery. J Intern Med. 2013;273(3):219–34.
9. Ikramuddin S, et al. Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia: the Diabetes Surgery Study randomized clinical trial. JAMA. 2013;309(21):2240–9.
10. Schauer PR, Bhatt DL, Kashyap SR. Bariatric surgery versus intensive medical therapy for diabetes. N Engl J Med. 2014;371(7):682.
11. Mingrone G, Castagneto-Gissey L. Mechanisms of early improvement/resolution of type 2 diabetes after bariatric surgery. Diabetes Metab. 2009;35(6 Pt 2):518–23.
12. Dixon JB, et al. Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. JAMA. 2008;299(3):316–23.
13. Romero F, et al. Comparable early changes in gastrointestinal hormones after sleeve gastrectomy and Roux-En-Y gastric bypass surgery for morbidly obese type 2 diabetic subjects. Surg Endosc. 2012;26(8):2231–9.
14. Chambers AP, et al. Weight-independent changes in blood glucose homeostasis after gastric bypass or vertical sleeve gastrectomy in rats. Gastroenterology. 2011;141(3):950–8.
15. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care. 1999;22(9): 1462–70.

16. Tripathy D, et al. Contribution of insulin-stimulated glucose uptake and basal hepatic insulin sensitivity to surrogate measures of insulin sensitivity. Diabetes Care. 2004;27(9):2204–10.
17. Ferrannini E, et al. beta-cell function in obesity: effects of weight loss. Diabetes. 2004;53 Suppl 3:S26–33.
18. Ferrannini E, Mingrone G. Impact of different bariatric surgical procedures on insulin action and beta-cell function in type 2 diabetes. Diabetes Care. 2009;32(3):514–20.
19. Kelley DE, et al. Relative effects of calorie restriction and weight loss in noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab. 1993;77(5):1287–93.
20. Schauer PR, et al. Effect of laparoscopic Roux-en Y gastric bypass on type 2 diabetes mellitus. Ann Surg. 2003;238(4):467–84. discussion 84–5.
21. Wickremesekera K, et al. Loss of insulin resistance after Roux-en-Y gastric bypass surgery: a time course study. Obes Surg. 2005;15(4):474–81.
22. Isbell JM, et al. The importance of caloric restriction in the early improvements in insulin sensitivity after Roux-en-Y gastric bypass surgery. Diabetes Care. 2010;33(7):1438–42.
23. Jackness C, et al. Very low-calorie diet mimics the early beneficial effect of Roux-en-Y gastric bypass on insulin sensitivity and beta-cell function in type 2 diabetic patients. Diabetes. 2013;62(9):3027–32.
24. Petersen KF, et al. Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. Diabetes. 2005;54(3):603–8.
25. Bojsen-Moller KN, et al. Increased hepatic insulin clearance after Roux-en-Y gastric bypass. J Clin Endocrinol Metab. 2013;98(6):E1066–71.
26. Bojsen-Moller KN, et al. Early enhancements of hepatic and later of peripheral insulin sensitivity combined with increased postprandial insulin secretion contribute to improved glycemic control after Roux-en-Y gastric bypass. Diabetes. 2014;63(5):1725–37.
27. Pournaras DJ, et al. Remission of type 2 diabetes after gastric bypass and banding: mechanisms and 2 year outcomes. Ann Surg. 2010;252(6):966–71.
28. Laferrere B, et al. Effect of weight loss by gastric bypass surgery versus hypocaloric diet on glucose and incretin levels in patients with type 2 diabetes. J Clin Endocrinol Metab. 2008;93(7):2479–85.
29. Jorgensen NB, et al. Acute and long-term effects of Roux-en-Y gastric bypass on glucose metabolism in subjects with Type 2 diabetes and normal glucose tolerance. Am J Physiol Endocrinol Metab. 2012;303(1):E122–31.
30. Kashyap SR, et al. Acute effects of gastric bypass versus gastric restrictive surgery on beta-cell function and insulinotropic hormones in severely obese patients with type 2 diabetes. Int J Obes (Lond). 2010;34(3):462–71.
31. Dutia R, et al. Limited recovery of beta-cell function after gastric bypass despite clinical diabetes remission. Diabetes. 2014;63(4):1214–23.
32. Korner J, et al. Prospective study of gut hormone and metabolic changes after adjustable gastric banding and Roux-en-Y gastric bypass. Int J Obes (Lond). 2009;33(7):786–95.
33. Plum L, et al. Comparison of glucostatic parameters after hypocaloric diet or bariatric surgery and equivalent weight loss. Obesity (Silver Spring). 2011;19(11):2149–57.
34. Nannipieri M, et al. The role of beta-cell function and insulin sensitivity in the remission of type 2 diabetes after gastric bypass surgery. J Clin Endocrinol Metab. 2011;96(9):E1372–9.
35. Camastra S, et al. Long-term effects of bariatric surgery on meal disposal and beta-cell function in diabetic and nondiabetic patients. Diabetes. 2013;62(11):3709–17.
36. Guidone C, et al. Mechanisms of recovery from type 2 diabetes after malabsorptive bariatric surgery. Diabetes. 2006;55(7):2025–31.
37. Mari A, et al. Restoration of normal glucose tolerance in severely obese patients after biliopancreatic diversion: role of insulin sensitivity and beta cell function. Diabetologia. 2006;49(9):2136–43.
38. Salinari S, et al. First-phase insulin secretion restoration and differential response to glucose load depending on the route of administration in type 2 diabetic subjects after bariatric surgery. Diabetes Care. 2009;32(3):375–80.

39. Duran-Sandoval D, et al. Glucose regulates the expression of the farnesoid X receptor in liver. Diabetes. 2004;53(4):890–8.
40. Mencarelli A, et al. Dissociation of intestinal and hepatic activities of FXR and LXRalpha supports metabolic effects of terminal ileum interposition in rodents. Diabetes. 2013;62(10):3384–93.
41. Kashyap SR, et al. Metabolic effects of bariatric surgery in patients with moderate obesity and type 2 diabetes: analysis of a randomized control trial comparing surgery with intensive medical treatment. Diabetes Care. 2013;36(8):2175–82.
42. Nannipieri M, et al. Roux-en-Y gastric bypass and sleeve gastrectomy: mechanisms of diabetes remission and role of gut hormones. J Clin Endocrinol Metab. 2013;98(11):4391–9.
43. Abbatini F, et al. Long-term effects of laparoscopic sleeve gastrectomy, gastric bypass, and adjustable gastric banding on type 2 diabetes. Surg Endosc. 2010;24(5):1005–10.
44. Bradley D, et al. Matched weight loss induced by sleeve gastrectomy or gastric bypass similarly improves metabolic function in obese subjects. Obesity (Silver Spring). 2014;22(9): 2026–31.
45. Ahren B, et al. Clinical measures of islet function: usefulness to characterize defects in diabetes. Curr Diabetes Rev. 2008;4(2):129–45.
46. Byrne MM, et al. Insulin secretory abnormalities in subjects with hyperglycemia due to glucokinase mutations. J Clin Invest. 1994;93(3):1120–30.
47. Bradley D, et al. Gastric bypass and banding equally improve insulin sensitivity and beta cell function. J Clin Invest. 2012;122(12):4667–74.
48. Korner J, et al. Exaggerated glucagon-like peptide-1 and blunted glucose-dependent insulinotropic peptide secretion are associated with Roux-en-Y gastric bypass but not adjustable gastric banding. Surg Obes Relat Dis. 2007;3(6):597–601.
49. Bose M, et al. Weight loss and incretin responsiveness improve glucose control independently after gastric bypass surgery. J Diabetes. 2010;2(1):47–55.
50. Falken Y, et al. Changes in glucose homeostasis after Roux-en-Y gastric bypass surgery for obesity at day three, two months, and one year after surgery: role of gut peptides. J Clin Endocrinol Metab. 2011;96(7):2227–35.
51. Campos GM, et al. Improvement in peripheral glucose uptake after gastric bypass surgery is observed only after substantial weight loss has occurred and correlates with the magnitude of weight lost. J Gastrointest Surg. 2010;14(1):15–23.
52. le Roux CW, et al. Gut hormone profiles following bariatric surgery favor an anorectic state, facilitate weight loss, and improve metabolic parameters. Ann Surg. 2006;243(1):108–14.
53. Umeda LM, et al. Early improvement in glycemic control after bariatric surgery and its relationships with insulin, GLP-1, and glucagon secretion in type 2 diabetic patients. Obes Surg. 2011;21(7):896–901.
54. Camastra S, et al. Early and longer term effects of gastric bypass surgery on tissue-specific insulin sensitivity and beta cell function in morbidly obese patients with and without type 2 diabetes. Diabetologia. 2011;54(8):2093–102.
55. Salinari S, et al. Insulin sensitivity and secretion changes after gastric bypass in normotolerant and diabetic obese subjects. Ann Surg. 2013;257(3):462–8.
56. Anderwald CH, et al. Alterations in gastrointestinal, endocrine, and metabolic processes after bariatric Roux-en-Y gastric bypass surgery. Diabetes Care. 2012;35(12):2580–7.
57. Goldfine AB, et al. Patients with neuroglycopenia after gastric bypass surgery have exaggerated incretin and insulin secretory responses to a mixed meal. J Clin Endocrinol Metab. 2007;92(12):4678–85.
58. Patti ME, et al. Severe hypoglycaemia post-gastric bypass requiring partial pancreatectomy: evidence for inappropriate insulin secretion and pancreatic islet hyperplasia. Diabetologia. 2005;48(11):2236–40.
59. Service GJ, et al. Hyperinsulinemic hypoglycemia with nesidioblastosis after gastric-bypass surgery. N Engl J Med. 2005;353(3):249–54.
60. Meier JJ, et al. Hyperinsulinemic hypoglycemia after gastric bypass surgery is not accompanied by islet hyperplasia or increased beta-cell turnover. Diabetes Care. 2006;29(7):1554–9.

61. Salehi M, Gastaldelli A, D'Alessio DA. Altered islet function and insulin clearance cause hyperinsulinemia in gastric bypass patients with symptoms of postprandial hypoglycemia. J Clin Endocrinol Metab. 2014;99(6):2008–17.
62. Salehi M, Prigeon RL, D'Alessio DA. Gastric bypass surgery enhances glucagon-like peptide 1-stimulated postprandial insulin secretion in humans. Diabetes. 2011;60(9):2308–14.
63. Salehi M, Gastaldelli A, D'Alessio DA. Blockade of glucagon-like peptide 1 receptor corrects postprandial hypoglycemia after gastric bypass. Gastroenterology. 2014;146(3):669–680. e2.
64. Camastra S, et al. Beta-cell function in severely obese type 2 diabetic patients: long-term effects of bariatric surgery. Diabetes Care. 2007;30(4):1002–4.
65. Madsbad S, Dirksen C, Holst JJ. Mechanisms of changes in glucose metabolism and bodyweight after bariatric surgery. Lancet Diabetes Endocrinol. 2014;2(2):152–64.
66. Peterli R, et al. Metabolic and hormonal changes after laparoscopic Roux-en-Y gastric bypass and sleeve gastrectomy: a randomized, prospective trial. Obes Surg. 2012;22(5):740–8.
67. Lee WJ, et al. Laparoscopic sleeve gastrectomy for diabetes treatment in nonmorbidly obese patients: efficacy and change of insulin secretion. Surgery. 2010;147(5):664–9.
68. Nauck M, et al. Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. Diabetologia. 1986;29(1):46–52.
69. Eckerle Mize DL, Salehi M. The place of GLP-1-based therapy in diabetes management: differences between DPP-4 inhibitors and GLP-1 receptor agonists. Curr Diab Rep. 2013;13(3):307–18.
70. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet. 2006;368(9548):1696–705.
71. Laferrere B, et al. Incretin levels and effect are markedly enhanced 1 month after Roux-en-Y gastric bypass surgery in obese patients with type 2 diabetes. Diabetes Care. 2007;30(7):1709–16.
72. Dirksen C, et al. Postprandial diabetic glucose tolerance is normalized by gastric bypass feeding as opposed to gastric feeding and is associated with exaggerated GLP-1 secretion: a case report. Diabetes Care. 2010;33(2):375–7.
73. McLaughlin T, et al. Reversible hyperinsulinemic hypoglycemia after gastric bypass: a consequence of altered nutrient delivery. J Clin Endocrinol Metab. 2010;95(4):1851–5.
74. Jimenez A, et al. GLP-1 action and glucose tolerance in subjects with remission of type 2 diabetes after gastric bypass surgery. Diabetes Care. 2013;36(7):2062–9.
75. Jorgensen NB, et al. Exaggerated glucagon-like peptide 1 response is important for improved beta-cell function and glucose tolerance after Roux-en-Y gastric bypass in patients with type 2 diabetes. Diabetes. 2013;62(9):3044–52.
76. Salehi M, et al. Effect of endogenous GLP-1 on insulin secretion in type 2 diabetes. Diabetes. 2010;59(6):1330–7.
77. Habegger KM, et al. GLP-1R responsiveness predicts individual gastric bypass efficacy on glucose tolerance in rats. Diabetes. 2014;63(2):505–13.
78. Rubino F, et al. The early effect of the Roux-en-Y gastric bypass on hormones involved in body weight regulation and glucose metabolism. Ann Surg. 2004;240(2):236–42.
79. Miyawaki K, et al. Glucose intolerance caused by a defect in the entero-insular axis: a study in gastric inhibitory polypeptide receptor knockout mice. Proc Natl Acad Sci U S A. 1999;96(26):14843–7.
80. Lund A, et al. The separate and combined impact of the intestinal hormones, GIP, GLP-1, and GLP-2, on glucagon secretion in type 2 diabetes. Am J Physiol Endocrinol Metab. 2011; 300(6):E1038–46.
81. Nauck MA, et al. Preserved incretin activity of glucagon-like peptide 1 [7-36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. J Clin Invest. 1993;91(1):301–7.
82. Cummings DE, et al. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. N Engl J Med. 2002;346(21):1623–30.
83. Bohdjalian A, et al. Sleeve gastrectomy as sole and definitive bariatric procedure: 5-year results for weight loss and ghrelin. Obes Surg. 2010;20(5):535–40.

84. Dixon AF, Dixon JB, O'Brien PE. Laparoscopic adjustable gastric banding induces prolonged satiety: a randomized blind crossover study. J Clin Endocrinol Metab. 2005;90(2):813–9.
85. Hanusch-Enserer U, et al. Plasma ghrelin in obesity before and after weight loss after laparoscopical adjustable gastric banding. J Clin Endocrinol Metab. 2004;89(7):3352–8.
86. Faraj M, et al. Plasma acylation-stimulating protein, adiponectin, leptin, and ghrelin before and after weight loss induced by gastric bypass surgery in morbidly obese subjects. J Clin Endocrinol Metab. 2003;88(4):1594–602.
87. Korner J, et al. Effects of Roux-en-Y gastric bypass surgery on fasting and postprandial concentrations of plasma ghrelin, peptide YY, and insulin. J Clin Endocrinol Metab. 2005;90(1):359–65.
88. Peterli R, et al. Improvement in glucose metabolism after bariatric surgery: comparison of laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy: a prospective randomized trial. Ann Surg. 2009;250(2):234–41.
89. Cummings BP, et al. Ileal interposition surgery improves glucose and lipid metabolism and delays diabetes onset in the UCD-T2DM rat. Gastroenterology. 2010;138(7):2437–46. 2446.e1.
90. Patriti A, et al. Early improvement of glucose tolerance after ileal transposition in a non-obese type 2 diabetes rat model. Obes Surg. 2005;15(9):1258–64.
91. Strader AD, et al. Ileal interposition improves glucose tolerance in low dose streptozotocin-treated diabetic and euglycemic rats. Obes Surg. 2009;19(1):96–104.
92. Strader AD, et al. Weight loss through ileal transposition is accompanied by increased ileal hormone secretion and synthesis in rats. Am J Physiol Endocrinol Metab. 2005;288(2):E447–53.
93. Gaitonde S, Kohli R, Seeley R. The role of the gut hormone GLP-1 in the metabolic improvements caused by ileal transposition. J Surg Res. 2012;178(1):33–9.
94. Rubino F, et al. The mechanism of diabetes control after gastrointestinal bypass surgery reveals a role of the proximal small intestine in the pathophysiology of type 2 diabetes. Ann Surg. 2006;244(5):741–9.
95. Jiao J, et al. Restoration of euglycemia after duodenal bypass surgery is reliant on central and peripheral inputs in Zucker fa/fa rats. Diabetes. 2013;62(4):1074–83.
96. Klein S, et al. Moderate effect of duodenal-jejunal bypass surgery on glucose homeostasis in patients with type 2 diabetes. Obesity (Silver Spring). 2012;20(6):1266–72.
97. Sandler BJ, et al. Human experience with an endoluminal, endoscopic, gastrojejunal bypass sleeve. Surg Endosc. 2011;25(9):3028–33.
98. Verdam FJ, et al. An update on less invasive and endoscopic techniques mimicking the effect of bariatric surgery. J Obes. 2012;2012:597871.
99. Gerhard GS, et al. A role for fibroblast growth factor 19 and bile acids in diabetes remission after Roux-en-Y gastric bypass. Diabetes Care. 2013;36(7):1859–64.
100. Kohli R, et al. Weight loss induced by Roux-en-Y gastric bypass but not laparoscopic adjustable gastric banding increases circulating bile acids. J Clin Endocrinol Metab. 2013;98(4):E708–12.
101. Patti ME, et al. Serum bile acids are higher in humans with prior gastric bypass: potential contribution to improved glucose and lipid metabolism. Obesity (Silver Spring). 2009;17(9):1671–7.
102. Pournaras DJ, et al. The role of bile after Roux-en-Y gastric bypass in promoting weight loss and improving glycaemic control. Endocrinology. 2012;153(8):3613–9.
103. Steinert RE, et al. Bile acids and gut peptide secretion after bariatric surgery: a 1-year prospective randomized pilot trial. Obesity (Silver Spring). 2013;21(12):E660–8.
104. Ryan KK, et al. FXR is a molecular target for the effects of vertical sleeve gastrectomy. Nature. 2014;509(7499):183–8.
105. Jansen PL, et al. Alterations of hormonally active fibroblast growth factors after Roux-en-Y gastric bypass surgery. Dig Dis. 2011;29(1):48–51.
106. Aron-Wisnewsky J, Dore J, Clement K. The importance of the gut microbiota after bariatric surgery. Nat Rev Gastroenterol Hepatol. 2012;9(10):590–8.

107. Liou AP, et al. Conserved shifts in the gut microbiota due to gastric bypass reduce host weight and adiposity. Sci Transl Med. 2013;5(178):178ra41.
108. Zhang H, et al. Human gut microbiota in obesity and after gastric bypass. Proc Natl Acad Sci U S A. 2009;106(7):2365–70.
109. Furet JP, et al. Differential adaptation of human gut microbiota to bariatric surgery-induced weight loss: links with metabolic and low-grade inflammation markers. Diabetes. 2010;59(12):3049–57.
110. Dirksen C, et al. Mechanisms of improved glycaemic control after Roux-en-Y gastric bypass. Diabetologia. 2012;55(7):1890–901.
111. Depoortere I. Taste receptors of the gut: emerging roles in health and disease. Gut. 2014;63(1):179–90.
112. Newgard CB, et al. A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. Cell Metab. 2009;9(4):311–26.
113. Tome D, et al. Protein, amino acids, vagus nerve signaling, and the brain. Am J Clin Nutr. 2009;90(3):838S–43.
114. Tremblay F, et al. Role of dietary proteins and amino acids in the pathogenesis of insulin resistance. Annu Rev Nutr. 2007;27:293–310.
115. Laferrere B, et al. Differential metabolic impact of gastric bypass surgery versus dietary intervention in obese diabetic subjects despite identical weight loss. Sci Transl Med. 2011;3(80):80re2.
116. Magkos F, et al. Effect of Roux-en-Y gastric bypass and laparoscopic adjustable gastric banding on branched-chain amino acid metabolism. Diabetes. 2013;62(8):2757–61.

Part III

Surgery for Diabetes and the Metabolic Syndrome

The Metabolic Effects of Laparoscopic Adjustable Gastric Banding

11

Marina Kurian and John Loy

Being overweight or obese is the main modifiable risk factor for type 2 diabetes. Obese adults are five times more likely to be diagnosed with diabetes than adults of a healthy weight. Type 2 diabetes is fast becoming the health burden of our time with billions of health care dollars worldwide being spent on the management of the complications of obesity related diabetes [1]. Currently 90 % of adults with type 2 diabetes are overweight or obese. People with severe obesity are at greater risk of type 2 diabetes than obese people with a lower body mass index (BMI) [2]. People with diabetes are also at a greater risk of a range of chronic health conditions including cardiovascular disease, blindness, amputation, kidney disease, and depression than people without diabetes. Diabetes leads to a twofold excess risk for cardiovascular disease, and diabetic retinopathy is the leading cause of preventable sight loss among people of working age in Western Europe. It is also a major cause of premature mortality in the developed world [1].

The huge cost of treating diabetes has led to much focus on bariatric surgery as an effective treatment. There is good evidence from randomized controlled trials (RCTs) that surgery is superior to medical therapy in improving diabetes control and the metabolic syndrome [3]. Surgery reduces the number of hypoglycemic medications required, including getting patients off insulin. Simply considering the reduced costs of diabetes treatment, surgery pays for itself within 2–3 years [4]. It also puts many diabetics into remission (normal HbA1c, normal fasting glucose, off all medication) and markedly reduces incidence of diabetes compared to matched patients not having surgery [5]. It is also accepted that the BMI threshold for surgery may be reduced by some 2.5 kg/m^2 for patients from the Asian population, as this

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ethnic group has a greater susceptibility to diabetes and the metabolic syndrome, in theory as a consequence of increased density of visceral fat [6].

Theories about how obesity leads to type 2 diabetes include abdominal obesity causing fat cells to release pro-inflammatory mediators. These chemicals can make the body less sensitive to the insulin it produces by disrupting the function of insulin responsive cells and their ability to respond to insulin [7].

Obesity may also trigger changes to the body's metabolism that cause adipose tissue to release increased amounts of fatty acids, glycerol, hormones, pro-inflammatory cytokines and other factors that are involved in the development of insulin resistance. When insulin resistance is accompanied by dysfunction of pancreatic islet beta-cells it leads to failure to control blood glucose levels.

Type 2 diabetes is just one consequence of obesity. Obesity exerts its harmful effects on the body in many ways. It is generally accepted that obesity creates a pro-inflammatory state in which circulating inflammatory mediator levels rise contributing to end organ damage. The metabolic syndrome refers to a clustering of cardiovascular risk factors whose underlying pathophysiology may be related to insulin resistance. Obesity and the metabolic syndrome are also associated with an increased risk of some common cancers such as colon and endometrial cancer [8].

The International Diabetes Federation (IDF) and American Heart Association definition of the metabolic syndrome has been agreed [9].

Any three or more of the following factors constitute a diagnosis of metabolic syndrome:

- Increased waist circumference: ethnicity specific—e.g., Caucasian men ≥94 cm and women ≥80 cm; South Asian men ≥90 cm and women ≥80 cm.
- Body mass index is over 30 kg/m^2, central obesity can be assumed and waist circumference does not need to be measured.
- Raised triglycerides:
  - >150 mg/dL (1.7 mmol/L)
  - Or specific treatment for this lipid abnormality
- Reduced HDL-cholesterol:
  - <40 mg/dL (1.03 mmol/L) in men
  - <50 mg/dL (1.29 mmol/L) in women
  - Or specific treatment for this lipid abnormality
- Raised blood pressure:
  - Systolic ≥130 mmHg
  - Diastolic ≥85 mmHg
  - Or treatment of previously diagnosed hypertension
- Raised fasting plasma glucose:
  - Fasting plasma glucose ≥100 mg/dL (5.6 mmol/L)
  - Most people with type 2 diabetes will have metabolic syndrome based on these criteria

It is not only the adult population in whom the epidemic of diabetes is progressing. Physicians are seeing more pediatric patients with obesity related complications

such as diabetes and more recently a worrying increase in fatty liver disease [10, 11]. Approximately 12.5 million (17 %) children and adolescents aged 2–19 years in the USA are obese [12]. Non-alcoholic fatty liver disease (NAFLD) has emerged to become the most common form of pediatric chronic liver disease in the world. This is linked to the sharp rise in prevalence of morbid obesity in younger patients, along with the earlier onset of type 2 diabetes and the other components of the metabolic syndrome [13]. There is a strong association between the metabolic syndrome and NAFLD in younger patients, with most researchers agreeing NAFLD represents metabolic syndromes hepatic manifestation. Children with a diagnosis of NAFLD are also reported to have significantly decreased quality of life. Diabetes, fatty liver disease, and the other components of the metabolic syndrome are all improved with weight loss [14].

Weight loss in the obese, however achieved is beneficial to health. For morbidly obese patients who consider and proceed with bariatric surgery there is a choice of which surgery to elect for. Traditionally this choice is between a restrictive procedure such as gastric band (LAGB), sleeve gastrectomy (SG) and malabsorptive surgery such as Roux-en-Y gastric bypass (RYGB), duodenal switch (DS), biliopancreatic diversion (BPD). Worldwide the three predominating surgeries are RYGB, SG and LAGB. The traditional teaching has been that the malabsorptive surgeries have a greater metabolic effect and the restrictive procedures, although good for weight loss, have a less dramatic metabolic benefit, certainly in diabetic patients.

Gastric banding has been in routine use since its introduction around 1993. Its popularity as a primary bariatric procedure increased throughout the 1990s and first decade of this century. Surgeons and patients are attracted to the band for its ease of insertion as an ambulatory laparoscopic procedure, quick recovery and reproducibly good weight loss results. The safety profile was recently highlighted in the November 2014 United Kingdom National Bariatric Surgery Registry reporting the collective results of the majority of UK bariatric surgeons. There were no reported deaths in the 3402 patients undergoing gastric banding in the UK from 2011 to 2013. Only 0.8 % of patients were reported as having a complication within 30 days of surgery, showing that gastric banding is inherently safe. Excess weight loss (%EWL) with the band at 3 years postoperatively is 54 % in the UK Registry resulting in excellent resolution of most comorbidities [15].

So how does gastric banding actually exert its beneficial metabolic effects? The band is positioned around the upper part of the stomach just below the gastro esophageal junction and can be filled with saline to restrict the amount of food consumed. In the early years of banding it was thought the band solely achieved its effect by physical restriction and the creation of a small gastric pouch. We now understand its mechanisms of action a little better. The laparoscopic adjustable gastric band (LAGB) is ideally placed on the cardia of the stomach, just below the esophagogastric junction. In the past it was assumed that the presence of a band in this position caused a meal to accumulate in the pouch of stomach proximal to it, before gradually being released into the remainder of the gut. Thus, the band was thought to work by restricting the volume of food ingested to that able to be accommodated in the proximal pouch.

This small volume of food was thought to stretch the stomach and cause early satiety. Gradual emptying of the proximal pouch into the infra-band stomach was thought responsible for prolonged inter-meal satiation. Recent studies from Melbourne confirm that mechanism of action of LAGB is the induction of early and prolonged satiety; however, the intraluminal events that lead to this are far more complex than simple retention of food in the proximal pouch [16]. The hormonal effects of gastric banding are now thought to contribute to a greater extent to the weight loss than the simple mechanism of portion restriction alone. By combining high-resolution video manometry with nuclear studies of gastric emptying, the Australian group demonstrated that the expected physiology of a LAGB at its optimal volume does not cause a food bolus to rest above the band in the proximal pouch. Rather, the bolus will transit across the band in stages over a period of 45–60 s due to four to six repeated contractions of the lower esophagus. The infra-band stomach subsequently empties normally. These findings are important and emphasize the attention needed to each patient to ensure optimal filling of the band to ensure weight loss without the creation of a pathological supra-band pouch and its consequent problems.

The endocrine function of the stomach is mainly exerted through the actions of ghrelin, an acylated peptide hormone that is the first known and so far most extensively studied endogenous orexigenic substance. The satiety-hunger balance is kept in check by many anorexigenic gut hormones among which is the deacylated form of ghrelin—des-acyl ghrelin. The interplay of gut hormones affects the brain directly, as most gut hormones cross the blood–brain barrier and bind to their respective receptors in the central nervous system.

The receptor for ghrelin is found on the same cells in the brain as the receptor for leptin the satiety hormone that has opposite effects from ghrelin. Although numerous studies have investigated serum ghrelin levels following bariatric surgery, there is no solid agreement yet as to the direction or magnitude of its change, or even its impact on weight loss. Some studies have found an increase in ghrelin, some have found a decrease, and others have found no change in ghrelin following bariatric surgery. This indicates the complex nature of the exact relationship existing between gut hormones, hunger and the development of obesity.

Other hormones like obestatin and nesfatin are secreted from the stomach along with ghrelin, yet their physiological function is to be elucidated. The importance of the satiety-hunger balance can be seen in its most typical derangement—obesity. Some studies imply that ghrelin, along with other gut hormones, plays an important part in the pathophysiology of obesity. More importantly, it seems that the mechanisms by which bariatric surgery procedures induce weight loss are primarily based on changing the gut hormone levels, including ghrelin.

Weight loss reduces insulin resistance, and bariatric surgery is the most successful way to induce and maintain weight loss. The procedures associated with the most weight loss have the most pronounced effects on insulin resistance. Reduction in peripheral insulin resistance occurs only once weight loss has been established, but hepatic insulin resistance can change earlier. The acute calorie restriction immediately after bariatric surgery and before substantial weight loss improves insulin sensitivity. Thus, to establish the relative contribution of calorie restriction and factors

related to surgically induced changes in gastrointestinal structure and function remains difficult. The usual return of compensatory hunger after a period of calorie restriction and weight loss does not happen with bariatric surgery. Dixon and colleagues' double-blind crossover study of weight-stable patients after laparoscopic adjustable gastric band surgery showed that an active band provided reduced hunger after a fast, greater early satiation after a small meal, and prolonged satiety after meals. The effect, possibly due to gentle intraluminal pressure on vagal afferent mechanoreceptors at the gastric band, could be the main mechanism that allows patients to reduce meal size without a compensatory increase in meal frequency and maintain a substantially lower energy intake than before surgery.

Whilst there is accepted consensus that patients undergoing gastric bypass have earlier remission of type 2 diabetes, even before weight loss begins, patients with a gastric band can also achieve reasonable and sustained remission of diabetes rates. The theory as to the rapid improvement in diabetes in the RYGB patients relates to an early alteration of the gut hormone profile and improved insulin sensitivity. It is accepted that in patients with a gastric band, no significant incretin or gut hormone changes occur however. Improvement in glycemia, insulin secretion and insulin resistance is directly related to weight loss. With regular and careful follow-up, similar improvements in T2DM control with gastric banding and the more "metabolic" RYGB can be obtained [17]. However, when comparing gastric banding and RYGB, improvements in T2DM are more marked in the latter [18]. Figure 11.1

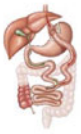
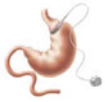
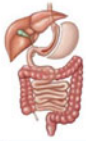
	RYGB	AGB	VSG
			
Lipid homeostasis	Elevated HDL Reduced triglycerides Reduced total cholesterol, LDL	Elevated HDL Reduction in triglycerides not as dramatic as RYGB or VSG	Elevated HDL Reduced triglycerides
Glucose homeostasis	Improved fasting blood glucose and insulin sensitivity, prior to weight loss	Improvements are slower and not as dramatic as after VSG or RYGB	Improved fasting blood glucose and insulin sensitivity, prior to weight loss
Role of gastric restriction	Has not yet been directly tested	Failure of band leads to less gastric restriction and less weight loss	Gastric restriction is not the critical factor in preventing hyperphagia
Gastric emptying	Few published studies	No overall change in gastric emptying rate; Emptying rate of proximal pouch created by band is enhanced	Most papers show increase
Energy expenditure	Controversial	Not reported	Uncharged, but only reported in one study
Ghrelin	Reduced total ghrelin; Controversial, but no change in acyl-ghrelin levels	Increased circulating ghrelin	Reduced total ghrelin; Controversial, but no change in acyl-ghrelin levels
CCK	No change	No change	Not measured
GLP-1 (postprandial)	Weight loss-independent postprandial increase	Increased circulating GLP-1, but much less than RYGB or VSG	Weight loss-independent increase comparible to RYGB
PYY (postprandial)	Increased postprandial PYY levels; Reduced body weight loss in PYY knockout mice	No change	Increased postprandial PYY levels, comparable to levels after RYGB
Bile acids	Increased plasma bile acids	Not reported	Increased plasma bile acids
Diet change	Decreased fat intake, more fruits and vegetables	Decrease bread intake and increase in caloric liquids; Greater fat intake and fewer fruits/vegetables than RYGB	Decreased fat intake, similar to RYGB
Food intolerance	Some dumping syndrome, usually well-tolerated	More persistent and problematic than RYGB; Mainly vomiting	Little or none

Fig. 11.1 Mechanisms and comparisons of each of the three major bariatric procedures

below shows the mechanisms and comparisons of each of the three major bariatric procedures and how they can alter gut hormones.

Bariatric surgery provides additional benefits through improvements in other obesity-related co morbidities—e.g., dyslipidemia and obstructive sleep apnea. Additionally, health-related quality of life improves, symptoms of depression are reduced, and other psychosocial benefits are noted. Several studies have shown improvements in survival—specifically, reduced mortality from cardiovascular disease, cancer in women, and type 2 diabetes itself [19–21]. Available analyses suggest that bariatric surgery is cost effective and, in some circumstances, reduces health-care costs [22]. Despite these findings, surgery is underutilized; fewer than 1 % of patients eligible for surgery are treated each year. Reasons include stigmatization and discrimination against obese people and methods to treat obesity, professional boundaries (i.e., thinking of diabetes as a medical rather than surgical disorder), little awareness of surgical options in patients and physicians, barriers to access to surgical care, cost, and concerns about effectiveness and risks.

The growing body of evidence that weight loss achieved through bariatric surgery produces health benefits, improving quality of life and reducing health care costs is hard to dismiss by health care providers. Whether the patient chooses a gastric band, bypass or sleeve is a matter for each individual patient to choose in conjunction with advice from their surgeon. Advocates of each surgery are able to produce convincing results for their preferred procedure and it is now accepted by the surgical body that each procedure is only as good as the correct patient selection, technical proficiency in carrying out the surgery safely and offering close follow-up in conjunction with the patient's primary care physician and whole team.

References

1. Tham JC, Howes N, le Roux CW. The role of bariatric surgery in the treatment of diabetes. Ther Adv Chronic Dis. 2014;5(3):149–57.
2. Ginter E, Simko V. Diabetes type 2 pandemic in 21st century. Bratisl Lek Listy. 2010;111(3):134–7.
3. Sjöström L. Review of the key results from the Swedish Obese Subjects (SOS) trial - a prospective controlled intervention study of bariatric surgery. J Intern Med. 2013;273(3):219–34.
4. Picot J, Jones J, Colquitt JL, Gospodarevskaya E, Loveman E, Baxter L, et al. The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: a systematic review and economic evaluation. Health Technol Assess. 2009;13(41):1.
5. Mingrone G, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. N Engl J Med. 2012;366(17):1577–85.
6. Cummings DE, Cohen RV. Beyond BMI: the need for new guidelines governing the use of bariatric and metabolic surgery. Lancet Diabetes Endocrinol. 2014;2(2):175–81.
7. Weghuber D, Mangge H, Hochbrugger E, Stulnig TM. Impact of age and metabolic syndrome on the adipokine profile in childhood and adult obesity. Exp Clin Endocrinol Diabetes. 2014;122(6):363–7.
8. Gong Y, Dou LJ, Liang J. Link between obesity and cancer: role of triglyceride/free fatty acid cycling. Eur Rev Med Pharmacol Sci. 2014;18(19):2808–20.

9. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome-a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med. 2006;23(5):469–80.
10. Vanni E, Bugianesi E, Kotronen A, De Minicis S, Yki-Järvinen H, Svegliati BG. From the metabolic syndrome to NAFLD or vice versa? Dig Liver Dis. 2010;42:320–30.
11. Kistler KD, Molleston J, Unalp A, et al. Symptoms and quality of life in obese children and adolescents with nonalcoholic fatty liver disease. Aliment Pharmacol Ther. 2009;31:396–406.
12. Ogden C, Carroll M. Prevalence of obesity among children and adolescents: United States, trends 1963–1965 through 2007–2008. Hyattsville, MD: Division of Health and Nutrition Examination, National Center for Health Statistics; 2010.
13. Loomba R, Sirlin CB, Schwimmer JB, Lavine JE. Advances in pediatric nonalcoholic fatty liver disease. Hepatology. 2009;50:1282–93.
14. Loy JJ, Youn H, Schwack B, et al. Improvement in non-alcoholic fatty liver disease in adolescents undergoing bariatric surgery. Surg Obes Relat Dis. 2015;11(2):442–9.
15. Welbourn CR. The United Kingdom National Bariatric Surgery Registry 2nd Report. Henley on Thames, Oxfordshire: Dendrite Clinical Systems Ltd.; 2014.
16. Burton PR, Yap K, Brown WA, et al. Effects of adjustable gastric bands on gastric emptying, supra- and infraband transit and satiety: a randomized double-blind crossover trial using a new technique of band visualization. Obes Surg. 2010;20:1690.
17. O'Brien P, Dixon J. Lap-band: outcomes and results. J Laparoendosc Adv Surg Tech A. 2003;13:265–70.
18. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004;292:1724–37.
19. Ashrafian H, Ahmed K, Rowland SP, et al. Metabolic surgery and cancer: protective effects of bariatric procedures. Cancer. 2011;117(9):1788–99.
20. Adams TD, Stroup AM, Gress RE, et al. Cancer incidence and mortality after gastric bypass surgery. Obesity. 2009;17(4):796–802.
21. Sjostrom L, Gummesson A, Sjostrom CD, et al. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. Lancet Oncol. 2009;10(7):653–62.
22. Neff KJ, Chuah LL, Aasheim ET, et al. Beyond weight loss: evaluating the multiple benefits of bariatric surgery after Roux-en-Y gastric bypass and adjustable gastric band. Obes Surg. 2014;24(5):684–91.

Sleeve Gastrectomy

12

Gregg H. Jossart

In the USA, there are over 100 million Americans with diabetes and pre-diabetes and over 72 million Americans with obesity. Two thirds of adult onset diabetes is directly associated with obesity.

Diabetes is a heterogeneous disease with three main types: type 1, type 2 and latent autoimmune diabetes. Obesity has been associated as a significant risk factor for the development of type 2 diabetes. Individuals with a body mass index > 35 kg/m^2 are 20 times more likely to develop diabetes than those with a BMI < 25 kg/m^2 [1]. The main condition that develops in type 2 diabetes is insulin resistance. In type 1 diabetes and LADA, lack of insulin production is the primary condition but one should be aware that many of these patients also develop a resistance to exogenous insulin if they become obese. It is generally well understood that any weight loss or improved dietary management can help to control diabetes. However, when these attempts prove ineffective, bariatric surgery is considered. In 1995, Walter Pories published an article in the *Annals of Surgery* titled, "Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus" [2]. Almost 20 years later, bariatric surgery has proven to be an effective treatment for obesity related diabetes. This chapter reviews the current role of the Sleeve Gastrectomy in the treatment of obesity related diabetes. Concepts reviewed include diabetes outcomes by BMI, duration of diabetes, time to resolution, C-peptide production, Pouch/Bougie size, and comparison to other procedures. The heterogeneity of diabetes and the variations in sleeve gastrectomy technique make it difficult to analyze outcomes but many reasonable conclusions can be made.

The sleeve gastrectomy (or gastric sleeve) has emerged as an acceptable procedure for almost any bariatric patient. During the open bariatric surgery era, it was

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the restrictive component of the Duodenal Switch [3]. The advent of laparoscopic bariatric surgery facilitated the sleeve gastrectomy as a first stage, lower risk option in high risk patients [4]. In the last 5 years, it has proven to be a reasonable single stage option for the lower BMI group of patients and for patients with unique contraindications to adjustable gastric banding or intestinal bypass procedures [5, 6]. In addition, recent reports have revealed that the sleeve can yield durable diabetes improvement [7]. There is also some proof that removing the volume part of the stomach (greater curvature) also removes most of the cells that produce ghrelin, which may also contribute better than expected weight-loss results and diabetes outcomes in the absence of malabsorption [8].

Historically, Buchwald et al. [9] revealed a gradation of effect on diabetes resolution based on the procedure being purely restrictive versus having a large component of malabsorption. The Bilopancreatic Diversion/Duodenal Switch had a 98.9 % diabetes resolution whereas the purely restrictive Gastroplasty procedures had a 71.6 % diabetes resolution. It is difficult to extrapolate these outcomes to the sleeve gastrectomy but the pouch is generally smaller than with the duodenal switch and the gastric resection may contribute to diabetes resolution more than just a gastroplasty. At least it is reasonable to conclude that pure restriction can improve diabetes.

A 2009 systematic review of sleeve gastrectomy by Brethauer et al. [10] included 10 studies and 754 patients with follow-up on comorbidities. The overall remission rate for diabetes was 56 % with an additional 37 % demonstrating improvement. A 2010 systematic review by Gill et al. [11] including 27 studies and 673 patients revealed that diabetes resolved in 66.2 % and improved in 26.9 % of patients. Other small sleeve gastrectomy series have reported diabetes resolution rates from 80 to 88.9 % at 1 year [12–15]. Menenakos et al. [16], in a prospective single center study with 1 year follow-up confirmed a diabetes resolution rate of 84 % (30 of 36 diabetics). These early reports did not comment on the duration or severity of diabetes or differentiate between BMI groups or pouch sizes.

The results of sleeve gastrectomy on diabetes when associated with BMI are limited to date. Basso et al. [17] reported a diabetes cure rate of 69 % in a higher BMI group of patients (BMI 54 kg/m^2) compared to 88 % cure in a lower BMI group (BMI 45 kg/m^2). Both groups had improvement, but the lower BMI group achieved a superior result. Magee et al. [18] reported a very low diabetes improvement rate of only 23 % in a group of patients with a BMI > 60 kg/m^2. Conversely, Abbatini et al. [19] reported a diabetes cure rate of 88 % (8/9) in nine low BMI (30–35 kg/m^2) diabetics undergoing sleeve gastrectomy compared to 0 % cure rate for nine diabetics under medical treatment. The one diabetic that was not cured was diabetic for 20 years.

Diabetes resolution correlating with pouch size is controversial and may be more closely related to actual weight lost. Atkins et al. [20] reported a longitudinal retrospective study of 294 sleeve patients. 106 patients had a sleeve gastrectomy done using a 50 French bougie and 185 patients had it done using a 40 French bougie. Diabetes resolution was 5.2 times greater at 4 years postoperative with the smaller bougie. Similar outcomes were seen for dyslipidemia and hypertension. The %EBMIL was greater for the 40 French group (60.2 % compared to 45.4 %).

Spivak et al. [21] used a retrospective case control study of 66 patients undergoing a sleeve gastrectomy with a 42 French bougie and 54 patients undergoing a sleeve gastrectomy with a 32 French bougie. Both groups had the antral resection start 1–2 cm from the pylorus. At 1 year, %excess weight loss was 67 and 65 % and diabetes resolution was 79 and 83 %. The difference was not significant. Abdallah et al. [22] reported the impact of the extent of antral resection in a prospective randomized study of 105 patients. Fifty-two patients had the antral resection start 2 cm from the pylorus and 53 patients had the antral resection start 6 cm from the pylorus. The group with the staple line starting 2 cm from the pylorus had significantly better weight loss (71.8%EWL at 2 years) compared to the 5 cm group (61%EWL at 2 years). There were only 16 diabetics in the study but the group with the smaller antrum had a diabetes resolution of 80 % (4/5) and the group with the larger antrum had a diabetes resolution of only 36.4 % (4/11).

Time to resolution of diabetes after sleeve gastrectomy has been variably reported. Rizzello et al. [23] reported on 17 diabetics early after sleeve gastrectomy and noted that within 5 days of surgery there was a reduction in glucose, insulin, and insulin resistance that persisted beyond 60 days. The diabetes cure appeared rapid and before weight loss occurs. Rosenthal et al. [24] reported on 30 diabetics undergoing sleeve gastrectomy at 2 and 6 months postoperatively. At 2 months, diabetes resolution was 27 % and at 6 months it was 63 %. The best resolution was in those with a shorter duration of diabetes and better weight loss. Casella et al. [25] reported on the duration of diabetes as a prognostic factor. A group of 40 sleeve gastrectomy patients with diabetes duration less than 10 years had a 100 % diabetes remission rate whereas a group of 16 sleeve gastrectomy patients with diabetes duration more than 10 years had only a 31 % remission rate. Additional reports provide more detail on time to resolution. Shah et al. [26] noted that a diabetes cure can take more than 1 month and up to 1 year. In a series of 53 diabetics, 81 % of patients were off diabetic medications at 1 month postoperative and 96 % at 1 year. Slater et al. [27] reported on a series of 22 diabetics with diabetes resolution of 62 % at 2 months and 75 % at 12 months. The duration of cure has been reported to range from 69 % at 3 years [28] to 100 % at 5 years [15] in studies with less than 25 patients. There are a myriad of reasons for the disparity in resolution between studies such as starting BMI, patient ethnic background, pouch size, duration of diabetes, etc.

There are reports comparing the time to diabetes resolution between the sleeve gastrectomy and the gastric bypass [14, 29–31]. They appear to have similar cure rates at 2, 4, and 12 months. Recent meta-analyses have confirmed these similar rates out to 3 years with only a slight advantage for the Roux-en-Y gastric bypass. Yip et al. [32] reported a systematic review and meta-analysis including 33 studies and 1375 patients. Diabetes resolution between the gastric bypass and the sleeve gastrectomy was compared. Unique to this meta-analysis was defining the remission criteria of a hemoglobin A1c of <6.5 %. Most studies previously mentioned considered diabetes resolved if the patient was off of medication. In this study, diabetes remission at 3 years postoperative was 81 % for gastric bypass and 80 % for sleeve gastrectomy. There was no significant difference in either diabetes resolution or weight loss between the gastric bypass and sleeve gastrectomy at 3 years. The other two

meta-analyses [33, 34] confirm these findings with the exception that at some time points after surgery the gastric bypass may have slightly better weight loss and a slightly better resolution of diabetes—but neither is statistically significant. One study does report a much higher diabetes resolution rate for the RNY compared to the sleeve gastrectomy. Lee et al. [35] reported on 60 low BMI (25–35 kg/m^2) diabetic in Taiwan with poor diabetic control (A1c >7.5). The diabetes resolution at 12 months for the RNY in this group was 93 % compared to only 47 % for sleeve gastrectomy patient group. This study does suggest that the RNY may be superior for the more severe diabetics. However, other similar outcomes have yet to be reported. 86 % of the patients in the study were RNY patients which may have skewed the conclusions. The authors also noted that the highest cure rates were in those with diabetes for less than 5 years and with BMI>30 kg/m^2 (presumably this group has more obesity related insulin resistance). Interestingly, all of these studies presumably represent a time point when the surgeon has already optimized the gastric bypass technique but may still be relatively early in the sleeve gastrectomy technique. These reviews suggest that this early sleeve technique is comparable to the more established gastric bypass technique. The sleeve gastrectomy diabetes resolution rates may continue to improve with surgeon experience and patient selection.

Comparative studies between the adjustable gastric band and the sleeve gastrectomy show the sleeve to have a superior diabetes resolution. Omana et al. [36] compared 49 sleeve patients with 74 band patients. There were 29 diabetics and 17 diabetics in each group, respectively. The sleeve group had a higher BMI of 52 kg/m^2 compared to 44 kg/m^2 in the band group yet the sleeve diabetes resolution was 100 % and only 48 % for the bands. Abbattini et al. [37] reported similar outcomes with a band diabetes resolution rate of 60.8 % compared to 80.9 % for the sleeve group.

Bariatric surgery versus medical therapy studies have recently revealed how effective surgery is compared to medical therapy for diabetes treatment outcomes. Schauer et al. [38] randomized 150 patients with uncontrolled diabetes to receive intensive medical therapy alone or medical therapy and either Roux-en-Y gastric bypass or a sleeve gastrectomy. This group of patients had a mean HgA1c of 9.3 % preoperatively and thus they represented a group that would be difficult to cure with surgery. In addition, the endpoint of a HgA1c of 6.0 % off medications was considered stringent but of course desirable. At 3 years postoperatively, only 5 % of the medical therapy group met the endpoint while 38 % of the gastric bypass and 24 % of the sleeve group met the endpoint. This suggests the Roux-en-Y to be slightly superior but the sleeve pouch size may have also skewed the results.

All of these studies confirm that the sleeve gastrectomy does improve diabetes. It is superior to adjustable gastric banding and has outcomes similar to the gastric bypass. Its limitations parallel the other procedures. The greater the amount of weight loss, generally the higher the rate of diabetes resolution. The smaller pouch (bougie size and antral resection) generally yields better weight loss and diabetes resolution. A duration of diabetes greater than 3 years and certainly more than 10 years has a lower resolution rate. Those patients with early diabetes and only oral medications are likely to have an acceptable cure rate with a sleeve gastrectomy. Ultimately, the decision between a sleeve gastrectomy and a Roux-en-Y gastric

bypass in diabetics may often need to be based on nondiabetic factors such as: risk, need for anticoagulation, history of nephrolithiasis, need to use NSAIDS, prior intestinal surgery, the presence of Barrett's esophagus, the presence of Crohn's disease, history of organ transplantation, etc. Fortunately, the sleeve gastrectomy is universally indicated as the procedure can always be converted to a gastric bypass or a second stage duodenal switch if indicated later. In fact, if the only goal is diabetes resolution in the most severe and obese diabetic even with a high medical risk, a two stage duodenal switch with the first stage being a sleeve gastrectomy has proven to be an excellent option [39, 40].

Finally, it is wise to use caution when offering an intestinal bypass procedure to a diabetic because it may yield a higher cure rate of diabetes. The benefit of diabetes resolution could be offset by bypass related complications such as ulcer, intestinal obstructions, vitamin deficiencies, dumping, etc. In fact, the most severe diabetics may have minimal pancreatic function and a bypass procedure may not yield a higher cure rate of diabetes due to the lack of beta cell function. These patients may still be on significant doses of insulin and have all the side effects of intestinal bypass procedures. Interestingly, this group may benefit from a sleeve gastrectomy as they would at least reduce their exogenous insulin usage and not be subjected to the bypass related complications and side effects.

References

1. Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes and obesity-related health risk factors, 2001. JAMA. 2003;289(1):76–9.
2. Pories WJ, Swanson MS, MacDonald KG, et al. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. Ann Surg. 1995;222(3):339–50.
3. Hess DS, Hess DW. Biliopancreatic diversion with a duodenal switch. Obes Surg. 1998;8(3):267–82.
4. Ren CJ. Early results of laparoscopic biliopancreatic diversion with duodenal switch: a case series of 40 consecutive patients. Obes Surg. 2000;10(6):514–23. discussion 524.
5. Lee CM. Vertical gastrectomy for morbid obesity in 216 patients: report of two-year results. Surg Endosc. 2007;21(10):1810–6.
6. Bellanger DE, Greenway FL. Laparoscopic sleeve gastrectomy, 529 cases without a leak: short term results and technical considerations. Obes Surg. 2011;21:146–50.
7. Mechanik JI, et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient. Obesity. 2013;21:S1–27.
8. Langer FB, et al. Sleeve gastrectomy and gastric banding: effects on plasma ghrelin levels. Obes Surg. 2005;14:1024–9.
9. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric Surgery: a systematic review and meta-analysis. JAMA. 2004;292:1724–37.
10. Brethauer A, Hammel JP, Schauer PR. Systematic review of sleeve gastrectomy as staging and primary bariatric procedure. Surg Obes Relat Dis. 2009;5(4):469–75.
11. Gill RS, Sharma AM, Al-Adra DP, et al. The impact of bariatric surgery in patients with Type-2 diabetes mellitus. Curr Diabetes Rev. 2011;7:185–9.
12. Silecchia G, Boru C, Pecchia A, et al. Effectiveness of laparoscopic sleeve gastrectomy (first stage of biliopancreatic diversion with duodenal switch) on co-morbidities in super-obese high-risk patients. Obes Surg. 2006;16:1138–44.

13. Cottam D, Dureshi FG, Mattar SF, et al. Laparoscopic sleeve gastrectomy as an initial weight loss procedure for high-risk patients with morbid obesity. Surg Endosc. 2006;20:859–63.
14. Vidal J, Ibarzabal A, Romero F, et al. Type 2 diabetes mellitus and the metabolic syndrome following sleeve gastrectomy in severely obese subjects. Obes Surg. 2008;18:1077–82.
15. Kehagias I, Spyropoulos C, Karamanakos S, et al. Efficacy of sleeve gastrectomy as sole procedure in patients with clinical severe obesity. Surg Obes Relat Dis. 2013;9(3):363–9.
16. Menenkakos E, Stamou K, Albanoupoulos K, et al. Laparoscopic sleeve gastrectomy performed with intent to treat morbid obesity: a prospective single-center study of 261 patients with a median follow-up of 1 year. Obes Surg. 2010;20:276–82.
17. Basso N, Casella G, Rizzello M. Laparoscopic sleeve gastrectomy as first stage or definitive intent in 300 consecutive cases. Surg Endosc. 2011;25:444–9.
18. Magee CJ, Barry J, Arumugasamy M. Laparoscopic sleeve gastrectomy for high-risk patients: weight loss and comorbidity improvement-short-term results. Obes Surg. 2011;21(5):547–50.
19. Abbatini F, Capoccia D, Basso N. Type 2 diabetes in obese patients with body mass index of 30-35 kg/m2: sleeve gastrectomy versus medical treatment. Surg Obes Relat Dis. 2012;8(1):20–4.
20. Atkins ER, Preen DB, Cohen LD. Improved obesity reduction and co-morbidity resolution in patients treated with 40 French bougie versus 50 French bougie four years after laparoscopic sleeve gastrectomy. Analysis of 294 patients. Obes Surg. 2012;22(1):97–104.
21. Spivak H, Moshe R, Sadot E. Laparoscopic sleeve gastrectomy using a 42-French versus a 32 French bougie: the first-year outcome. Obes Surg. 2014;24(7):1090–3.
22. Abdallah E, El Nakeeb A, Yousef T. Impact of extent of antral resection on surgical outcomes of sleeve gastrectomy for morbid obesity (A prospective randomized study). Obes Surg. 2014;24(10):1587–94.
23. Rizzello M, Abbatine F, Casella G. Early postoperative insulin-resistance changes after sleeve gastrectomy. Obes Surg. 2010;20(1):50–5.
24. Rosenthal R, Li X, Somstein S. Effect of sleeve gastrectomy on patients with diabetes mellitus. Surg Obes Relat Dis. 2009;5(4):429–34.
25. Casella G, Basso N. Ten-year duration of type 2 diabetes mellitus as a prognostic factor for remission after sleeve gastrectomy. Surg Obes Relat Dis. 2011;7:697–702.
26. Shah PS, Todkar JS, Shah SS. Effectiveness of laparoscopic sleeve gastrectomy on glycemic control in obese Indians with type 2 diabetes mellitus. Surg Obes Relat Dis. 2010;6(2):138–41.
27. Slater BJ, Bellatorre N, Eisenberg D. Early postoperative outcomes and medication cost savings after laparoscopic sleeve gastrectomy in morbidly obese patients with type 2 diabetes. J Obes. 2011;2011:350523.
28. Todkar JS, Shah SS, Shah PS, et al. Long-term effects of laparoscopic sleeve gastrectomy in morbidly obese subjects with type 2 diabetes mellitus. Surg Obes Relat Dis. 2010;6(2):142–5.
29. Vidal J, Ibarzabal A, Lacy A. Short term effects of sleeve gastrectomy on type 2 diabetes mellitus in severely obese subjects. Obes Surg. 2007;17:1069–74.
30. Bayham BE, Greenway FL, Bellanger DE, et al. Early resolution of type 2 diabetes seen after Roux en Y gastric bypass and vertical sleeve gastrectomy. Diabetes Technol Ther. 2012;14(1):30–4.
31. Pham S, Gancel A, Scotte M. Comparison of the effectiveness of four bariatric surgery procedures in obese patients with type 2 diabetes: a retrospective study. J Obes. 2014;2014:638203.
32. Yip S, Plank LD, Murphy R. Gastric bypass and sleeve gastrectomy for type 2 diabetes: a systematic review and meta-analysis of outcomes. Obes Surg. 2013;23:1994–2003.
33. Zhang C, Yuan Y, Qiu C, et al. A meta-analysis of 2-year effect after surgery: laparoscopic Roux en Y gastric bypass versus laparoscopic sleeve gastrectomy for morbid obesity and diabetes mellitus. Obes Surg. 2014;24:1528–35.
34. Zhang Y, Wang J, Sun X, et al. Laparoscopic sleeve gastrectomy versus laparoscopic Roux en Y gastric bypass for morbid obesity and related comorbidities: a meta-analysis of 21 studies. Obese Surg. 2015;25:19.
35. Lee WJ, Hur KY, Lakadawala M, et al. Gastrointestinal metabolic surgery for the treatment of diabetic patients: a multi-institutional intertnational study. J Gastrointest Surg. 2012;16: 45–51.

36. Oman JJ, Nguyen SQ, Herron D. Comparison of comorbidity resolution and improvement between laparoscopic sleeve gastrectomy and laparoscopic adjustable gastric banding. Surg Endosc. 2010;24:2513–7.
37. Abbatini F, Rizzello M, Casella G. Long-term effects of laparoscopic sleeve gastrectomy, gastric bypass, and adjustable gastric banding on type 2 diabetes. Surg Endosc. 2010;24:1005–10.
38. Schauer PR, Bhatt DL, Kirwan J. Bariatric surgery versus intensive medical therapy for diabetes- 3 year outcomes. N Engl J Med. 2014;371(7):682.
39. Iannelli A, Schneck AS, Topart P. Laparoscopic sleeve gastrectomy followed by duodenal switch in selected patients versus single-stage duodenal switch for superobesity: case-control study. Surg Obes Relat Dis. 2013;9(4):531–8.
40. Prachand VN, Ward M, Alverdy JC. Duodenal switch provides superior resolution of metabolic comorbidities independent of weight loss in the super-obese (BMI > 50kg/m2) compared with gastric bypass. J Gastrointest Surg. 2010;14:211–20.

Roux-en-Y Gastric Bypass

13

Eric J. DeMaria and Saba Ansari

13.1 History

Gastric bypass (GBP) was developed and described by Drs. Mason and Ito in 1967 [1]. The procedure was created on the basis of the weight loss initially observed in patients undergoing partial gastrectomy for treatment of ulcers. Over the past several decades, the gastric bypass has been modified into its current most performed form, using a Roux-en-Y limb (RYGBP). According to the American Society for Metabolic and Bariatric Surgery (ASMBS), 179,000 bariatric surgeries were performed in 2013, of which 34.2 % were RYGBP.

13.2 Procedure

Gastric bypass procedures typically involve creating a proximal gastric pouch reservoir with a surgical anastomosis between the pouch and the small intestine. Thus oral intake "bypasses" the remaining stomach, duodenum and some variable portion of the small intestine, depending upon how much intestinal bypass is performed. The procedure is most commonly accepted with creation of a Roux-en-Y limb of jejunum for anastomosis to the proximal gastric pouch; however, techniques for creating a loop gastrojejunostomy are also done in some parts of the world. Gastric pouch creation is accomplished with surgical stapling devices, the more modern iterations of these staplers (and those used uniformly in laparoscopic gastric bypass) typically staple and transect the tissue between the rows of staples, creating what has been called a "divided" gastric bypass. In contrast, when performed via "open" surgical access, many surgeons

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did not transect the gastric pouch from the distal gastric remnant, creating a gastric bypass with "in continuity" gastric stapling. The gastric pouch volume recommended is small, on the order of 25–30 cm^3 or less, but there is controversy as to whether pouch volume is a critical component of the procedure from the perspective of the metabolic effects of the surgery which will be described in detail below. It is likely that a small gastric pouch volume contributes primarily to the restrictive effect of the procedure, specifically influencing the degree of weight loss and, perhaps, the risk of weight regain following the procedure, although these issues are also controversial and not well proven in the surgical scientific literature.

Gastric bypass is often referred to as the "gold standard" for bariatric surgical procedures, in part because the initial weight loss induced by the surgical procedure is somewhat greater and overall less variable than other commonly performed procedures like the adjustable gastric band and the sleeve gastrectomy. The average morbidly obese patient undergoing gastric bypass surgery will typically lose between 60 and 75 % of their calculated excess body weight, and total excess weight is determined by comparison of preoperative body weight to Metropolitan Life tables, which provide information regarding Ideal Body Weight. In contrast, the typical excess weight loss following the restrictive sleeve gastrectomy procedure is in the range of 50–60 % of excess, while the adjustable gastric band procedure typically results in excess weight loss below 50 % of excess.

13.3 Post op Management and Complications

The current overall mortality rate for bariatric surgery, according to the American Society for Metabolic and Bariatric Surgery, is approximately 0.1 %, with the overall possibility of major complications 4.3 %. Complications of RYGBP include anastomotic leaks, internal hernia, stomal stenosis, marginal ulcers, cholelithiasis, dumping syndrome, changes in nutritional absorption, along with any other issues that may occur as a consequence of surgery (i.e., wound infections, atelectasis, pneumonia, deep vein thrombosis, etc.).

Patients who have undergone laparoscopic RYGBP are selectively examined postoperatively with a double contrast (water-soluble contrast and barium sulfate) upper gastrointestinal series (UGI). The purpose of the study is to evaluate for the presence of an anastomotic leak. If no evidence of leak is apparent, patients are initiated on a clear liquid diet, with a rate often no greater than 60 mL/h initially. After the patient tolerates the liquid diet for 24 h, some surgeons advance the diet to pureed food (with no added sugar). The pureed diet is continued for 1 month postoperatively, after which regular food may be gradually incorporated. Patients should be instructed to abstain from any foods and liquids that are high in simple carbohydrates and to avoid sugars and sweets.

13.3.1 Anastomotic Leaks

The two sites of anastomoses (gastrojejunostomy and jejunojejunostomy) may serve as a potential source of complications. Anastomotic leak risks range from 0.8 to 6 %, with most generally occurring within 1 week of surgery, but may occur up

to 1 month postoperatively. The patient presentation may include signs such as low-grade fevers, respiratory distress and/or tachycardia (greater than 120 beats per minute). If a leak is suspected clinically, even if imaging is negative, emergent surgical exploration is indicated, and is often done laparoscopically. To test for a possible leak intraoperatively, methylene blue or endoscopy may be utilized. For evaluation with the dye test, methylene blue with saline is injected via a nasogastric tube while a bowel clamp is placed distal to the gastrojejunostomy. To evaluate endoscopically, saline is used to submerge the gastrojejunostomy while the roux-limb is clamped and the pouch is insufflated via the endoscope. Air bubbles present in the saline around the pouch may indicate the presence of a leak. Treatment for an anastomotic leak includes drainage, broad-spectrum antibiotic coverage and identification/repair of the defect when feasible. A gastric tube may be placed for feeding or intravenous feedings may be used.

13.3.2 Stomal Stenosis

Stomal stenosis is a stricture that may form at the gastrojejunal anastomosis. Incidence of stomal stenosis after RGYBP is reported to be between 3.1 and 15.7 %. The etiology of stenosis may be related to the method used for anastomosis, with the greatest risk seen in the use of a 21 mm circular staple, followed in order by a 25 mm circular stapler, linear stapler, and hand-sewn anastomosis [2]. Patients present 1–2 months postoperatively with nausea, vomiting, dysphagia, and/or gastroesophageal reflux, with ultimate progression of intolerance of oral intake. Diagnosis is made by endoscopy or upper GI series. Treatment is endoscopic dilation as the preferred and less invasive option. A therapeutic endoscope is inserted through the gastrojejunostomy along with a balloon dilator which is pneumatically insufflated based on the stoma size. The complication rate is about 3 %, and repeated dilation may be required for some patients. Surgical revision is reserved for patients who have persistent stenosis despite repeated endoscopic dilations.

13.3.3 Marginal Ulcers

Marginal ulcers are mucosal erosions that occur at the gastrojejunal anastomosis, most commonly on the jejunal side. The ulcers typically occur when the gastric remnant is stapled but not divided. The incidence is reported to be between 0.6 and 16 %. Possible etiologies of marginal ulcers include nonsteroidal anti-inflammatory (NSAID) drug use, Helicobacter pylori (H. pylori) infection, smoking, poor tissue perfusion secondary to excess tension or ischemia at the anastomosis, increased exposure to acid in the gastric pouch due to gastrogastric fistula formation, and presence of foreign material (suture or staples). Patient presentation includes nausea, pain, with possible bleeding and/or perforation. Diagnosis is made by upper endoscopy. Initial management includes medical treatment with gastric acid suppression (proton pump inhibitors) with or without sucralfate. Patients should be

strongly encouraged to stop NSAID use and smoking. Patients with H. pylori colonization should be treated with triple therapy (proton pump inhibitor, clarithromycin and amoxicillin).

13.3.4 Cholelithiasis

Cholelithiasis may develop in up to 38 % of patients undergoing gastric bypass surgery, and up to 41 % of these patients become symptomatic. Rapid loss of weight can contribute to the formation of gallstones by increasing the lithogenicity of bile. This risk can be significantly reduced to 2 % when patients are postoperatively treated with a 6 month course of ursodeoxycholic acid [3]. Unfortunately compliance with ursodeoxycholic acid prophylaxis may be poor due to gastrointestinal side effects of the medication. Symptomatic patients should be evaluated preoperatively or intraoperatively for cholelithiasis and should have a cholecystectomy performed at the time of gastric bypass if gallstones are present. Asymptomatic patients may be managed expectantly as a minority will come to cholecystectomy during follow-up.

13.3.5 Dumping Syndrome

Dumping syndrome is a well-known physiologic phenomenon associated with gastric bypass, as it occurs in procedures that involve partial or complete gastrectomy. Dumping typically occurs when patients ingest high levels of simple carbohydrates. Hormones thought to be involved in this mechanism include enteroglucagon, vasoactive intestinal peptide (VIP), peptide YY (PYY), pancreatic polypeptide, and neurotensin. Dumping may be divided into early and late phenomena. Early dumping occurs within 15–30 min of ingestion and is due to rapid gastric emptying. The high osmolality of the food causes rapid fluid shifts from the plasma into the bowel, which leads to hypotension and reflex sympathetic nervous system activation. Patients will present with symptoms of colicky abdominal pain, diarrhea, nausea, and tachycardia. Late dumping occurs 1–3 h after meal ingestion, and presents with symptoms of hypoglycemia (dizziness, fatigue, diaphoresis, weakness, confusion). Rapid gastric emptying leads to a high glucose concentration, which is rapidly absorbed and triggers insulin secretion, leading to the signs and symptoms of hypoglycemia. Sigstad's scoring system may be used for diagnosing dumping syndrome, where a score greater than seven is suggestive of dumping, and a score less than four suggests other diagnoses. To avoid dumping, patients are advised to avoid foods high in simple carbohydrates, and are encouraged to eat diets with high fiber content, complex carbohydrates, and high protein content. Furthermore, patients are instructed to eat small, frequent meals (up to six per day), and to avoid drinking with meals or in the first 2 h after a meal. If these first line measures fail, somatostatin analogue use may be considered, which are administered subcutaneously three times a day

or intramuscularly once every 2–4 weeks. Although dumping is an unpleasant consequence that patients may have to withstand, the condition actually aids the patient in adhering to the prescribed dietary restrictions by acting as negative feedback to the ingestion of sugar [4].

13.3.6 Nutritional Changes

Changes in nutritional needs are important to be considered when managing a post-gastric bypass patient. Patients are advised to obtain a significant amount of their daily calories from protein (50–60 g per day). Daily supplementation also includes 500 μg of vitamin B12, 1200 mg of calcium, and a multivitamin tablet. Women who menstruate are also asked to take 650 mg of ferrous sulfate daily. Serum levels of these supplements should be checked during regular clinic appointments [5].

13.4 Endocrine Physiology After Gastric Bypass

Gastric bypass not only alters the anatomy of gastrointestinal tract, but also the hormonal and neural mechanisms that control the physiologic function. In particular, the peptide hormones ghrelin and peptide YY, and leptin have been examined to evaluate the neural changes evident post-RYGBP.

13.4.1 Ghrelin

Ghrelin is a 28 amino acid peptide, produced by the A cells in the oxyntic glands of the stomach fundus in increased concentrations during periods of fasting or starvation. Ghrelin is low after eating, with hyperglycemia and in obesity. It binds to the growth hormone secretagogue receptor, stimulating release of growth hormone, increases intake of food and produces weight gain.

Weight loss achieved through caloric restriction alone is associated with an increase in plasma ghrelin concentration. Increased concentrations have also been seen in weight loss through lifestyle modifications, chronic exercise, cancer anorexia, cardiac cachexia, hepatic cachexia and anorexia nervosa. In contrast, cross-sectional and prospective studies have shown an alteration in the levels of ghrelin post-gastric bypass surgery. These findings imply that the increased levels may contribute to weight regain. Therefore, in order to maintain weight loss, the appropriate method must inhibit the normal compensatory rise in ghrelin [6].

Gastric bypass patients lack the normal premeal increase in plasma ghrelin, with cumulative secretion of ghrelin decreased [7]. The reduced ghrelin secretion seen after surgery may contribute to the improved glucose tolerance. Ghrelin normally stimulates the secretion of insulin counterregulatory hormones (i.e., glucagon), suppresses adinopectin secretion and inhibits insulin secretion. Several studies have

observed low and/or suppressed ghrelin levels following RYGB. One prospective study by Geloneze et al., demonstrated a significant drop in ghrelin concentrations in both diabetic and nondiabetic patients 1 year after the surgery [8]. Furthermore, ghrelin levels decreased even with a 38 % loss in weight, a change that would normally be expected to stimulate ghrelin release. Additionally, ghrelin levels in RYGB patients were approximately one fourth as high as in those in body mass index-matched patients who had comparable weight loss following biliopancreatic division or adjustable gastric banding surgeries. Some studies have demonstrated the opposite, however, showing an increase in ghrelin concentration in patients who have achieved substantial weight loss after surgery. These differences may be attributed to surgical differences at the various centers, such as the sizes of the gastric pouch, Roux limb, gastrojejunal stoma, and biliopancreatic limb. An override inhibition model has been described, in which an empty stomach and duodenum acutely increase ghrelin levels, whereas there is a paradoxical inhibition when continuously present after RYGBP. This model predicts that bariatric surgeries that do not eliminate the sites of major ghrelin-producing tissue from coming in contact with food would be ineffective at inhibiting ghrelin. The location of the staple line within the stomach may also determine the degree of ghrelin suppression, as the gastric fundus holds the majority of cells responsible for producing ghrelin [6].

13.4.2 PYY

Peptide YY (PYY) is a 36 amino acid hormone secreted from the L cells in the mucosa of the ileum and the H cells in the colon and rectum. PYY is released in response to food intake, in particular fatty foods. It inhibits vagally stimulated gastric acid secretion, and when released into the bloodstream can inhibit gastric emptying and intestinal motility, therefore delaying the delivery of additional ingested food to the intestine, a concept known as the “ileal brake”. PYY also signals to the brain, specifically to the neuropeptide Y2 receptors in the hypothalamus, causing a disinhibition of the release of anorectic peptides (alpha-melanocyte-stimulating hormone (α-MSH) and cocaine-and-amphetamine-regulated-transcript) causing a decrease in food intake. Infusion of PYY decreases the 24 h food intake in both lean and obese patients [9]. Obese patients are known to have lower levels of fasting PYY plasma levels in comparison to normal weight control individuals, suggesting that PYY deficiency may contribute to the development of obesity.

13.4.3 Leptin

Leptin is a hormone encoded by the ob gene and is expressed primarily in adipocytes. In mice, leptin administration causes a decrease in food intake through various mechanisms. Leptin decreases the content of neuropeptide Y (NPY) mRNA and increases the content of proopiomelanocortin (POMC) mRNA in neurons within the arcuate nucleus of the hypothalamus. Alpa-MSH, produced by the cleavage of POMC,

decreases food intake. In humans, BMI and body fat show a strong correlation with leptin production. The concentration of leptin normally reflects the amount of adipose tissue present. Excessive eating also increases serum leptin concentrations, whereas fasting and weight loss reduces serum leptin concentrations. Significant reductions in leptin can be seen in the early postoperative period following RYGBP, even when the BMI is within the morbidly obese range [10].

13.5 Glucose and Insulin: Early Effects

The long term effects of RYGBP on glucose metabolism and diabetes are evident and have often been correlated to the decrease in BMI. However, the effects on glucose metabolism are apparent within days postoperatively, before weight loss has been achieved [11]. Patients seen 3 weeks postoperatively showed significant decreases in blood glucose, insulin, and leptin levels when compared to their preoperative values [10]. Patients with type 2 diabetes on oral hypoglycemic agents may become euglycemic without medications within 3 weeks of surgery, and exhibit rapid normalization of blood glucose levels.

13.5.1 GIP and GLP-1, Insulin

Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide (GLP-1) are incretins released from the duodenal K cells and ileal L cells, respectively. Their combined effect is responsible for approximately 50 % of postprandial insulin secretion. In addition to its stimulatory effect on insulin secretion, GLP-1 also delays gastric emptying, decreases appetite, promotes weight loss, inhibits glucagon, and may enhance insulin sensitivity. In T2DM patients, the incretin effect on insulin secretion is impaired. Studies evaluating GLP-1 levels after gastric bypass have consistently shown significant increases in GLP-1, by factor of 5–10 in response to a meal or to oral glucose. The effect of GBP on GIP levels has yielded less consistent results, as elevated and decreased levels have been reported. However, the incretin effect on insulin secretion has been reported, normalized to the levels of nondiabetic controls at 1 month and 1 year postoperatively [12]. A study by Kindel et al. on rats showed that administration of the GLP-1 antagonist, exendin 9–39, reversed the improved glucose tolerance after duodenojejunal bypass [13]. Use of exendin 9–39 in a study testing human subjects showed improved postprandial hypoglycemia after GBP [14]. A prospective study examined the effect of weight loss versus GBP on incretins. Although it showed that both surgical and non-surgical weight loss resulted in a similar decrease in fasting glucose and fasting insulin, recovery of early insulin secretion after oral glucose and the improvement in incretin levels and effect were only seen in the GBP group. This data suggests that GBP has a weight loss-independent effect on glucose balance. Cross-sectional data has shown that these effects are evident even 20 years after bypass, when compared to non-surgical obese controls [15].

The mechanism behind the improved incretin effect after GBP has been suggested by the foregut and hindgut hypotheses demonstrated in rats. The foregut hypothesis suggests that exclusion of the upper gut, rather than sole weight loss, enhances glucose tolerance. Rats who has undergone gastrojejunal bypass exhibited better glucose tolerance when compared to sham-operated pair-fed controls with equal body weight and in rats with gastrojejunal anastomosis. The hindgut hypothesis states that rapid stimulation of the ileum by food causes an increase in GLP-1 levels, and thus a positive effect on glucose tolerance.

It is well known that amino acids are linked to insulin resistance and diabetes. Studies have also looked at the reduction in circulating branched-chain amino acid (BCAA) and aromatic amino acids levels after GBP. GBP patients had lower levels of BCAA and phenylalanine (Phe) and tyrosine (Tyr) when compared to a match control group that lost the same amount of weight through diet. Better glycemic control and improved insulin secretion was seen in patients that had greater reductions in BCAAs, Tyr, and Phe.

13.6 Surgery and Metabolic Syndrome

Obesity is associated with many comorbid conditions, and predisposes to the development of glucose intolerance, T2DM, dyslipidemia, hypertension, obstructive sleep apnea, and many others. Therefore, treating obesity with bariatric surgery causes a reduction in the obesity-related comorbidities and metabolic syndrome.

13.6.1 Long Term Effects of Obesity and Diabetes

Several studies have shown partial or complete resolution of type 2 diabetes mellitus (T2DM) following gastric bypass. When studied over a 5-year period after RYGBP, patients with preoperative T2DM exhibit normal fasting blood glucose levels (<110) and decrease in hemoglobin A1c (HbA1c) to normal levels (≤5.5 %) [16].

Bariatric surgery has been proven superior to medical management alone for the improvement in T2DM, as seen in short-term randomized trials [17]. The 3-year results from the Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial of 150 patients, found that gastric bypass and sleeve gastrectomy were superior to intense medical treatment alone in obese diabetic patients. Patients who underwent surgical interventions exhibited better glycemic control and reduction in cardiovascular risk factors, with decreased dependence on pharmacological management of T2DM. The mean BMI of patients in the study was 36 ± 3.5, and a mean HgbA1c of 9.3 ± with average duration of diabetes 8.3 ± 5.1 years. At the 3-year end point of the trial, only 5 % of the medical-therapy group was able to reach the target HgbA1c of ≤6 %, whereas 38 % of the gastric bypass group ($p < 0.001$) and 24 % of the sleeve gastrectomy group ($p < 0.01$) were able to achieve the goal. Furthermore, 80 % of subjects that were able to achieve glycemic control at the 1-year mark but relapsed at 3 years were in the medical-therapy

group. The gastric bypass group had the most significant reduction in use of diabetic medications, when compared with both the sleeve-gastrectomy and medical-therapy groups. The surgical groups also showed sustained control in cardiovascular markers (with lower triglyceride levels and higher high-density lipoprotein (HDL) levels) with a reduction in the number of medications needed to manage hyperlipidemia.

13.6.2 Low BMI Diabetics and RYGBP

Gastric bypass has been shown to produce significant improvement in diabetes in obese patients with BMI less than 35 kg/m^2. An analyses of 675 patients performed by Reis et al. showed a significant ($p<0.001$) reduction in BMI, fasting plasma glucose, and HgbA1c levels after bariatric surgery, with 84 % of these patients demonstrating a resolution of T2DM (HgbA1c <7 %). Patients who had undergone RGYBP (both laparoscopic and open), mini-gastric bypass, and laparoscopic ileal resection showed the highest efficiency for diabetes resolution. RYGBP patients had improved glucose and insulin levels and increased GLP-1 and PYY secretion within a few months of surgery.

13.6.3 Weight Regain After RYGBP

It is known that some amount of weight gain occurs after bariatric surgery, when compared to the lowest weight observed between 18 and 24 months postoperatively. Regain is most commonly seen between 2 and 5 years post-GBP. Factors that may contribute to weight regain include the type of surgery performed, presence of binge eating disorders, patient compliance with support groups, and the preoperative BMI. A retrospective study evaluating weight regain 10 years after surgery found a significant increase in BMI in morbidly obese (<50 kg/m^2) and super obese (>50 kg/m^2) patients, with no difference in those with short limb (10 cm afferent limb, 40 cm Roux-en-Y limb, 15–20 mL gastric pouch) versus long limb (100 cm afferent limb, 100 cm Roux-en-Y limb, and 15–20 mL gastric pouch) surgeries. Despite the weight gain found in this study, there was a low mortality rate (3.1 %) among the 209 subjects, and the obesity-related comorbidities remained low (assessed by the medications used by the subjects) [18].

13.6.4 Weight Regain After RYGBP and Relation to Diabetes

There has been conflicting evidence about weight regain after RGYBP and the potential reemergence of diabetes. Some studies have shown that weight regain after GBP leads to recurrence of T2DM, whereas others have shown that weight regain did not have an associated relapse of diabetes. The reemergence of T2DM is theorized to be due to loss of peripheral insulin sensitivity that occurs with weight regain (from increased caloric intake). However, there is likely a multifactorial

contribution to the recurrence of T2DM. These factors may include the loss of the foregut or hindgut hormonal action over time, due to possible receptor down regulation within the pancreatic beta cells or the peripheral tissues. A retrospective cohort study published by DiGiorgi et al. interestingly found that patients that regained weight and had T2DM recurrence or worsening had lower initial BMIs preoperatively, versus those whose T2DM resolved or improved. Although obesity is a known risk factor for the development of T2DM, many patients with the disease are not obese. It is possible that patients who are prone to develop T2DM at lower BMI levels may have lower inherent insulin production or may have significant insulin resistance with minimal weight gain. This phenomenon was demonstrated in the study, as patients who had recurrence of their T2DM had lower BMI levels and were on insulin preoperatively, suggesting they had more severe T2DM.

A recent clinical trial study by Tamboli et al. in 45 RYGBP patients found that early weight regain (at 1 and 2 years postoperatively) did not affect insulin sensitivity. Subjects who had at least 5 % weight regain within the first and second preoperative years did not have reductions in either peripheral or hepatic insulin sensitivity [19]. At this time, more longitudinal studies are needed to evaluate the role of weight regain and the recurrence of T2DM after GBP.

References

1. Mason EE, Ito C. Gastric bypass in obesity. Surg Clin North Am. 1967;47(6):1345–51.
2. Nguyen NT, DeMaria E, Ikramuddin S, et al. The SAGES manual: a practical guide to bariatric surgery. New York, NY: Springer Science & Business Media; 2008.
3. Sugerman HJ, Brewer WH, Shiffman ML, et al. A multicenter, placebo-controlled, randomized, double-blind, prospective trial of prophylactic ursodiol for the prevention of gallstone formation following gastric-bypass-induced rapid weight loss. Am J Surg. 1995;169(1):91–6.
4. Tack J, Deloose E. Complications of bariatric surgery: dumping syndrome, reflux and vitamin deficiencies. Best Pract Res Clin Gastroenterol. 2014;28(4):741–9.
5. DeMaria EJ, Jamal MK. Surgical options for obesity. Gastroenterol Clin North Am. 2005;34(1):-127–42. Review.
6. Cummings DE, Weigle DS, Frayo RS, et al. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. N Engl J Med. 2002;346(21):1623–30.
7. Inui A, Asakawa A, Bowers CY, et al. Ghrelin, appetite, and gastric motility: the emerging role of the stomach as an endocrine organ. FASEB J. 2004;18(3):439–56.
8. Geloneze B, Tambascia MA, Pilla VF, Geloneze SR, Repetto EM, Pareja JC. Ghrelin: a gut-brain hormone: effect of gastric bypass surgery. Obes Surg. 2003;13(1):17–22.
9. Batterham RL, Cohen MA, Ellis SM, et al. Inhibition of food intake in obese subjects by peptide YY3-36. N Engl J Med. 2003;349(10):941–8.
10. Rubino F, Gagner M, Gentileschi P, et al. The early effect of the Roux-en-Y gastric bypass on hormones involved in body weight regulation and glucose metabolism. Ann Surg. 2004;240(2):236–42.
11. Pories WJ, Swanson MS, Macdonald KG, et al. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. Ann Surg. 1995;222(3):339–50.
12. Laferrère B. Do we really know why diabetes remits after gastric bypass surgery? Endocrine. 2011;40(2):162–7.
13. Kindel TL, Yoder SM, Seeley RJ, D'alessio DA, Tso P. Duodenal-jejunal exclusion improves glucose tolerance in the diabetic, Goto-Kakizaki rat by a GLP-1 receptor-mediated mechanism. J Gastrointest Surg. 2009;13(10):1762–72.

14. Salehi M, Prigeon RL, D'alessio DA. Gastric bypass surgery enhances glucagon-like peptide 1-stimulated postprandial insulin secretion in humans. Diabetes. 2011;60(9):2308–14.
15. Näslund E, Backman L, Holst JJ, Theodorsson E, Hellström PM. Importance of small bowel peptides for the improved glucose metabolism 20 years after jejunoileal bypass for obesity. Obes Surg. 1998;8(3):253–60.
16. Schauer PR, Burguera B, Ikramuddin S, et al. Effect of laparoscopic Roux-en Y gastric bypass on type 2 diabetes mellitus. Ann Surg. 2003;238(4):467–84.
17. Schauer PR, Kashyap SR, Wolski K, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med. 2012;366(17):1567–76.
18. Christou NV, Look D, Maclean LD. Weight gain after short- and long-limb gastric bypass in patients followed for longer than 10 years. Ann Surg. 2006;244(5):734–40.
19. Tamboli RA, Breitman I, Marks-shulman PA, et al. Early weight regain after gastric bypass does not affect insulin sensitivity but is associated with elevated ghrelin. Obesity (Silver Spring). 2014;22(7):1617–22.

Biliopancreatic Diversion with Duodenal Switch

14

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14.1 Introduction

Current prescribed interventions for type 2 diabetes (T2D) and other metabolic disorders along with lifestyle modifications often do not result in meaningful improvement in cardiovascular outcomes [1–4]. In contrast, an emerging body of literature from the past decade has described dramatic and sustained improvements in both blood sugar and cardiovascular outcomes in individuals with T2D that undergo surgery for morbid obesity. Various surgical options exist for the treatment of obesity and its comorbidities, but the biliopancreatic diversion and duodenal switch (BPD-DS) results both in the greatest weight reduction and most pronounced improvement in obesity related metabolic conditions [5].

14.2 Biliopancreatic Diversion and Duodenal Switch

Indications for bariatric surgery are BMI>40 or 35 kg/m^2 with a comorbidity such as diabetes. While performed on less than 1 % of eligible patients, bariatric surgery is the most effective treatment for obesity and metabolic conditions [6]. Robust long term data shows that bariatric surgery patients, maintain excess weight loss of greater than 50 %, and considerably, have a significant risk reduction of mortality [7–9]. This reduction in mortality is largely due to a reduction in cardiovascular events and improvement in metabolic conditions. Gastric bypass (GB), laparoscopic adjustable gastric banding (LAGB), and now the vertical sleeve gastrectomy (SG) are the more commonly performed operations. While these procedures result in sustained weight loss and resolve comorbidities, there are populations in which these interventions are not universally

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effective. For example, those with a BMI>50 kg/m^2 rarely achieve a BMI<35 kg/m^2 and are subject to weight recidivism [10].

The biliopancreatic diversion with duodenal switch (BPD-DS) combines a restrictive component (sleeve gastrectomy) with a significant intestinal rearrangement. The biliopancreatic diversion with or without duodenal switch induces the greatest weight loss and resolution of metabolic conditions, making it the most effective weight loss operation. These results are durable beyond 15-year follow-up [11, 12]. Despite this, BPD-DS constitutes only a minority of weight loss operations. This unpopularity may be explained by several factors, including the perceived rate of nutritional complications, the higher surgical risk, and the increased technical challenge of doing the procedure laparoscopically. Large series, however, from specialty centers have demonstrated this procedure can be performed with acceptable risk and nutritional complications.

Scopinaro originally described the biliopancreatic diversion (BPD). This procedure maintained malabsorption while eliminating the long blind limb believed to contribute to many of the long-term problems with jejunoileal bypass (JIB), particularly cirrhosis. A distal gastrectomy was performed with a Roux-en-Y reconstruction anastomosing a 250 cm distal Roux limb to the proximal stomach, with the long biliopancreatic limb connected at 50 cm from the ileocecal valve thus creating a very short common channel [13].

While an improvement on the JIB, the Scopinaro procedure is associated with a dumping syndrome and marginal ulcers. The BPD was modified by Marceau to create the duodenal switch (DS) with vertical (or sleeve) gastrectomy rather than a distal gastrectomy and anastomosing the Roux limb to the stapled (non-divided) proximal duodenum. This technique preserves the pylorus, theoretically reducing dumping and ulcers [14]. Hess and Hess further modified the duodenal switch with the division of the duodenum, leading to the modern-day BPD-DS [15].

The current laparoscopic BPD-DS, as originally described by Gagner, consists of a sleeve gastrectomy with an alimentary limb of approximately 150–200 cm anastomosed to the proximal duodenum, and a variable 50–100 cm common channel [16].

Successful implementation of this operation hinges on patient selection and maintaining patient follow-up. Due to the inherent malabsorptive nature of the BPD-DS, patients must be fully engaged in preoperative education and commit to lifelong maintenance and follow-up. They must be aware of the more intense vitamin supplementation and higher protein intake requirements. Patients need to undergo full nutritional and psychological counseling, and demonstrate understanding of appropriate expectations. In general, we reserve BPD-DS for patients with BMI>50 kg/m^2, those with diabetes for >5 years, those that are insulin dependent, or those who have insufficient weight loss or diabetes resolution after vertical sleeve gastrectomy. A team approach is necessary to ensure patients are well prepared to navigate through this surgical journey. If patients are considered higher risk, due to very high BMI (>60 kg/m^2), multiple comorbidities, unfavorable body habitus, or questionable psychosocial circumstance, we consider and often prefer a staged approach. Here, a vertical sleeve gastrectomy can be performed first to allow for significant weight loss, with later conversion to BPD-DS. Indeed, the

introduction of the now popular sleeve gastrectomy as a stand-alone weight loss and metabolic procedure is the result of this strategy. There is limited long-term data as to how many of these patients will benefit from conversion to BPD-DS [17]. Using this strategy, Iannelli reported that DS could be avoided in nearly two-thirds of patients who undergo a sleeve first [18].

Much discussion and reservation is had about technical demands of BPD-DS and perioperative considerations. In most large and current series, particularly published in the laparoscopic era, the risks for BPD-DS are generally comparable to laparoscopic gastric bypass. Ikramudin, noted that the only significant difference between DS and GB was a slightly higher ER visit rate [19]. In 5-year follow-up of a randomized trial comparing duodenal switch to gastric bypass in the super-obese, both groups were noted to have a similar number of adverse events, but the DS group needed more reoperations. The patients in the DS group were much more likely to have a BMI < 40 kg/m^2, have lower fasting glucose, and have lower serum lipids [20]. Therefore, it is important to contextualize the relative risk of this procedure with the fact that it is the most effective intervention for obesity and metabolic comorbidities. In the meta-analysis by Buchwald, it appeared that the benefit of BPD-DS came at a significantly higher risk, with mortality reported at 1.1 % [21]. As stated earlier, many series from large centers demonstrate mortality at a rate 0.5–0.6 %, particularly in the laparoscopic era [15, 22].

In terms of the nutritional deficiencies long-term data suggest that >75 % of patients actually have adequate parameters. Low levels of iron, hemoglobin, vitamin D, vitamin A, and calcium range from 10 to 20 % of patients. Only about 3 % of patients are frankly deficient in any one of the above parameters [23]. Clearly, with the shorter common channels, BPD-DS necessitates more intense supplementation than gastric bypass. This largely explains the findings of Scandinavian randomized trial between GB and DS, where DS patients were noted to require more adjustments for deficiencies over the baseline vitamin regimen [24]. In 5-year follow-up, Serum concentrations of vitamin A, 25-hydroxyvitamin D, and ionized calcium decreased significantly and parathyroid hormone increased significantly after duodenal switch compared with gastric bypass. There was no difference in B vitamins, folate or prevalence of anemia [20]. Very severe nutritional deficiencies can be "rescued" by limb lengthening, but this is rarely necessary (4 %) [15].

14.3 Diabetes

The link between weight loss surgery and improvement in diabetes is now well established. Reported results are striking, with more than 50 % of patients with HbA1C <7 and many free from medications. The results are striking given the varied modalities used in various reports, along with inconsistent techniques and terminology. In the comprehensive meta-analysis involving 136 studies and over 22,000 patients, Buchwald reported 77 % resolution or improvement in diabetes in patients undergoing bariatric surgery. Of note, only 15 % of all patients were diabetic. Procedure-specific resolution was 48 % for LAGB, 68 % for vertical banded

gastroplasty (VBG), 84 % for gastric bypass and an incredible 98 % for BPD/DS, suggesting increasing impact on diabetes with greater manipulation of the gastrointestinal tract [21].

The effect of BPD-DS on diabetes often occurs soon after surgery and lasts for decades after. With the BPD, Scopinaro reported that three-fourths of patients had normal fasting glucose just months after surgery. Within 1 year, the vast majority had fasting glucose under 90 mg/dl, and this phenomenon was maintained out to 10 and 20-year follow-up. When examining those that do not see diabetes resolution, the usual pattern of long-standing diabetes and insulin dependence emerges, suggesting residual beta cell mass is critical for the effect of BPD-DS [25]. Due to the scarce population that actually remain medication dependent after BPD-DS limited conclusions have been made in the literature about what factors will predict failure with this particular operation. Predictors are similar to those seen for gastric bypass, where duration and severity of diabetes are negative factors [26].

There are certain populations that appear to benefit more from BPD-DS than other bariatric surgeries. The super-morbidly obese (BMI > 50) are less likely to achieve high levels of weight loss and have significant weight regain with gastric bypass [27]. Moreover, this group is less likely to resolve obesity related comorbidities. Prachand et al. found in a case controlled study that all super-morbidly obese patients who underwent BPD-DS were free of medication as compared to 60 % of patients who underwent gastric bypass. Significantly, the patients in the BPD-DS cohort had more severe diabetes, further pointing to the potency of this procedure [28]. This difference was not seen in the short-term follow-up from the Scandinavian randomized trial between BPD-DS and GB. While the DS patients lost more weight, patients in both groups had improved glycemia. At 5 year follow-up, all patients had improvement in diabetes, on patient in the GB group was using oral medication, but DS patients had lower fasting blood glucose and lower HbA1c overall (5.6 % vs. 4.8 %) It is important to note that there were only a small percentage of diabetic patients in this trial, and that a study with greater power would likely demonstrate a difference [20, 29].

14.4 Metabolic Mechanism of BPD-DS

On the surface, one could conclude that the degree of weight loss directly correlates to the resolution of diabetes. In the randomized trial of medical weight loss to gastric banding, the ability of the patients to lose and sustain excess weight loss was the major predictor of diabetes resolution [30]. BPD-DS results in both massive weight loss and frequent resolution of diabetes. The mechanism by which diabetes is affected by BPD-DS does not appear to be totally a consequence of weight loss. We observe that parameters such as fasting glucose, oral glucose tolerance, HbA1C and dependence on medications often improve in the days to weeks following surgery. This improvement often occurs before significant weight loss is achieved [31]. Additionally, bariatric procedures that escalate gastrointestinal rearrangement and increase malabsorption have a higher impact on diabetes resolution. Non-surgical

caloric restriction also does not have the rapid and early effect on diabetes, as does BPD-DS or gastric bypass. Results of randomized trials that compare BPD, gastric bypass and intensive medical therapy for diabetes show that surgery more frequently resolves diabetes, with BPD trending towards the greatest impact [32]. Lastly, in several experimental surgical models where the GI tact is rearranged without restricting caloric intake such as the duodenal jejunal bypass and ileal transposition, glycemia dramatically improves. It would appear that the GI tract itself plays a role in regulating blood glucose levels [5].

These dramatic clinical and experimental observations increase our appreciation for how the gut functions as an endocrine organ in addition to its role in digestion. Various portions of the GI tract elaborate an array of hormones, particularly peptides that regulate glucose homeostasis, appetite and satiety. The nutrient stream and bile acids stimulates the production of these hormones. This fact is corroborated by the observation that orally ingested glucose raises insulin levels higher than IV glucose. Hormones that augment insulin secretion are called incretins. There likely are hormones that counter-regulate this process, or "anti-incretins" [33].

Rapid transit of nutrients into the ileum results in a more pronounced secretion of incretin hormones, in particular GLP-1 (glucagon like peptide-1), which then improves beta-cell secretion of insulin. The production of enteroglucagon and peptide YY are also increased by the L-cells of the ileum, affecting glucose metabolism, intestinal motility and satiety. Direct stimulation of the terminal ileum and cecum by food hydrolysate in patients with BPD-DS was shown to dramatically augment release of these hormones [34]. Further evidence that highlights the importance of the hindgut can be seen in the ileal transposition (IT). This is an experimental procedure that transposes the terminal ileum in to a more proximal position in the gut, resulting in earlier rise in GLP-1 and peptide YY in response to ingested food. Improved glycemic control is observed without restriction or significant weight loss [35]. Glycemic control was improved in 87 % of patients with type 2 diabetes and BMI < 35 kg/m^2 who underwent IT. Long-term data for this procedure is not available, but the importance of the hindgut and a weight loss independent mechanism to diabetes resolution by gastrointestinal rearrangement is illustrated [36, 37].

The proximal gut or foregut probably also plays a role in glucose homeostasis. Overstimulation of the foregut by oral intake (duodenum and proximal jejunum), may result in a chronically hyperinsulinemic state and subsequent insulin resistance. Patients with T2D have chronically elevated levels of the hormone GIP (Glucose-dependent insulinotropic polypeptide), an incretin. Sequestering the duodenum or proximal small bowel from the stream of nutrients, as is done in gastric bypass and BPD-DS, decreases GIP levels. Excluding the proximal small bowel also may suppress the release of "anti-incretins" that counteract the appropriate function of GIP [38]. The duodenal-jejunal bypass (DJB) is an experimental procedure that excludes the duodenum, but does not result in significant weight loss. In both lean and obese diabetic animals, this procedure results in improved glycemia and decreased levels of GIP [39]. Ramos reported a series of 20 patients with improved fasting glucose and significantly reduced HbA1C. Eighteen of 20 patients were free of medication [40].

The hindgut and foregut mechanisms to improved glucose homeostasis are applicable to both the gastric bypass and BPD-DS. The greater malabsorption seen in BPD-DS together with the more significant weight loss function synergistically with GI hormonal changes to yield a more pronounced metabolic effect. With decreased absorption of lipids, there is a more significant depletion of intracellular energy stores and lower levels of plasma lipid concentrations [25]. This results in improved peripheral insulin sensitivity. Despite having better glycemic control and more pronounced beta-cell function, patients with BPD-DS have overall lower levels of insulin secretion compared to gastric bypass [41]. Compared to gastric bypass, glucose metabolism after BPD-DS appears to be more efficient and is a consequence of both enhanced insulin secretion, and enhanced insulin sensitivity [42].

14.5 Lipid Metabolism and BPD-DS

The dramatic metabolic effects of BPD-DS are likely closely linked to the handling of high-energy nutrients, namely lipids. The obligate reabsorption of bile acids, rapid intestinal transit time, and limited mixture of nutrients with digestive enzymes increase lipid losses and decrease available circulating lipids. These fat losses are closely linked with the greater loss of percentage of body fat seen after BPD-DS. As noted by Strain et al., while all bariatric procedures reduce BMI, BPD-DS has the greatest impact on body mass composition [10]. Needless to say, the impact of body mass composition is critical in the improved insulin sensitivity seen after BPD-DS. This is not only due to the composition of the periphery, but also due to changes in gene expression that improve intracellular energy management [43].

As a result of these mechanistic differences in lipid handling the clinical outcome on cardiovascular risk factors as measured by serum lipid profiles is generally superior with BPD-DS. Buchwald noted in his meta-analysis a near 100 % improvement in circulating lipid levels [21]. When comparing the outcomes of super-obese patients undergoing either BPD-DS or GB, our group found nearly a threefold likelihood of improvement of lipid profiles. And, more recently the 5-year outcomes from the randomized study between gastric bypass and duodenal switch demonstrated that only BPD-DS resulted in sustained decrease in LDL [20].

No doubt, the superior clinical impact of BPD-DS is multifactorial, but as stated earlier is probably linked to dietary fat loss due to intestinal rearrangement. The Canadian group recently reported that in their large experience, some patients who only had the intestinal component of BPD-DS (without sleeve gastrectomy) enjoyed nearly the same resolution of hyperlipidemia (82 %) as those that had a full BPD-DS (100 %). Those that had sleeve alone were only half as likely to have lipid profile improvement (41 %) [44].

14.6 Conclusion

Cardiovascular complications from poorly controlled type two diabetes result in significant morbidity and mortality. Reversing this has proven challenging with medical therapy but early intervention is associated with the best outcomes [45].

Few diabetics achieve an HbA1C <7 by conventional means [4]. Increasing the intensity of medical strategies has also yielded disappointing results [1–3].

When compared to medical therapy, bariatric surgery is much more effective in improving glycemia and even allowing people to be medication free. This is now evident in randomized trials with short and medium-term follow-up [32, 46, 47]. There is a significant risk reduction of microvascular and macrovascular events in actual 20-year follow-up [48]. While weight loss is an inherent benefit of these procedures, the metabolic improvements seen appear to occur in part through a weight independent mechanism [8, 49].

Biliopancreatic diversion and duodenal switch is the most effective surgical procedure both in terms of weight loss, resolution of diabetes and lipid metabolism. This is a complex procedure and has added surgical and nutritional risks. Many of these can be overcome with proper training and patient selection. Altered secretion of gut hormones by gastrointestinal rearrangement and depletion of intracellular energy stores improves insulin secretion and reduces peripheral insulin resistance. This not only makes BPD-DS the most effective metabolic procedure but also the most efficient. While not all patients would be candidates for this procedure, there may be subpopulations that would most benefit from BPD-DS. Further understanding the mechanism of BPD-DS may help us treat all patients with diabetes and associated metabolic disease.

References

1. TAC Group. Intensive blood glucose control and vascular outcome in patients with type 2 diabetes. N Engl J Med. 2008;258(24):2560–72.
2. TAC Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358(24):2545–59.
3. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in Veterans with type 2 diabetes. N Engl J Med. 2009;360:129–39.
4. Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. JAMA. 2004;291(3):335–42.
5. Rubino F, Schauer P, Kaplan LM, Cummings DE. Metabolic surgery to treat type 2 diabetes: clinical outcomes and mechanism of action. Annu Rev Med. 2010;61:393–411.
6. National Institutes of Health UDoHaHS. Gastrointestinal surgery for severe obesity. Consensus statement of the NIH consensus development conference. 1991 [updated 1991; cited]; Available from: http://consensus.nih.gov/1991/1991GISurgeryObesity084html.ntm
7. Adams TD, Gress R, Smith DC, et al. Long-term mortality after gastric bypass surgery. N Engl J Med. 2007;357:753–61.
8. LA Sjostrom L, Peltonen M, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med. 2004;351:2683–93.
9. Sjostrom L, Norbro K, Sjostrom CD, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med. 2007;357:741–52.
10. Strain GW, Gagner M, Pomp A, et al. Comparison of weight loss and body composition changes with four surgical procedures. Surg Obes Relat Dis. 2009;5:582.
11. Prachand VN, Davee R, Alverdy JC. Duodenal switch provides superior weight loss in the super-obese (BMI > 50kg/m2) compared with gastric bypass. Ann Surg. 2006;244:611.
12. Scopinaro N, Papadia F, Marinari G, et al. Long-term control of type 2 diabetes mellitus and the other major components of the metabolic syndrome after biliopancreatic diversion in patients with BMI < 35 kg/m2. Obes Surg. 2007;17:185–92.

13. Scopinaro N, Gianetta E, Civalleri D, et al. Biliopancreatic bypass for obesity: II. Initial experience in man. Br J Surg. 1979;66:618–20.
14. Marceau P, Hould F, Simard S, et al. Biliopancreatic diversion with a duodenal switch. World J Surg. 1998;22:947–54.
15. Hess DS, Hess D. Biliopancreatic diversion with duodenal switch. Obes Surg. 1998;8:267–82.
16. Ren CJ, Patterson E, Gagner M. Early results of laparoscopic biliopancreatic diversion with duodenal switch: a case series of 40 consecutive patients. Obes Surg. 2000;10:514–23.
17. Gagner M, Inabnet WB, Pomp A. Laparoscopic gastrectomy with second stage biliopancreatic diversion and duodenal switch in the super-obese. In: Inabnet WB, DeMaria ED, Ikramuddin S, editors. Laparoscopic bariatric surgery. Philadelphia, PA: Lippincott Williams & Wilkins; 2005. p. 143–9.
18. Iannelli A, Schneck AS, Topart P, Carles M, Hebuterne X, Gugenheim J. Laparoscopic sleeve gastrectomy followed by duodenal switch in selected patients versus single-stage duodenal switch for super obesity: case-control study. Surg Obes Relat Dis. 2013;9(4):531–8.
19. Dorman RB, Rasmus NF, Al-Haddad BJ, Serrot FJ, Slusarek BM, Sampson BK, et al. Benefits and complications of the duodenal switch/biliopancreatic diversion compared to the Roux-en-Y gastric bypass. Surgery. 2012;152(4):758–65. discussion 65–7.
20. Risstad H, Sovik TT, Engstrom M, Aasheim ET, Fagerland MW, Olsen MF, et al. Five-year outcomes after laparoscopic gastric bypass and laparoscopic duodenal switch in patients with body mass index of 50 to 60: a randomized clinical trial. JAMA Surg. 2015;150:352.
21. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004;292:1724–37.
22. Scopinaro N, Adami G, Marinari GM, et al. Biliopancreatic diversion. World J Surg. 1998;22:936.
23. Asheim ET, Björkman S, Sphvik TT, et al. Vitamin status after bariatric surgery: a randomized study of gastric bypass and duodenal switch. Am J Clin Nutr. 2009;90:15.
24. Aasheim ET, Bjorkman S, Sovik TT, Engstrom M, Hanvold SE, Mala T, et al. Vitamin status after bariatric surgery: a randomized study of gastric bypass and duodenal switch. Am J Clin Nutr. 2009;90(1):15–22.
25. Scopinaro N, Marinari G, Camerini GB, et al. Specific effect of biliopancreatic diversion on the major components of metabolic syndrom: a long-term follow-up study. Diabetes Care. 2005;28:2406–11.
26. Vage V, Nilsen RM, Berstad A, Behme J, Sletteskog N, Gasdal R, et al. Predictors for remission of major components of the metabolic syndrome after biliopancreatic diversion with duodenal switch (BPDDS). Obes Surg. 2013;23(1):80–6.
27. Christou NV, Look D, Maclean LD. Weight gain after short- and long-limb gastric bypass in patients followed for longer than 10 years. Ann Surg. 2006;244(5):734–40.
28. Prachand VN, Ward M, Alverdy JC. Duodenal switch provides superior resolution of metabolic comorbidities independent of weight loss in the super-obese (BMI > 50kg/m2) compared with gastric bypass. J Gastrointest Surg. 2010;14:211–20.
29. Sovik TT, Aasheim ET, Taha O, Engstrom M, Fagerland MW, Bjorkman S, et al. Weight loss, cardiovascular risk factors, and quality of life after gastric bypass and duodenal switch: a randomized trial. Ann Intern Med. 2011;155(5):281–91.
30. Dixon JB, O'Brien P, Playfair J, et al. Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. JAMA. 2008;299:316–23.
31. Thaler JP, Cummings D. Hormonal and metabolic mechanisms of diabetes remission after gastrointestinal surgery. Endocrinology. 2009;150:2518–25.
32. Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Leccesi L, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. N Engl J Med. 2012;366(17):1577–85.
33. Kamvissi V, Salerno A, Bornstein SR, Mingrone G, Rubino F. Incretins or anti-incretins? A new model for the "entero-pancreatic axis". Horm Metab Res. 2015;47(1):84–7.
34. Buchwald H, Dorman RB, Rasmus NF, Michalek VN, Landvik NM, Ikramuddin S. Effects on GLP-1, PYY, and leptin by direct stimulation of terminal ileum and cecum in humans: implications for ileal transposition. Surg Obes Relat Dis. 2014;10(5):780–6.

35. LA Morinigo R, Casamitjana R, et al. GLP-1 and changes in glucose tolerance following gastric bypass surgery in morbidly obese subjects. Obes Surg. 2006;16:1594–601.
36. DePaula AL, Macedo A, Prudente AS, et al. Laparoscopic sleeve gastrectomy with ileal transposition ("neuroendocrine brake") -- pilot study of a new operation. Surg Obes Relat Dis. 2006;2:464–7.
37. DePaula AL, Macedo A, Rassi N, et al. Laparoscopic treatment of type 2 diabetes mellitus for patients with a body mass index less than 35. Surg Endosc. 2008;22:706–16.
38. Rubino F, Forgione A, Cummings DE, et al. The mechanism of diabetes control after gastrointestinal bypass surgery reveals a role of the proximal small intestine in the pathophysiology of type 2 diabetes. Ann Surg. 2006;244:741–9.
39. Rubino F, Marescaux J. Effect of duodenal-jejunal exclusion in a nonobese animal model of type 2 diabetes: a new perspective for an old disease. Ann Surg. 2004;239:1–11.
40. Ramos AC, Galvão Neto M, de Souza YM, et al. Laparoscopic duodenal-jejunal exclusion in the treatment of type 2 diabetes mellitues in patients with BMI <30kgm2. Obes Surg. 2009;19:307–12.
41. Mingrone G, Castagneto M. Bariatric surgery: unstressing or boosting the beta-cell? Diabetes Obes Metab. 2009;11(Suppl4):130–42.
42. Mingrone G. Role of the incretin system in the remission of type 2 diabetes following bariatric surgery. Nutr Metab Cardiovasc Dis. 2008;18(8):574–9.
43. Rosa G, Mingrone G, Manco M, Euthine V, Gniuli D, Calvani R, et al. Molecular mechanisms of diabetes reversibility after bariatric surgery. Int J Obes (Lond). 2007;31(9):1429–36.
44. Marceau P, Biron S, Marceau S, Hould FS, Lebel S, Lescelleur O, et al. Biliopancreatic diversion-duodenal switch: independent contributions of sleeve resection and duodenal exclusion. Obes Surg. 2014;24(11):1843–9.
45. Holman RR, Sanjoy P, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359:1577–89.
46. Schauer PR, Kashyap SR, Wolski K, Brethauer SA, Kirwan JP, Pothier CE, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med. 2012;366(17):1567–76.
47. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Brethauer SA, Navaneethan SD, et al. Bariatric surgery versus intensive medical therapy for diabetes--3-year outcomes. N Engl J Med. 2014;370(21):2002–13.
48. Sjostrom L, Peltonen M, Jacobson P, Ahlin S, Andersson-Assarsson J, Anveden A, et al. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. JAMA. 2014;311(22):2297–304.
49. Pories WJ, Swanson M, MacDonald KG, et al. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. Ann Surg. 1995;222:339–50.

Ileal Interposition with Sleeve Gastrectomy for the Treatment of Type 2 Diabetes

15

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15.1 Introduction

Type 2 diabetes mellitus (T2DM) and obesity are predicted to be two of the greatest public health problems of the coming decades globally. Worldwide, the prevalence of Diabetes is increasing and vascular complications are the main cause of death [1]. Indeed, during 1988–2000 the annual all-cause mortality rates among T2DM patients were 25.2 per 1000 person-years compared with 9.5 per 1000 person-years in those without diabetes in the US population age 35–74 years. Cardiovascular (CV) disease mortality in this diabetic population was 11.1 per 1000 person-years compared to 3.4 per 1000 person-years in those without diabetes [2].

The possibility that gastrointestinal surgeries may lead to improvement in glucose homeostasis through mechanisms beyond reduced food intake and weight loss have been extensively explored. The different bariatric procedures can be mainly restrictive, malabsorptive, and mixed. As there is not an ideal operation, a number of variations of each of these procedures have been performed over the years, in order to optimize the results and decrease their disadvantages. Our incomplete understanding of the physiology of normal appetite and satiety regulation, and the pathophysiology of obesity, are certainly key points in explaining the multiple surgical alternatives. A quite recent meta-analysis supports the assumption that the most effective operations in relation to weight loss and resolution of associated diseases are the biliopancreatic diversion (BPD) and duodenal switch (DS). However, the overall morbidity is high and there is an increased risk of significant malabsorption with an attendant requirement for indefinite supplementation [3].

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An analysis of 621 studies in the literature, including over 135,000 morbidly obese patients undergoing bariatric surgery, reported resolution of T2DM in 78 % of cases [4]. Furthermore, in a retrospective cohort of 7925 bariatric patients, deaths attributed to diabetes were reduced by a remarkable 92 % [5]. Thus, in the morbid obese patient with T2DM, bariatric surgery appears to be a highly effective treatment alternative. However, when using a more restricted definition of diabetes resolution, with complete remission defined as glycated hemoglobin (HbA_{1c}) less than 6 % and fasting blood glucose (FBG) less than 100 mg/dL off diabetic medications, Brethauer et al. [6] demonstrated long-term (5 years or more) complete remission of T2DM in 31 % of patients following gastric bypass, 9 % after sleeve gastrectomy and none after gastric banding.

On the other hand, the most frequent kind of T2DM, the hyperglycemia after the fourth decade of life in moderately obese subjects, is a progressive disease, and resolution, whether spontaneous or by treatment, is uncommon [7]. Saydah SH et al. [8] demonstrated that only 7 % of 404 adult diabetic patients from the NHANES study achieved $HbA_{1c} < 7$ %, blood pressure <130/80 mmHg and total cholesterol < 200 mg/dL %. From the Steno2 study [9], approximately 17 % of the patients were able to reach HbA_{1c} below 6.5 %. A strategy of intensive glucose control to lower the HbA_{1c} value to 6.5 % yielded a 10 % relative reduction in major macrovascular and microvascular events [10]. In another study, an intensive glucose control in patients with poorly controlled T2DM had no significant effect on the rates of major CV events, deaths, or microvascular complications [11]. In the ACCORD study [12], high risk T2DM patients submitted to intensive therapy to lower HbA_{1c} had an increased mortality and no significantly reduced major CV events, as compared with standard therapy. So, there is a clear need to offer diabetic patients an alternative treatment modality with better results.

A straightforward option would be to push the limits of the indication of the different bariatric surgeries to non-morbid obese diabetic patients. However, it is not easy to justify some of the tactic components of the different bariatric operations, like the small stomach performed with the gastric bypass and the important malabsorption associated to the BPD-DS surgeries. Recent data have demonstrated that the good results of bariatric surgeries to morbid obese diabetic patients could not be reproduced for lower body mass index (BMI) patients. Schauer et al. [13] conducted a prospective, randomized, controlled trial in 150 obese patients with uncontrolled T2DM to receive either intensive medical therapy alone or intensive medical therapy plus Roux-en-Y gastric bypass or sleeve gastrectomy. Mean BMI was 36. The primary end point was HbA_{1c} level of 6.0 % or less. At 36 months, 38 % of patients following gastric bypass, 24 % after sleeve gastrectomy and 5 % in the intensive medical treatment were able to reach $HbA_{1c} \leq 6$. In another randomized trial at four teaching hospitals, Ikramuddin et al. [14] compared lifestyle-intensive medical management and Roux-en-Y gastric bypass surgery. The primary outcome was considered successful if patients achieved the composite of a triple end point: an HbA_{1c} of less than 7.0 %, an LDL cholesterol level of less than 100 mg/dL and systolic blood pressure less than 130 mmHg. After 12 months, 49 % of the patients in the gastric bypass group and 19 % in the lifestyle-medical management group achieved the primary end points.

An alternative to the different bariatric surgeries would be an operation, specifically designed to the treatment of T2DM, and based on the pathophysiology of the disease; very much like a regular antidiabetic medication.

According to the literature, ileal interposition was first described in 1928 [15]. Dorton in 1985 and Halberg in 1986 [16, 17] first suggested its use for the treatment of obesity. Dr. E. Mason, in 1999 [18], suggested its use for both obesity and/or diabetes. In 2003, we proposed the combination of an ileal interposition up into the jejunum (JII-SG) or into the duodenum (DII-SG) associated to a tailored sleeve gastrectomy [19]. Further on, a selected group of 19 morbid obese patients had ileal interposition associated with a sleeve gastrectomy. In this highly selected group, diabetes was resolved early in the postoperative period [20].

15.2 Pathophysiology of T2DM and Ileal Interposition with Sleeve Gastrectomy

Under normal physiological conditions, unabsorbed nutrients can achieve the distal small intestine (ileum), resulting in the activation of a neuroendocrine negative feedback mechanism, the "ileal brake." These combined effects influence digestive process, ingestive behavior, glucose and lipid metabolism and involves a number of different mechanisms, including increased secretion of peptides, like glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) from L cells of the ileum [21]. The relevance of the ileal brake as a potential target for weight and metabolic management is based on several findings: First, activation of the ileal brake has been shown to reduce food intake and increase satiety levels. Second, activation of the ileal brake determines weight loss and improves glycemic control. Third, these effects seem to be maintained over time [22].

The pathophysiology of T2DM involves failure of beta-cells to secrete adequate amounts of insulin, insulin resistance (IR) in peripheral tissues and liver, increased endogenous glucose production, accelerated lipolysis, deficiency or incretin resistance, hyperglucagonemia, increased glucose reabsorption in the kidneys, and insulin resistance in the brain [23]. The complexity of the pathophysiology is such, that the whole is bigger than the sum of the parts. Furthermore, there are other key concepts to be evaluated: (1) The pathophysiology of T2DM has also genetic and environmental components; (2) The different hormones, peptides and other agents are part of a complex regulatory system, with emphasis that multiple redundant and compensatory factors exists; (3) There is no animal model that matches the complex etiology of human T2DM; (4) During the progression of the disease, diabetic patients have different responses to the therapy applied, a greater chance of hypoglycemia and they are prone to gain weight; (5) An individual approach is suggested, with multiple targets (glycemic control, dyslipidemia normalization, blood pressure stabilization, microalbuminuria reversion, adjustable and long-lasting weight control).

Although the cellular mechanisms underlying ileal interposition with sleeve gastrectomy remains speculative, the operation intends to primarily target the pathophysiology of T2DM. The first characteristic of the operation is to provide an early

contact of ingested nutrients to the interposed distal ileum resulting in an early and significant rise of glucagon-like peptide 1 (GLP-1), with its consequent impact on the defective early (first-phase) insulin secretion. The second characteristic is the correction of the defective amplification of the late phase plasma insulin response to glucose by GIP. Both characteristics were addressed in a publication of the hormonal changes before and after ileal interposition with sleeve gastrectomy [24]. The third characteristic is the amelioration of insulin resistance. An attractive hypothesis for the rapid improvement of insulin sensitivity and associated pancreatic beta-cell function could be related to short-circuiting the entero-hepatic bile acid recycling through an early reabsorption of primary bile acids. Another possibility could be related to surgical ablation of the majority of GIP-secreting intestinal K-cells. The association of variable amounts of stomach resection, tailored to weight, in a sleeve format intends to provide long-lasting control of obesity, to decrease caloric intake, to accelerate gastric emptying and to decrease the circulating levels of ghrelin. Based on the above pathophysiology, we assumed the possibility that the DII-SG would give better results in relation to JII-SG, as it addresses more aspects of the pathophysiology of the disease. These operations encompassed both the hindgut and foregut hypothesis.

All therapeutic procedures need to have efficacy balanced against risk. As with obesity, TD2M remains a major cause of illness and death. Although bariatric surgery appears to be the only procedure that determines a significant and long-lasting treatment for diabetic morbid obesity patients, T2DM in patients with a lower BMI can be treated with medications. It is really not the same disease, nor the same patient.

15.3 Animal Studies

Animal studies have shown that ileal interposition surgery delays the onset of diabetes in University of California at Davis type 2 diabetes mellitus rats (UCD-T2DM). This effect may be related to increased nutrient-stimulated secretion of GLP-17–36 and PYY and improvements of insulin sensitivity, beta-cell function, and lipid metabolism [25].

Patriti et al. [26] demonstrated in a nonobese type 2 diabetes rat model (Goto–Kakizaki) that ileal interposition improved glucose tolerance and was associated with a higher GLP-1 levels. The same author also demonstrated that ileal interposition improves glucose metabolism and beta-cell function through an enhanced proglucagon gene expression and L-cell number [27].

Ileal interposition was compared to different operations in animal models. Boza et al. [28] observed that obese diabetic rats when submitted to an ileal interposition with sleeve gastrectomy had a significant weight loss and diabetes improvement. The operation proved to be as effective as gastric bypass in the short term on weight progression, with no bypass of the proximal gut. In a nonobese rat model with T2DM, ileal interposition determined similar control of diabetes as BPD, with a better postoperative recovery [29].

15.4 Technique

Two different techniques have been performed: ileal interposition up into the jejunum associated with a tailored sleeve gastrectomy and ileal interposition up into the duodenum associated with a tailored sleeve gastrectomy. A standard five- to six-port laparoscopic technique is used after establishment of pneumoperitoneum.

The first technique, JII-SG, starts with division of the jejunum 20 cm from the ligament of Treitz using a linear stapler. An ileal segment of 150–170 cm is created 30 cm proximal to the ileocecal valve, interposing it peristaltically into the proximal jejunum. All three anastomoses are performed functionally side by side using 45-mm linear staplers, with care taken to close mesenteric defects with interrupted 3-0 polypropylene sutures. For standardization purposes, intestinal measurements are performed with traction along the antimesenteric border using a 10-cm marked atraumatic grasper. The tailored sleeve gastrectomy is performed according to preoperative BMI. It starts with devascularization of the greater curvature, beginning in the distal portion of the antrum, 5 cm proximal to the pylorus, or opposite to the incisura angularis or even 3 cm proximal to this point, using the Ultrasonic Scalpel or Ligasure. A 33-Fr Fouchet orogastric calibration tube is placed by the anesthesiologist along the lesser curvature toward the pylorus. The gastric resection is performed starting at the antrum or up in the body and continuing up to the angle of His using a linear 45- or 60-mm stapler. A 3-0 polypropylene running invaginating suture covers the staple line.

The second technique, DII-SG, is an ileal interposition up into the duodenum associated with a tailored sleeve gastrectomy. The sleeve gastrectomy is performed as mentioned earlier. After that, the devascularization along the greater curvature of the stomach continued to the duodenum, 3–4 cm beyond the pylorus. The duodenum is transected using a 60-mm linear stapler. A 3-0 polypropylene running invaginating suture covers the duodenal staple line. The gastric pouch and proximal duodenum are then transposed to the lower abdomen through the mesocolon. An ileal segment of 150–170 cm is created 30 cm proximal to the ileocecal valve, interposing and anastomosing it peristaltically to the proximal duodenum using a handsewing technique. A point in the jejunum 50 cm from the ligament of Treitz is measured and anastomosed to the distal part of the interposed ileum. Anastomoses are performed functionally using 45-mm linear staplers; with care taken to close mesenteric defects using interrupted 3-0 polypropylene sutures. The duodenum–ileum anastomose is performed in a two layer fashion with interrupted sutures. The trocars openings are closed.

15.5 Results and Discussion

Laparoscopic ileal interposition associated with sleeve gastrectomy is a safe operation in a nonobese population with T2DM. DePaula et al. [30] evaluated early morbidity and mortality in 454 patients with a mean BMI 29.7 ± 3.6 kg/m^2 (range 19–34.8). There was no conversion to open surgery. Mortality was 0.4 %. Major

complications were observed in 4.8 % of the patients and minor complications in 11.2 %. Reoperations were performed on eight patients (1.7 %). Readmissions to the hospital occurred in 20 patients (4.4 %). In another study [31], 360 patients were studied. Early mortality was 0.27 %. The total number of surgical complications was 6.1 and 1.94 % of the patients required reoperations.

Both procedures, ileal interposition up into the jejunum and ileal interposition up into the duodenum with tailored sleeve gastrectomy, are considered effective operations for diabetic patients with BMI below 35. Following a prospective randomized controlled trial comparing the two versions; the duodenum–ileal interposition resulted in a greater percentage of patients with HbA_{1c} below 6 (81.3 % versus 35.3 %) compared to the jejunum–ileal interposition [32]. Although the duodenum–ileal interposition is certainly a more effective diabetic operation, the jejunum–ileal interposition does not bypass the duodenum and can be indicated for early and mild diabetes.

Sustainability of effect is evident. At a mean follow-up of 39.1 months, ranging 25–61, mean HbA_{1c} decreased from 8.7 to 6.2 % after the JII-SG and to 5.9 % following the DII-SG. Hemoglobin A_{1c} below 7 % was seen in 89.9 % of the patients, below 6.5 % in 78.3 %, and below 6.0 % in 60.1 %. Although the difference between the two operations was not statistically significant, the DII-SG provided a greater decrease in the HbA_{1c} level and postprandial glucose compared to the JII-SG, and was utilized in more severely diabetic patients [33].

Overall, 86.4 % of patients were off antidiabetic medications. Hari Kumar et al. [34] reported a series of patients with BMI < 35 submitted to the laparoscopic sleeve gastrectomy associated to ileal interposition with a 70 % remission rate of T2DM at a 9-month follow-up. Tinoco et al. [35] in a mid-term outcome of 30 patients, described an 80 % remission rate, and Goel et al. [36] demonstrated that after 6 months of operation, 100 % of the patients with BMI < 35 submitted to JII-SG had HbA_{1c} below 7 %.

Although the percentage of weight loss is a predictor of remission of diabetes in morbidly obese diabetic patients [37], glucose control was not related to the amount of weight loss in the subset of patients with diabetes and BMI below 35. The operations induced progressively greater weight loss across the normal weight, overweight, and obesity (BMI >30 and <35) groups and did not induced adverse problems like protein malnutrition, fat and vitamins malabsorption.

We cannot determine whether the favorable survival effect of this operation is related to glucose control or due to any other beneficial effect. We speculate that beyond glycemic control, the two versions of ileal interposition associated with a tailored sleeve gastrectomy may eventually impact all-cause mortality as it statistically improves the usual risk variables, like cholesterol, triglycerides, weight, microalbuminuria and hypertension. It also provided an early and long-lasting control of postprandial glycemia. A relationship between mortality and postprandial glucose is known and is independent of the fasting glucose levels. Hypertension control was achieved in 87.5 % of patients without medication. The resolution rate of hypercholesterolemia and hypertriglyceridemia was 93.6 % and 81.8 %, respectively. Microalbuminuria was diagnosed in 82 (40.6 %) patients in the preoperative period. Resolution was achieved in 71.1 %.

DePaula et al. [38] also demonstrated that the operations induced changes on T2DM by mechanisms in part distinct from weight loss, principally involving restoration of insulin sensitivity and improvement of ß-cell function through oral glucose tolerance test (OGTT) evaluation. According to this study, insulin sensitivity was fully restored, total insulin output increased and ß-cell glucose sensitivity doubled. Moreover, patients with normal weight, overweight, and BMI between 30 and 35 kg/m^2 had similar postoperative HbA_{1c} levels.

The results of these operations suggest to the clinician that surgery may be an alternative treatment for diabetic patients at lower BMI's. More objective criteria of disease severity are certainly necessary, although surprisingly, we could not identify preoperative clinical predictors of success.

References

1. Fox CS, Coady S, Sorlie PD, D'Agostino Sr RB, Pencina MJ, Vasan RS, Meigs JB, Levy D, Savage PJ. Increasing cardiovascular disease burden due to diabetes mellitus: the Framingham Heart Study. Circulation. 2007;115:1544–50.
2. Gregg EW, Qiuping G, Cheng YJ, Venkat Narayan KM, Cowie CC. Mortality trends in men and women with diabetes, 1971 to 2000. Ann Intern Med. 2007;147:149–55.
3. Buchwald H, Estok R, Fahrbach K, Banel D, Sledge I. Trends in mortality in bariatric surgery: a systematic review and meta-analysis. Surgery. 2007;142(4):621–32.
4. Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, Pories WJ, Bantle JP, Sledge I. Weight and T2DM after bariatric surgery: systematic review and meta-analysis. Am J Med. 2009;122:248–56.
5. Adams T, Gress R, Smith S, Halverson C, Simper S, Rosamond W, LaMonte M, Stroup A, Hunt S. Long-term mortality after gastric bypass surgery. N Engl J Med. 2007;357:753–61.
6. Brethauer SA, Aminian A, Romero-Talamás H, Batayyah E, Mackey J, Kennedy L, Kashya SR, Kirwan JP, Rogula T, Kroh M, Chand B, Schauer PR. Can diabetes be surgically cured? Long-term metabolic effects of bariatric surgery in obese patients with type 2 diabetes mellitus. Ann Surg. 2013;258(4):628–37.
7. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with T2DM mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA. 1999;281:2005–12.
8. Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. JAMA. 2004;291:335–42.
9. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med. 2003;348:383–93.
10. The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358:2560–72.
11. The VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360:129–39.
12. ACCORD Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358:2545–59.
13. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Brethauer SA, Navaneethan SD, Aminian A, Pothier CE, Kim ESH, Nissen SE, Kashyap SR. Bariatric surgery versus intensive medical therapy for diabetes—3-year outcomes. N Engl J Med. 2014;370(21):2002–13.
14. Ikramuddin S, Korner J, Lee WJ, Connett JE, Inabnet III WB, Billington CJ, Thomas AJ, Leslie DB, Chong K, Jeffery RW, Ahmed L, Vella A, Chuang LM, Bessler M, Sarr MG, Swain

JM, Laqua P, Jensen MD, Bantle JP. Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia. The diabetes surgery study randomized clinical trial. JAMA. 2013;309(21):2240–9.
15. Stone HB. Ann Surg. 1928;88(3):593–6.
16. Kral JG. Obesity surgery – state of the art. In: Van Itallie TB, Hirsch J, editors. Recent advances in obesity research IV. London: John Libbey; 1985. p. 237–46.
17. Smithy WB, Cuadros C, Johnson H, Kral JG. Effects of ileal interposition on body weight and intestinal morphology in dogs. Int J Obes. 1986;10:453–60.
18. Mason EE. Ileal [correction of ilial] transposition and enteroglucagon/GLP-1 in obesity (and diabetic?) surgery. Obes Surg. 1999;9:223–8.
19. DePaula AL, Macedo ALV, Prudente A, Silva L, Schraibman V, GozaniNeto J, Pinus J, Cury EK, Szajnbok P, DiDario RP, Bertocco L, Diniz K, Gaudencio J, Bebin L, D'Orto U, Cison D, Penhavel F. Neuroendocrine brake for the treatment of morbid obesity. Preliminary report. Einstein. 2005;3(2):110–4.
20. De Paula AL, Macedo AL, Prudente AS, Queiroz L, Schraibman V, Pinus J. Laparoscopic sleeve gastrectomy with ileal interposition ("neuroendocrine brake"). Surg Obes Relat Dis. 2006;2:464–7.
21. Strader AD. Ileal transposition provides insight into the effectiveness of gastric bypass surgery. Physiol Behav. 2006;88:277–82.
22. Maljaars PW, Peters HP, Mela DJ, Masclee AA. Ileal brake: a sensible food target for appetite control. A review. Physiol Behav. 2008;95:271–81.
23. DeFronzo RA, et al. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes Care. 2009;58(4):773–95.
24. DePaula AL, Macedo LAV, Schraibman V, Mota BR, Vencio S. Hormonal evaluation following laparoscopic treatment of type 2 diabetes mellitus patients with BMI 20–34. Surg Endosc. 2009;23:1724–32.
25. Cummings PC, Strader DS, Stanhope KI, Graham JI, Lee J, Raybould HE, Baskin DG, Havel PJ. Ileal interposition surgery improves glucose and lipid metabolism and delays diabetes onset in the ucd-t2dm rat. Gastroenterology. 2010;138:2437–46.
26. Patriti A, Facchiano E, Annetti C, Aisa MD, Galli F, Fanneli C, Donini A. Early improvement of glucose tolerance after ileal transposition in a non-obese type 2 diabetes rat model. Obes Surg. 2005;15:1256–64.
27. Patriti A, Alsa MC, Sidoni A, Galli N, Donini A. How the hindgut can cure type 2 diabetes. Ileal transposition improves glucose metabolism and beta-cell function in Goto-Kakizaki rats through an enhanced Proglucagon gene expression an L-cell number. Surgery. 2007;142:74–85.
28. Boza C, Munoz R, Yung E, Mizone L, Gagner M. Sleeve gastrectomy with ileal transposition (SGIT) induces a significant weight loss and diabetes improvement without exclusion of the proximal intestine. J Gastrointest Surg. 2011;15:928–34.
29. Zhang GY, Wang TT, Cheng ZQ, Feng JB, Hu SY. Resolution of diabetes mellitus by ileal interposition compared with biliopancreatic diversion in a nonobese animal model of type 2 diabetes. Can J Surg. 2011;54(4):243–51.
30. DePaula A, Stival A, Halpern A, Vencio S. Thirty-day morbidity and mortality of the laparoscopic ileal interposition associated with sleeve gastrectomy for the treatment of type 2 diabetic patients with BMI <35: an analysis of 454 consecutive patients. World J Surg. 2011;35(1):102–8.
31. Celik A, Ugale S, Ofluoglu H, Asci M, Celik BO, Vural E, Aydin M. Technical feasibility and safety profile of laparoscopic diverted sleeve gastrectomy with ileal transposition (DSIT). Obes Surg. 2015;25:1184. doi:10.1007/s11695-14-1518-1.
32. DePaula AL, Stival AS, Macedo A, Ribamar J, Mancini M, Halpern A, Vencio S. Prospective randomized controlled trial comparing 2 versions of laparoscopic ileal interposition associated with sleeve gastrectomy for patients with type 2 diabetes with BMI 21–34 kg/m2. Surg Obes Relat Dis. 2010;6:296–305.

33. DePaula AL, Stival AR, DePaula CCL, Halpern A, Vencio S. Surgical treatment of type 2 diabetes in patients with BMI below 35: mid-term outcomes of the laparoscopic ileal interposition associated with a sleeve gastrectomy in 202 consecutive cases. J Gastrointest Surg. 2012;16(5):967–76.
34. Hari Kumar KVS, Ugale S, Gupta N, Naik V, Kumar P, Bhaskar P, Modi KD. Ileal interposition with sleeve gastrectomy for control of type 2 diabetes. Diabetes Technol Ther. 2009;11:785–9.
35. Tinoco A, El-Kadre L, Aquiar L, Tinoco R, Savassi-Rocha P. Short-term and mid-term control of type 2 diabetes mellitus by laparoscopic sleeve gastrectomy with ileal interposition. World J Surg. 2011;35:2238–44.
36. Goel R, Amin P, Goel M, Marik S. Early remission of type 2 diabetes mellitus by laparoscopic ileal transposition with sleeve gastrectomy surgery in 23–35 BMI patients. Int J Diabetes Dev Ctries. 2011;31(2):91–6.
37. Dolan K, Hatzifotis M, Newbury L. A comparison of laparoscopic adjustable gastric banding and biliopancreatic diversion in superobesitiy. Obes Surg. 2004;14:165–9.
38. DePaula AL, Halpern A, Muscelli E, Mari A, Stival A, Vencio V, Ferrannini E. Improvement in insulin sensitivity and b-cell function following ileal interposition with sleeve gastrectomy in type 2 diabetic patients: potential mechanisms. J Gastrointest Surg. 2011;15(8):1344–53.

Balancing Complications and Metabolic Benefit

16

Elias Chousleb, Soni Chousleb, and Natan Zundel

16.1 Introduction

In evaluating Bariatric Surgery as a treatment for obesity, one must propose the same questions as if we were introducing a new medical therapy, First we need to define the metabolic surgery and perform a limited evaluation of the safety profile of each one of them. **Is it effective**? We review the efficacy of the different procedures in resolving diabetes with the caveat that the definition of resolution is not uniformly established as we see. The last question would be: **Is it better than currently available therapy**? We briefly review medical therapy and the potential adverse effects from it.

According to the Centers for Disease Control, during the past 20 years, there has been an increase in obesity in the USA. More than one-third of US adults (35.7 %) and approximately 17 % of children and adolescents aged 2–19 years are obese. No state had a prevalence of obesity less than 20 %. With a rise in childhood obesity, this pandemic can potentially lead to a devastating health care crisis.

Worldwide, 382 million people have diabetes, and it is estimated by the International Diabetes Federation that by 2030 this number will rise to 552 million. Over 80 % of all type 2 diabetes mellitus patients are overweight and 50 % of these are obese [1]. Diabetes consumes approximately 11 % of the US health care budget ($245 billion), and has a 10 year mortality rate of 51 %. Diabetes is responsible for 68 % of fatal cardiovascular events and stroke according to the CDC. In the USA,

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25.8 million people are affected which is 8.3 % of the population. Diabetes is the leading cause of kidney failure, non-traumatic lower limb amputation, blindness among adults, major cause of stroke and heart disease, and the seventh cause of death.

Bariatric surgery emerged as an effective way to treat morbid obesity, and it was rapidly recognized to have the capability to improve diabetes mellitus type 2 (T2DM), reduce cardiovascular events and improve survival [2–5]. It has been suggested that 84 % of the patients with diabetes will undergo long-term remission after RYGB [6]. The bariatric procedures most commonly performed are Roux-en-Y gastric bypass (RYGB), laparoscopic adjustable gastric band (LAGB), laparoscopic sleeve gastrectomy (LSG) and biliopancreatic diversion (BPD) each with different magnitude in the excess weight loss, but with sustainable long-term results compared with medical group alone.

There is a misconception that bariatric surgery is extremely risky and that it has significant short- and long-term complications; however, this idea is not supported by current literature. A meta-analysis of 361 studies which included a total of 85,085 patients showed an overall mortality of 0.28 % within 30 days and a mortality of 0.35 % within 2 years of surgery [7]. The Longitudinal Assessment of Bariatric Surgery Consortium published their prospective data in the New England Journal of Medicine demonstrating mortality from bariatric surgery was similar to that of any other general surgery procedure such as laparoscopic cholecystectomy [8].

The first report on control of diabetes after gastric bypass was described by Pories et al. [9] in 1987 where he demonstrated 83 % cure rate after gastric bypass (Greenville Bypass). A meta-analysis by Buchwald et al. in 2004 [10] reviewed a total of 22,094 patients that underwent bariatric procedures: the mean percentage of excess weight loss was 61.2 % and included LAGB, RYGB, BPD, and DS. Diabetes was completely resolved in 76.8 % of patients and resolved or improved in 86.0 %. Hyperlipidemia, improved in 70 % or more of patients. Hypertension was resolved in 61.7 % of patients and resolved or improved in 78.5 %. Obstructive sleep apnea was resolved in 85.7 % of patients. Currently randomized and non-randomized trials have proven to effectively control diabetes and induce long-term remission with the different bariatric procedures. We review these procedures here and their impact on T2DM.

16.2 Metabolic Benefits

The mechanisms by which bariatric surgery improves glycemic control has been widely studied but are not completely understood. With the purely restrictive procedures (LAGB, vertical band gastroplasty) the improvement on glycemic control is directly related to weight loss, however for those procedures that combine restriction/malabsorption, two hypothesis have been proposed: the foregut hypothesis that emphasizes the importance of duodenal exclusion [11] and the hindgut hypothesis that emphasizes the benefit to the rapid passage of undigested food to the distal ileum [12]. The details of these hypotheses go beyond the scope of this chapter and

are discussed elsewhere. However, it is worth mentioning that new endoscopic methods are being trialed to see the effects of duodenal exclusion with a barrier type device, as well as surgical techniques such as the duodeno-jejunal bypass.

The definition of remission has some variability between authors, and it is important to distinguish between improvement and true remission. Blackstone and colleagues state that "remission should be defined as a threshold less than what would be expected to result in microvascular damage" [13], and some studies have shown that at a level of 5.7, HgA1c causes microvascular damage [14]. If remission is not obtained, improvement should be considered as a variable although it is much more difficult to objectively measure. Table 16.1 depicts a definition proposed by Brethauer and colleagues [15], to classify between cure and different levels of remission.

16.2.1 What Is the Evidence That Bariatric Surgery Improves T2DM?

Laparoscopic Adjustable Gastric Band is a purely restrictive procedure. Dixon et al. evaluated the glycemic control of LAGB versus medical management with life style modifications in 60 obese patients (BMI < 30 and <40) in a randomized control trial with 2 year follow-up. Remission of type 2 diabetes was achieved by 22 (73 %) in the surgical group and 4 (13 %) in the conventional-therapy group [16], however the glycemic control was directly related with the weight loss.

Mingrone et al. [17] in non-blinded randomized trail included 60 patients with a BMI of >35 and a history of at least 5 years of T2DM with a HgA1c of >7. Patients were randomly assigned to either intense medical management, BPD or RYGB, and at 2 years, the remission of T2DM occurred in 75 % of RYGB patients, 95 % of the BPD patients and none of the medical management group. (Remission was defined as Fasting glucose level of 100 mg/dl and a HgA1c of <6.5).

Table 16.1 Definitions of glycemic outcomes after bariatric surgery

Outcome	Definition
Complete remission	Normal measures of glucose metabolism (A1C < 6 %, FBG < 100 mg/dL) for 1 year in the absence of antidiabetic medications.
Partial remission	Sub-diabetic hyperglycemia (A1C 6–6.4 %, FBG 100–125 mg/dL) for 1 year in the absence of antidiabetic medications.
Improvement	Significant reduction in A1C (by >1 %) or FBG (by >25 mg/dL) OR reduction in A1C and FBG accompanied by a decrease in antidiabetic medication requirement (by discontinuing insulin or 1 oral agent, or 1/2 reduction in dose) for at least 1-year duration.
Unchanged	The absence of remission or improvement as described earlier.
Recurrence	FBG or A1C in the diabetic range (≥126 mg/dL and ≥6.5 %, respectively) OR need for antidiabetic medication after initial complete or partial remission.

At 2 years, the average baseline HgbA1c (8.65 ± 1.45 %) had decreased in all groups; patients in the two surgical groups had the greatest degree of improvement (average HgA1c, 7.69 ± 0.57 % in the medical-therapy group, 6.35 ± 1.42 % in the gastric-bypass group, and 4.95 ± 0.49 % in the biliopancreatic-diversion group).

Several Studies have compared sleeve gastrectomy, gastric bypass and gastric banding to medical therapy, and their results are pictured in Figs. 16.1, 16.2, 16.3, and 16.4

16.2.2 Is There a Metabolic Benefit in Patients with Lower BMI (<35 kg/m²)?

There is no doubt that improvement of glycemic control decreases cardiovascular events, and this raises the question: is there any benefit in performing these procedures in patients with BMI < 35 kg/m²?

In 2006, Rubino et al. [11] used an animal model, nonobese T2DM rats, and they underwent either duodeno-jejunal bypass (DJB), a stomach preserving RYGB, gastro-jejunostomy (GJ) and at 4 weeks they performed a duodenal exclusion. They noticed that DJB rats had markedly improved glucose tolerance, GJ rats had no difference in glucose tolerance until the rats where reoperated and the duodenum excluded. They concluded that the proximal exclusion of the proximal small intestine plays an important role in the pathogenesis of diabetes. With this encouraging result, it was thought that surgical control of diabetes could be obtained in patients with lower BMI.

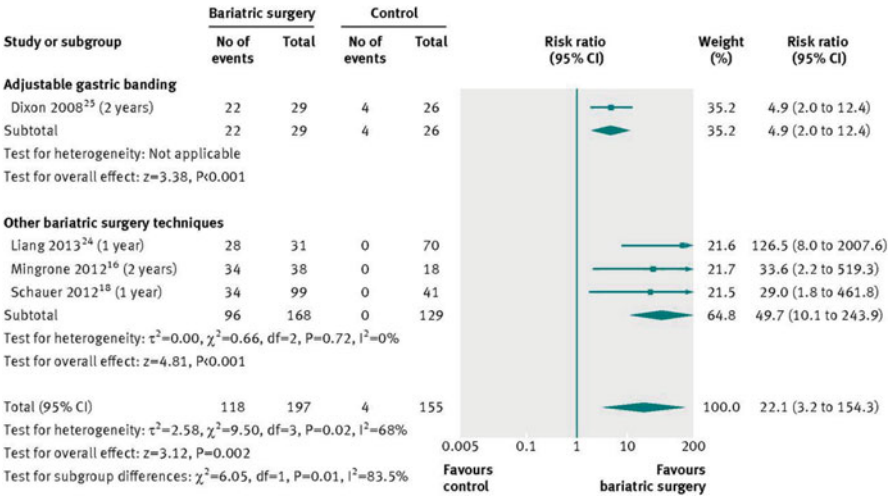

Fig. 16.1 Type 2 diabetes remission after bariatric surgery versus non-surgical treatment (control) for obesity [38]

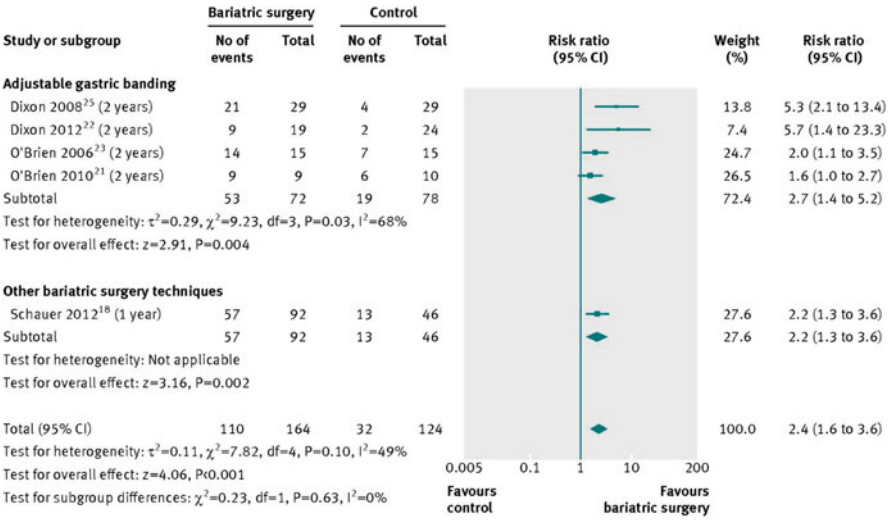

Fig. 16.2 Metabolic syndrome remission after bariatric surgery versus non-surgical treatment (control) for obesity [38]

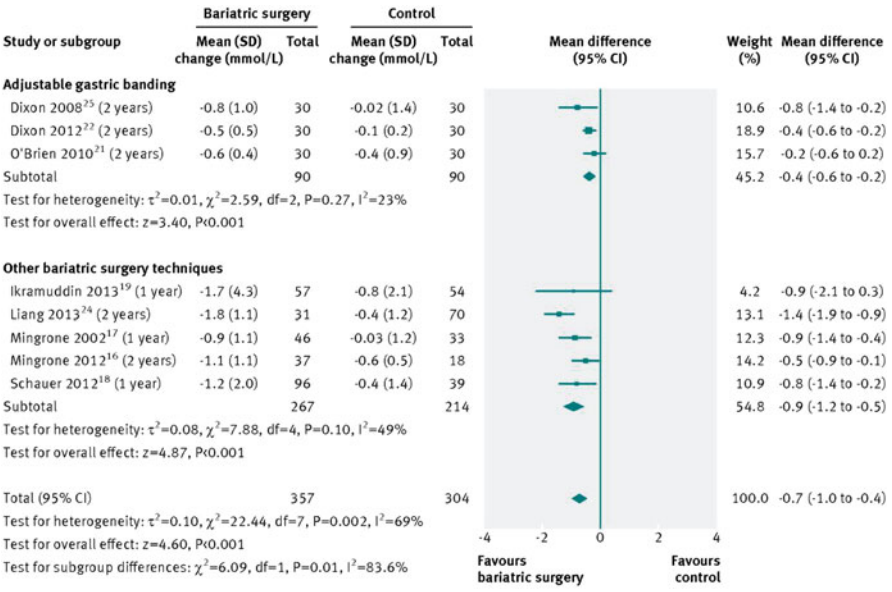

Fig. 16.3 Change in plasma triglyceride concentrations (mmol/L) after bariatric surgery versus non-surgical treatment (control) for obesity [38]

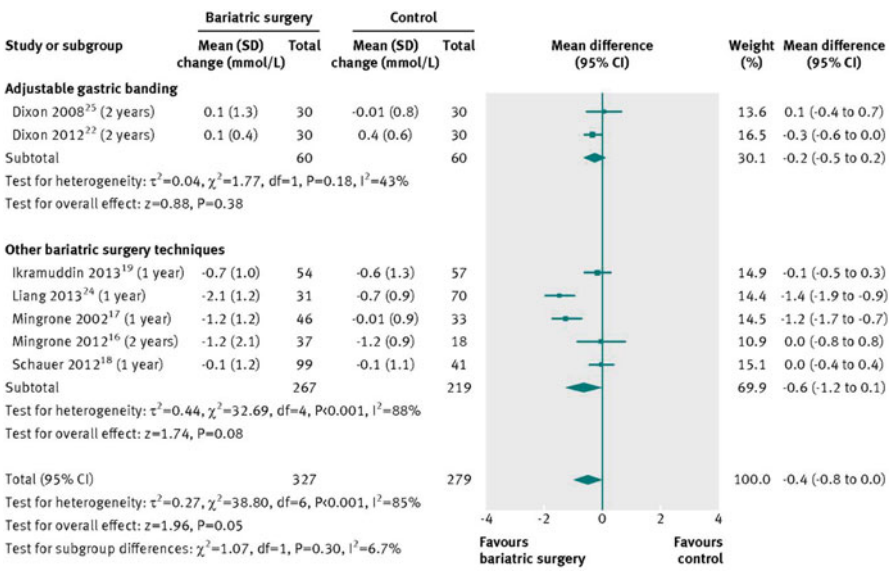

Fig. 16.4 Change in plasma total cholesterol concentration (mmol/L) after bariatric surgery versus non-surgical treatment (control) for obesity [38]

16.3 Roux en Y Gastric Bypass

Lee et al. [18] published a study in 2007 of 820 patients who underwent laparoscopic mini-gastric bypass. They identified 201 patients who had impaired fasting glucose or T2DM. All the clinical data were prospectively collected and stored. Patients with BMI < 35 kg/m^2 were compared with those of BMI > 35 kg/m^2. Successful treatment of T2DM was defined by HgbA1c < 7.0 %, LDL < 100 mg/dl, and triglyceride <150 mg/dl. Among the 201 patients 21.9 % had BMI < 35 kg/m^2. Patients with BMI < 35 kg/m^2 are significantly older, female predominant, had lower liver enzyme and C-peptide levels than those with BMI > 35 kg/m^2. One year after surgery, fasting plasma glucose returned to normal in 89.5 % of BMI < 35 kg/m^2 T2DM and 98.5 % of BMI > 35 kg/m^2 patients ($p = 0.087$) concluding that surgery is an available option and should be considered in patients with T2DM and a BMI < 35 kg/m^2.

Tavares de Sa et al. [19] reported a 48 % resolution of T2DM in 27 patients who underwent Roux-en-Y gastric bypass, and their definition of resolution was HgbA1c < 6 %. However the follow-up of these patients was only 20 months. The longest follow-up study comes from Cohen et al. [20] where he followed 66 patients prospectively for up to 6 years, and diabetes remission occurred in 88 % of cases. Mean HgbA1c decreased from 9.7 ± 1.5 to 5.9 ± 0.1 % ($p < 0.001$).

16.4 Biliopancreatic Diversion

Improvement in T2DM has also been studied in patients with BPD [16, 17]. Chiellini et al. [21] in the first prospective study demonstrated an adequate control of T2DM in 5 patients with a BMI < 35 kg/m^2 with a rapid remission primarily related to improving insulin sensitivity. HgbA1c levels where reduced to 6.28 in 3 months and 5.88 in 6 months. BMI decreased from 30.94 ± 1.05 to 25.36 ± 0.93 kg/m^2 in 12 months after BPD and remained stable after 18 months. However, this study only assesses short-term benefit, and more data is needed regarding long-term benefits. This procedure appears to be the most effective in controlling diabetes.

16.5 Sleeve Gastrectomy

Proponents of the sleeve gastrectomy, emphasize that complications from sleeve gastrectomy are significantly lower than RYGBP. Data from the SLEEVEPASS trial, a randomized prospective study involving 240 patients demonstrated a minor complication rate of 7.4 % vs. 17.1 % in bypass patients, similar major complication rates, and overall morbidity increased from 13.2 vs. 26.5 [22]. The SM-BOSS trial revealed early complication rates of 8.4 % vs. 17.2 % and major complications of 0.9 % vs. 4.5 %, although these differences did not reach statistical significance [23].

There are few reports regarding sleeve gastrectomy and improvement of diabetes. Lee [24] reported 50 % remission of T2DM 1 year postoperatively, and the effect was attributed to decrease in insulin resistance. Alamo et al. [25] in a prospective cohort study of 49 patients, with a mean BMI of 31.6 kg/m^2, identified a remission of T2DM in 81 % of patients and improvement in 18 % at a 1 year follow-up.

In RCT comparing patients with SG to RYGB, Lee et al. [26] enrolled 60 patients with BMI under 35. The follow-up was 12 months, remission of diabetes was achieved in 93 % of RYGB group compared 46.7 % of the SG group.

This preliminary data shows that SG, though a restrictive procedure, might have antidiabetic effect in the early postoperative period related to hormone response, however this effect cannot be supported by the foregut or hindgut theory.

A study performed by Brethauer and colleagues [15] evaluates the outcomes of 217 patients followed prospectively after different bariatric procedures with at least 5 year follow-up.

16.6 Ileal Transposition

Ileal transposition alone or associated SG plus duodenal exclusion (DE) have demonstrated in the animal model to be effective in metabolic control through different mechanisms, supporting the hindgut hypothesis.

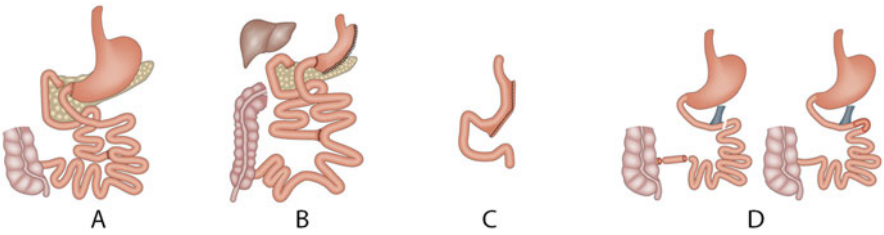

Fig. 16.5 Conventional bariatric procedures (Rubino et al. Ref. [8])

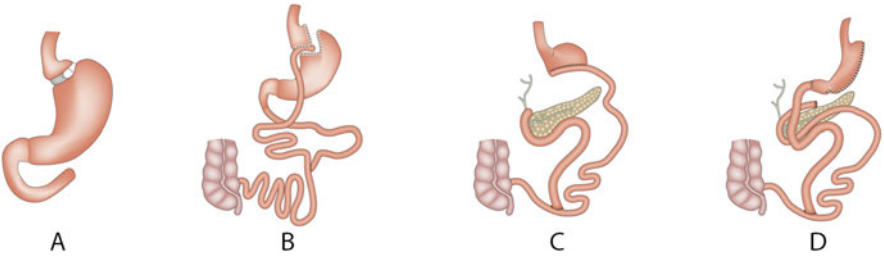

Fig. 16.6 Novel metabolic interventions (Rubino et al. Ref. [8])

Kota [27, 28], in patients with mean BMI of 29, reported a 47 % remission rate with HgbA1c of <6.5 % and improvement in the remaining patients after IT plus SG. Adding DE may improve results with better glycemic and lipid control.

De Paula [29] reported 85 % control of T2DM and HgbA1c < 7 % with IT plus SG. In a study of 72 Pts with an average BMI of 27, 50 % achieved total remission without diabetes medication, 36 % partial remission and 13.9 improved. These studies showed that foregut exclusion plays an important role in T2DM control (Figs. 16.5 and 16.6).

16.7 Complications

The 30 day mortality is low and is estimated to be 0.1–0.3 % for LRYGB, LAGB, and SLG with a slightly higher mortality to up to 1.1 % for BPD or DS. The most common complications are leaks (3 %), wound infection (2.3 %), pulmonary events (2.2 %), and hemorrhage (1.6 %).

The long-term complications include vitamin and mineral deficiencies, dumping syndrome, reactive hypoglycemia, and biliopancreatic diversion has been associated with the highest incidence of nutritional complications.

The Bariatric Outcomes Longitudinal database in 2012 compared the results of 23,106 patients with metabolic syndrome to 163,470 without metabolic syndrome who underwent bariatric surgery. RYGB was the most common operation in 62 % of the patients followed by LAGB in 32 %. Patients that had metabolic syndrome

had a higher rate of serious complications 2.4 % compared to 1 % of the patients without metabolic syndrome, and the readmission rate was also higher 6.2 % compared to 4.7 % [30].

Vitamin and mineral deficiencies are common after malabsorptive procedures, thus patients require lifelong monitoring for nutritional deficiencies. The most common vitamin deficiencies are B1, B12, C, A, D, K, and folate. Of the mineral deficiencies, iron is the most common one and needs lifelong supplementation to avoid related complications. Calcium and vitamin D absorption are also impaired and significant bone mineral density loss can be observed 1 year out. Other deficiencies in trace minerals such as zinc, copper, and selenium can also be observed to lesser proportion than iron.

16.7.1 Recurrence Rate of Diabetes After Bariatric Surgery

In the Swedish Obesity study the remission of diabetes after bariatric surgery was 72 %, however in the long-term follow-up at 10 years the rate had fallen to 36 % and at 15 years only 30 % [31].

Some studies show diabetes relapse in 24–43 % of the patients who initially had remission after RYGB. Interestingly weight gain was a not a good predictor of recurrence [32].

16.7.2 Is Intensive Medical Therapy a Better Alternative Than Surgery?

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) [33] determined whether there is a link between hypoglycemia and mortality in patients undergoing intensive medical therapy for T2DM (Intensive medical therapy HgbA1c < 6.0 % or standard medical therapy HgbA1c 7.0–7.9 %). 10,251 participants were enrolled in this retrospective study. The annual mortality among patients in the intensive glucose control arm was 2.8 % in patients who had episodes of hypoglycemia requiring medical assistance, and for those who had hypoglycemia that didn't require medical assistance, the mortality rate was 1.2 %. A similar pattern was seen among participants in the standard glucose control arm, 3.7 % vs. 1.0 %.

The ORIGIN trial [34] concluded that severe hypoglycemia is associated with an increased risk for cardiovascular outcomes in people at high cardiovascular risk and abnormal glucose metabolism, and they included 12,537 participants. Severe hypoglycemia was associated with a greater risk of cardiovascular events (HR: 1.58; 95 % CI: 1.24–2.02, $p < 0.001$), mortality (HR: 1.74; 95 % CI: 1.39–2.19, $p < 0.001$), CV death (HR: 1.71; 95 % CI: 1.27–2.30, $p < 0.001$), and arrhythmic death (HR: 1.77; 95 % CI: 1.17–2.67, $p = 0.007$).

A meta-analysis of randomized controlled trials that assessed the effect of intensive glucose lowering treatment on cardiovascular events and microvascular complications included 34,533 patients. 18,315 received intensive medical

therapy, and the overall results of this meta-analysis show limited benefits of intensive glucose lowering treatment on mortality and deaths from cardiovascular disease [35].

In a review and meta-analysis published in BMJ 2013 [36], the results of the different randomized trials are evaluated head to head with conventional medical therapy, evidencing favorable results for the surgical groups in almost all metabolic parameters. The results of this analysis are depicted on Figs. 16.1, 16.2, 16.3, and 16.4.

16.8 Discussion

The physiologic basis of how surgery improves diabetes is still not completely understood, with two main theories that do not fully explain the process. It has been seen that the improvement is not directly related to weight loss, because in most of the studies we see improvement in glycemic control before weight loss.

It is important to define resolution of diabetes as demonstrated by Cheng et al. [14] where microvascular alterations are seen at HgbA1c level of 5.7 %. Should we be basing these definitions purely on HgbA1c levels? Is a level of <7 % enough, or should we aim for lower levels of <6.5 %, keeping in mind the potential risks of severe hypoglycemia.

Another key aspect is to identify the patients that are more likely to respond to surgery, with a goal to achieve glycemic control to reduce the microvascular complications and cardiovascular events. Baseline BMI does not accurately predict the benefits of bariatric surgery. Patients with high visceral and hepatic fat accumulation augment their risk for metabolic syndrome [37]. Nonalcoholic fatty liver exacerbates insulin resistance and may contribute to worsening of cardiovascular complications. The most important predictor for cardiovascular events in patients with diabetes was high fasting insulin levels, high triglycerides, total cholesterol, and low LDL [3].

After the evaluation of the available clinical evidence, we can establish that bariatric surgery resolves or improves hyperglycemia and metabolic syndrome in the majority of patients with BMI > 35 kg/m^2 and a good number of patients with BMI < 35 kg/m^2. The patients who will most likely benefit are the ones with diabetes of less than 5 years of duration. Patients with type II and III obesity are most likely to be responsive to bariatric surgery. Procedures like RYGB and BPD have higher remission rates compared to LAGB and LSG, and although all of them are safe, the safety profile for the latter is more favorable.

Several questions come up regarding metabolic surgery, and the main one is "Can surgery cure diabetes or does it only slow the progression?" Some studies have shown a significant rate of relapse, but by slowing the progression do we impact the rate of micro and macrovascular complications? If so, we might be reducing our patient's long-term morbidity and mortality, however prospective randomized trials will be needed to assess this question.

References

1. Van Gaal L, De Block CE. Bariatric surgery to treat type 2 diabetes: what is the recent evidence. Curr Opin Endocrinol Diabetes Obes. 2012;19:352–8.
2. Buchwald H, Estok R, Fahrbach K, et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. Am J Med. 2009;122:248.
3. Sjostromk L, Peltonen M, Jacobson P, et al. Bariatric surgery and long term cardiovascular events. JAMA. 2012;307:56–65.
4. Adams TD, Gress RE, Smith SC, et al. Long term mortality after gastric bypass surgery. N Engl J Med. 2007;357:741–52.
5. Halperin F, Goldfine AB. Metabolic surgery for type 2 diabetes: efficacy and risks. Curr Opin Endocrinol Diabetes Obes. 2013;20:98–105.
6. Jurowich C, Thalheimer A, Hartmann D, et al. Improvement of type 2 diabetes mellitus after bariatric surgery - who fails in the early postoperative course. Obes Surg. 2012;22:1521–6.
7. LABS Consortium. Perioperative safety in the longitudinal assessment of bariatric surgery. N Engl J Med. 2009;361:445–54.
8. Rubino F, et al. Metabolic surgery: the role of the gastrointestinal tract in diabetes mellitus. Nat Rev Endocrinol. 2010;6:102.
9. Poires WJ, Caro JF, Flickinger EG, et al. The control of diabetes mellitus in the morbidly obese with the Greenville bypass. Ann Surg. 1987;206:316–23.
10. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004;292:1724–37.
11. Rubino F, Forgione A, Cummings DE, et al. The mechanism of diabetes control after gastrointestinal surgery reveals a role of the proximal small intestine in the pathophysiology of type 2 diabetes. Ann Surg. 2006;244:221–4.
12. Strader AD, Vahl TP, Jandacek RJ, et al. Weight loss through ileal transposition by increase ileal hormone secretion and synthesis in rats. Am J Physiol Endocrinol Metab. 2005;288:447–53.
13. Blackstone R, Bunt JC, Celaya M. Type 2 diabetes after gastric bypass: remission in five models using HbA1c, fasting blood glucose and medication status. Surg Obes Relat Dis. 2008;8:548–55.
14. Cheng Y, Gregg EW, Geiss LS, et al. Association of a1c and fasting plasma glucose levels with diabetic retinopathy prevalence in the U.S. population: implications for diabetes diagnostic thresholds. Diabetes Care. 2009;32:2027–32.
15. Brethauer SA, Aminian A, Romero-Talamas H, et al. Can diabetes be surgically cured? Long term metabolic effects of bariatric surgery in obese patients with type 2 diabetes mellitus. Ann Surg. 2013;258(4):628–37.
16. Dixon JB, Obrien PE, Playfair J, et al. Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. JAMA. 2008;299:319–23.
17. Mingrone G, Panunzi S, De Gaeteani A, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. N Engl J Med. 2012;366:1577–85.
18. Lee WJ, Wang W, Lee YC, Huang MT, et al. Effect of laparoscopic mini-gastric bypass for type 2 diabetes mellitus comparison of BMI >35 and <35 kg/m2. J Gastrointest Surg. 2008;12:945–52.
19. Tavares VC, Ferraz AA, Campos JM, et al. Gastric bypass in the treatment of type 2 diabetes in patients with BMI of 30 to 35 kg/m2. Obes Surg. 2011;21:283–7.
20. Cohen RV, Pinheiro JS, Schiavon CA, et al. Effects of gastric bypass in patients with type 2 diabetes and only mild obesity. Diabetes Care. 2012;35(7):1420–8.
21. Cheillini C, Rubino F, Castagneto M, et al. The effect of biliopancreatic diversion on type 2 diabetes patients with BMI <35 kg/m2. Diabetologia. 2009;52:1027–30.
22. Helmio M, Victorzon M, Ovazca J, et al. SLEEVEPASS: a randomized prospective multicenter study comparing laparoscopic sleeve gastrectomy and gastric bypass in the treatment of morbid obesity: preliminary results. Surg Endosc. 2012;26:2521–6.

23. Peterli R, Borbely Y, Kern B, et al. Early results of the swiss multicenter bypass or sleeve study (SM-BOSS): a prospective randomized trial comparing laparoscopic sleeve gastrectomy and Roux en Y gastric Bypass. Ann Surg. 2013;258:690–4.
24. Lee WJ, Ser K, Chong K, et al. Laparoscopic sleeve gastrectomy for diabetes treatment in non-morbidly obese patients: efficacy and change of insulin secretion. Surgery. 2010;147:664–9.
25. Alamo M, Sepúlveda M, Gellona J, et al. Sleeve gastrectomy with jejunal bypass for the treatment of type 2 diabetes mellitus in patients with body mass index <35 kg/m2. A cohort study. Obes Surg. 2012;22(7):1097–103.
26. Lee WJ, Chong K, Ser KH, et al. Gastric bypass vs sleeve gastrectomy for type 2 diabetes mellitus: a randomized controlled trial. Arch Surg. 2011;21:896–901.
27. Kumar KH, Ugale S, Gupta N, et al. Ileal interposition with sleeve gastrectomy for control of type 2 diabetes. Diabetes Technol Ther. 2009;11:785–9.
28. Kumar KH, Ugale S, Gupta N, et al. Ileal interposition with sleeve gastrectomy for treatment of type 2 diabetes Indian J. Endocrinol Metab. 2012;4:589–98.
29. De Paula AL, Stival AR, Macedo A, et al. Prospective randomized controlled trial comparing 2 versions of laparoscopic ileal transposition associated with sleeve gastrectomy for patients with type 2 diabetes with BMI 21-34 kg/m2. Surg Obes Relat Dis. 2011;3:296–304.
30. Inabnet III WB, Winegar DA, Sherif B, et al. Early outcomes of bariatric surgery in patients with metabolic syndrome: an analysis of the bariatric outcomes longitudinal database. J Am Coll Surg. 2012;214:550–7.
31. Sjostrom L, Lindroos AK, Pletonen M, et al. Lifestyle, diabetes and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med. 2004;351:2683–93.
32. DiGiorgi M, Rosen DJ, Choi JJ, et al. Re-emergence of diabetes after gastric bypass in patients with mid and long term follow-up. Surg Obes Relat Dis. 2010;6:249–53.
33. Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ. 2010;340:b4909.
34. Mellbin LG, Rydén L, Riddle MC, et al. Does hypoglycemia increase the risk of cardiovascular events? A report from the ORIGIN trial. Eur Heart J. 2013;34:3137–44.
35. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, et al. Effect of intensive glucose lowering treatment on all-cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomized controlled trials. BMJ. 2011;343:d4169.
36. Cohen RV, Schiavon CA, Pinheiro JS, et al. Duodenal Jejunal bypass for the treatment of type 2 diabetes in patients with body mass index of 22-34 kg/m2: a report of 2 cases. Surg Obes Relat Dis. 2007;3:195–7.
37. Stefan N, Haring H. The metabolically benign and malignant fatty liver. Diabetes. 2011;60:2011–7.
38. Gloy VL, Briel M, Bhatt DL, et al. Bariatric Surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomized trials. BMJ. 2013;347:5934.

Part IV

Future Treatments

Neural Modulation in the Treatment of Obesity

17

Michael G. Sarr and Todd A. Kellogg

With the obesity epidemic, multiple efforts have been directed at developing and evaluating new, novel, and innovative therapies to induce clinically relevant weight loss. The majority of bariatric procedures involve anatomic changes designed to restrict oral intake mechanically; these procedures are usually in conjunction with some other influences related to the neurohormonal sequelae of a duodenal bypass (Roux-en-Y gastric bypass) or the removal of the majority of the ghrelin-secreting tissue (sleeve gastrectomy). These procedures, however, require major surgery, and any less invasive, easily reversible intervention would generate tremendous interest if proven effective.

Recently, exploitation of neural modulation of physiologic function has become a viable option in several disciplines—cardiac, pulmonary, central nervous system, and, of course, gastrointestinal [1–5]. Research directed specifically at the brain–gut axis has had a long, renowned history in surgery—i.e., Dragsted's work on the role of vagal innervation on acid secretion, gastric emptying, and other unanticipated/unexpected and as yet poorly understood effects of vagotomy on appetite. The latter effects have spurned a renewed interest in the field of obesity.

17.1 Vagal Control of Upper Gut Function

Physiologically, the vagus nerves mediate the neural axis of acid secretion from the stomach as well as modulate gastric motility/emptying [6] via proximal gastric receptive relaxation and an ongoing, incompletely understood, and inconsistent effect on antropyloric contractile activity exploited by the Dragstedian operative strategy of vagotomy and pyloroplasty. The vagus neural innervation also modulates pancreatic enzyme secretion involved in luminal digestion of ingested food.

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In addition, vagal afferent pathways to the central nervous system serve as sensors of gastric distention, luminal nutrients, pH, and even more poorly understood signals from the mid gut. Thus, the vagus nerves are an active, two-way highway by which the brain and the gut communicate constantly. Thus, why not attempt to exploit this brain–gut axis to induce weight loss?

Early on (1970s/1980s), there was an interest in utilizing a truncal vagotomy to augment the effects of the various gastric partitionings (so-called "gastric staplings"). Interest in vagotomy and appetite was based on observations in patients undergoing vagotomy for peptic ulcer disease. The scientific basis for this assumption of a vagal role in satiety was, however, absent. Results were minimal at best, poorly documented, and even more poorly conceived, and well-designed, controlled studies were absent. The secondary concern and laboratory support of "adaptation" to the effects of complete neural transection (i.e., other neural pathways or end organ changes) which negate the initial effects have dampened markedly the interest in operative vagotomy.

More recently, however, the appreciation of vagal *afferent* pathways involved in appetite [7, 8] and the feeling of satiation have refocused the concepts and interest in neural modulation in the treatment of obesity—i.e., gastric neural "stimulation" and "intermittent reversible vagal blockade" to be discussed below.

17.2 Gastric Stimulation/Pacing for Treatment of Obesity

Early work by Cigaina from Venice working originally with pigs and especially with the pig "Lucky" in the early 1990s [9] generated tremendous interest in this form of neural modulation of eating, satiety, and ultimately weight loss. Cigaina studied the eating habits of pigs after electrodes were implanted within the musculature of the gastric wall and showed that these pigs consumed less food per day and lost weight when the electrodes were "stimulated" electrically [9, 10]. This work culminated in the first human study by Cigaina in five patients (1996–1998) with almost unbelievable success—mean percent body weight (% EBW) loss of 70 % without major dietary restrictions, no imposed changes in lifestyle, and no substantive side effects! Subsequent small groups of 10, 10, and 30 patients had less dramatic but clinically relevant mean weight losses of 20–40 % EBW. As of 2004, Cigaina had treated at total of 65 patients with this technique with, again, almost unbelievable success. Unfortunately, none of these "trials" had non-treated control patients.

As would be expected, this early, incredibly "attractive" concept spurned tremendous interest in the bariatric world, and even more so, when Cigaina suggested that an algorithm could better select patients most susceptible for this treatment. Several preliminary trials were initiated [11]—one in Europe, the Laparoscopic Obesity Stimulation Study (LOSS) of 65 patients at eight clinical sites [12] and another in the USA, the Dual-Lead Implantable Gastric Electrical Stimulation Trial (DIGEST) of 30 patients [13]. Early results in both trials were encouraging and suggested clinically relevant weight losses of 20–30 % EBW.

Early in this experience with these open-label, non-randomized, preliminary clinical trials, the "science" of gastric stimulation was investigated in more depth. Different algorithms of electrical stimulation (changes in pulse width, pulse frequency, duty cycle, etc.) as well as anatomic site of electrode placement were evaluated. It must be stated that this form of gastric stimulation is not gastric "pacing" as occurs with cardiac pacemakers. Although the human stomach does have an underlying cyclic myoelectric rhythm of 3 cycles/min generated by a pacemaker region in the body of the stomach that regulates gastric phasic contractile activity, the parameters of gastric stimulation used to treat obesity do not "entrain" or "pace" the contractile activity of the stomach. Indeed, the electrical parameters utilized include a frequency of 40 Hz (40/min), pulse width of 450 μs, and a "duty cycle" of 2 s on and 3 s off. Such an electrical input to the gastric wall is not necessarily designed to affect gastric function (gastric emptying), although some evidence suggests that this electrical algorithm may tend to decrease gastric empting by inducing proximal gastric relaxation, inducing stretch receptors, and thereby increasing the feeling of satiety and decreasing appetite. Others have suggested that this form of gastric stimulation induces central nervous system effects mediated through stimulation of vagal afferent nerves, leading to centrally mediated effects on appetite, changes in release of regulatory peptides in the brain, and even the potential for vagal blockade of both afferent signals from the gut and vagal (sympathetic?) efferent signals to the gut [8, 14]. Suffice it to say, no one really knows if or how this gastric stimulation works; nevertheless, global interest was tremendous. An excellent analysis of gastric electrical stimulation was published by the Medical Advisory Secretariat of the Ministry of Health and Long Term Care in Toronto, Canada, in 2006 [15]. The conclusion to date was that the efficacy for weight loss was as yet unproven, but the concept was attractive and potentially effective, albeit still experimental.

As with all open-label preliminary studies, proof of efficiency required carefully controlled trials with objective outcomes using accepted methodology. The Screened Health Assessment and Pacer Evaluation (SHAPE) trial was just such a well-designed, prospective, randomized, placebo-controlled, double-blind, multicenter study initiated in 2004 and reported in 2009. Shikora and colleagues from nine medical centers in the USA collaborated in this randomized and importantly double-blinded study of the efficacy of gastric stimulation therapy in severe (Classes II and III) obesity [16]. Based on prior non-controlled work, a so-called Baroscreen algorithm derived to select "ideal" candidates was used to screen 4800 potential candidates. Ultimately, 190 patients were selected; 87 % were women and overall mean age was 44 years. The gastric stimulation electrodes were bipolar electrodes pulled through a subserosal tunnel to ensure appropriate placement within the gastric wall and checked endoscopically. The stimulator device was positioned within the anterior abdominal wall.

Two weeks postoperatively, these fully functional electrodes and stimulator devices were tested for electrical function. Patients were then randomized to a pretested algorithm tailored to the individual patient to minimize feelings of bloating, nausea, or the perception of tingling or "electrical stimulation" based on prior studies. The control patients had no electrical stimulation. Patients in both groups were

assessed monthly for a total of 12 months for feelings of satiety and weight loss; stimulation parameters were then "readjusted." The primary end point was percent body weight loss.

At 1 year of gastric stimulation, the results were very disappointing clinically with no difference between control and treatment groups. The treatment group lost 11.9 ± 17.1 % excess body weight ($x \pm$ SD) while the control group lost 12.2 ± 17.4 % ($p = 0.717$). This well-designed, well-controlled, and double blind study has quelled interest in direct gastric stimulation using this approach to induce weight loss and satiety. The early success by Cigaina and others remains unexplained, but such early, preliminary, and uncontrolled trials must be subjected to scientific scrutiny before adopted widely.

As the attempt to induce neural modulation was being developed and tested using the approach of gastric electrical stimulation, other groups were exploring and developing the concept of direct vagal blockade to modulate signals to and from the brain in an attempt to induce weight loss. The initial thoughts were that vagal blockade via classic gastrointestinal physiology would slow gastric emptying and potentially decrease pancreatic exocrine secretion [17] and thereby help to cause weight loss. Although these effects do occur, tachyphylaxis to surgical vagotomy (permanent transection of the vagus nerves) by an inherent adaptive mechanism negates the early effects of vagotomy on the gut [18]. But there persisted interest in the role of the vagus nerves in mediating centrally based satiety [7, 8].

The initial work involved a non-controlled, open-label study in 31 patients with medically complicated obesity (BMI 35–50) in three centers using this vagal blocking (VBLOC) therapy [19]. Specially designed C-shaped electrodes were positioned laparoscopically around the anterior and posterior intra-abdominal vagus nerves connected to a subcutaneous neuroregulator. Electrical algorithms were then generated by an externally placed, controllable generator placed over the neuroregulator by the patient. The electrical algorithm involved intermittent (5 min on, 5 min off) electrical signals (6 mA, 5000 Hz) for up to 12 h a day. The initial results were encouraging with mean percent excess body weight loss of 14 % at 6 months (maximum 37 %); the safety profile was acceptable without any device-related serious adverse events. Importantly, caloric intake was decreased (by 30 %) as was hunger and feeling of satiation ($p \leq 0.01$). This open-label study served as the basis for a larger, controlled trial of VBLOC therapy.

The EMPOWER study involved a randomized, prospective, double-blind trial using intermittent vagal blockade as a therapy for morbid obesity in 15 centers. Two hundred ninety four patients with BMIs 35–45 were randomized 1–3 weeks after implantation of a fully active device of vagal electrodes and neuroregulator as in the original open-label trial [20]; randomization was a 2:1 design, i.e., 2 treatment–1 control. All patients were encouraged to use the "device" for 9–16 h a day, which required them to wear the external controller (electrical generator). All patients were given 15 individual counseling sessions on weight management over the 12-month trial. Patients filled out validated questionnaires of hunger and appetite, eating, depression, and quality of life. The primary end point was percent excess body weight loss.

The results ($x \pm$SEM) at 1 year post-treatment were disappointing initially—treatment group = 17 ± 2 % vs control group = 16 ± 23 % (p = NS). Nevertheless, further analysis revealed what were deemed potentially important findings by the investigators. Both treated and control groups showed consistent effects of increased weight loss, satiety, and decreased hunger that were associated with increased duration of daily use of the device. These effects occurred in both groups. The investigators specifically and consciously wanted to maintain active devices in both groups throughout the study and had programmed into the control group a safety and efficacy (of the electrode system) electrical check algorithm while the "non-active" device was worn. This safety and efficacy check delivered less than 1000th the electrical signal to the vagus nerves, but did deliver a very small electrical input, raising the question of whether this small electrical input had physiologic effects. Post hoc experimental work on the rat sciatic nerve model showed that even such small external input led to prolonged effect on the mean compound action potential when evaluated 16 min later. These findings questioned the lack of efficacy in the EMPOWER trial and supported a subsequent randomized trial—the ReCharge trial [18].

These investigators reassembled and developed a new prospective, randomized, double-blind trial of intermittent vagal blockade using a fully implantable device that, unlike the previous study, reliably delivered 12 h a day VBLOC therapy to 162 participants. The control group (n = 77) had a non-active, sham neuroregulator implanted that delivered no electrical signals to the vagus nerves. Otherwise, the design of the study was very similar to the EMPOWER study [18].

The results of this study became available in August 2014 [18]. The treatment group at 12 months had lost 24.4 % of their excess weight compared to the control group of 15.9 % (p = 0.002); 52 % of the treatment group lost ≥20 % excess body weight and 38 % achieved ≥25 %. Safety remained acceptable. These results suggest a therapeutic, albeit somewhat limited (25 % excess body weight loss) effect of intermittent vagal inhibition of food intake/body weight loss. Unknown questions remain of whether weight loss will continue, remain stable, or persist at longer term follow-up.

17.3 Summary

Much interest lately has focused on various aspects of peripheral and central neural modulation in the control of many aspects of physiologic function of the heart, diaphragm, and more recently the gut. While classic bariatric surgery has targeted the restriction of oral intake and/or selective or total maldigestion/malabsorption, the potential for central neural modulation of oral intake, satiety, and satiation (and possibly even peripheral metabolism) exists, is being studied actively, and offers a new, novel, yet still investigational approach for the treatment of obesity in the future.

References

1. Deitel M. Applications of electrical pacing in the body. Obes Surg. 2004;14 Suppl 1:S3–8.
2. Plachta DT, Gierthmuehlen M, Cota O, Espinosa N, Boeser F, Herrera TC, et al. Blood pressure control with selective vagal nerve stimulation and minimal side effects. J Neural Eng. 2014;11(3):036011.
3. De Ridder D, Vanneste S, Engineer ND, Kilgard MP. Safety and efficacy of vagus nerve stimulation paired with tones for the treatment of tinnitus: a case series. Neuromodulation. 2014;17(2):170–9.
4. Ogbonnaya S, Kaliaperumal C. Vagal nerve stimulator: evolving trends. J Nat Sci Biol Med. 2013;4(1):8–13.
5. Krahl SE, Clark KB. Vagus nerve stimulation for epilepsy: a review of central mechanisms. Surg Neurol Int. 2012;3 Suppl 4:S255–9.
6. Song GQ, Chen JD. Gastric electrical stimulation on gastric motility in dogs. Neuromodulation. 2011;14(3):271–7. discussion 7.
7. Gil K, Bugajski A, Thor P. Electrical vagus nerve stimulation decreases food consumption and weight gain in rats fed a high-fat diet. J Physiol Pharmacol. 2011;62(6):637–46.
8. Chen J. Mechanisms of action of the implantable gastric stimulator for obesity. Obes Surg. 2004;14 Suppl 1:S28–32.
9. Cigaina V. Long-term follow-up of gastric stimulation for obesity: the Mestre 8-year experience. Obes Surg. 2004;14 Suppl 1:S14–22.
10. Cigaina VV, Pinato G, Rigo VV, Bevilacqua M, Ferraro F, Ischia S, et al. Gastric peristalsis control by mono situ electrical stimulation: a preliminary study. Obes Surg. 1996;6(3):247–9.
11. Shikora SA. Implantable gastric stimulation for weight loss. J Gastrointest Surg. 2004;8(4):408–12.
12. Dargent J. Implantable gastric stimulation as therapy for morbid obesity: preliminary results from the French study. Obes Surg. 2002;12 Suppl 1:21S–5.
13. Shikora SA, Storch K. Implantable gastric stimulation for the treatment of severe obesity: the American experience. Surg Obes Relat Dis. 2005;1(3):334–42.
14. Aronne LJ, Waitman JA. Gastric pacing is not enough: additional measures for an effective obesity treatment program. Obes Surg. 2004;14 Suppl 1:S23–7.
15. Medical Advisory Secretariat. Gastric electrical stimulation: an evidence-based analysis. Ont Health Technol Assess Ser. 2006;6(16):1.
16. Shikora SA, Bergenstal R, Bessler M, Brody F, Foster G, Frank A, et al. Implantable gastric stimulation for the treatment of clinically severe obesity: results of the SHAPE trial. Surg Obes Relat Dis. 2009;5(1):31–7.
17. Smith RB, Edwards JP, Johnston D. Effect of vagotomy on exocrine pancreatic and biliary secretion in man. Am J Surg. 1981;141(1):40–7.
18. Ikramuddin S, Blackstone RP, Brancatisano A, Toouli J, Shah SN, Wolfe BM, et al. Effect of reversible intermittent intra-abdominal vagal nerve blockade on morbid obesity: the ReCharge randomized clinical trial. JAMA. 2014;312(9):915–22.
19. Sarr MG, Billington CJ, Brancatisano R, Brancatisano A, Toouli J, Kow L, et al. The EMPOWER study: randomized, prospective, double-blind, multicenter trial of vagal blockade to induce weight loss in morbid obesity. Obes Surg. 2012;22(11):1771–82.
20. Camilleri M, Toouli J, Herrera MF, Kulseng B, Kow L, Pantoja JP, et al. Intra-abdominal vagal blocking (VBLOC therapy): clinical results with a new implantable medical device. Surgery. 2008;143(6):723–31.

Endoscopic Duodenal–Jejunal Bypass: Endobarrier

18

Manoel Galvao Neto and Josemberg Marins Campos

18.1 Introduction

Bariatric surgery procedures such as Roux-en-Y gastric bypass promote significant and lasting weight loss and improved glycemic control. However, besides being that effective, the procedures are associated with considerable short-term and long-term risks. For these reasons, endoscopic approaches emerge as a minimally invasive, safer, reversible, and cost-effective [1] technique. The Endobarrier Gastrointestinal Liner™ (GI Dynamics Inc, Lexington, MA) or duodenal–jejunal bypass sleeve or Liner (DJBS or DJBL) is a fully reversible procedure that has been developed to treat obesity and type 2 diabetes.

The device consists of a nitinol anchor used to reversibly affix the device to the wall of the duodenum, and a fluoropolymer sleeve extending 60 cm into the small bowel, creating a duodenal–jejunal bypass (Fig. 18.1). The sleeve is impermeable, isolating the duodenum and a portion of the jejunum. It creates a barrier to absorption and delays mixing of food with digestive enzymes, which flow outside of the sleeve, with an effect similar to surgical gastric bypass (Fig. 18.8).

Besides providing effective weight loss, the Endobarrier™ has proven to be a valid option for diabetes mellitus treatment. Its main indication is for diabetic obese patients, especially grade I moderate obese with difficult control diabetes [2, 3]. Other possible options include morbid obesity with bariatric surgery contraindication or prior to

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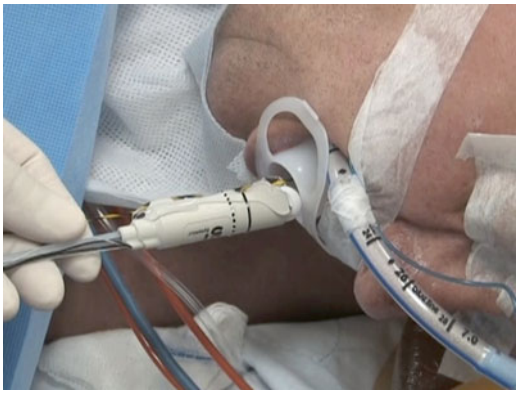

Fig. 18.1 Capsule containing the sleeve and the stent positioned over-the-wire to be inserted

surgery to ensure effectiveness or decrease complications. Initial studies began in 2005 in Chile, then in Netherlands and Brazil. The device now has clinical approval for 12 m implant in Chile, Europe, Israel and Australia. Approval will be granted for clinical use in Brazil, Argentina and Colombia this year and is currently under an FDA trial in US. Prototypes are under evaluation in trials in Chile for 2 and 3 year implant time.

The aims of the procedure include a rapid improvement in the plasma glucose and HbA1c levels, reduction in diabetes medicine intake, decreased appetite, and increased satiety and weight loss.

The Endobarrier™ is endoscopically placed, under direct and fluoroscopic visualization, using a "push" technique. Removal is also achieved endoscopically, with the aid of foreign body forceps. The procedure is designed to be ambulatory and carried out in endoscopy units.

18.2 Technique

Initial access to the stomach and duodenum is achieved using a standard gastroscope.

- The implant is delivered using an over-the-wire catheter system, contained within a capsule at the distal end of the catheter.
- The end of the catheter at the tip of the capsule has an atraumatic ball, which helps prevent trauma to the intestinal wall during sleeve deployment.
- The capsule is positioned over-the-wire into duodenal bulb (Figs. 18.1 and 18.2). After that, the ball with the sleeve is extended into duodenum and proximal jejunum up to 60 cm with X-ray guidance (Fig. 18.3).
- After full extension of the sleeve, the ball is released and the anchor deployed in the duodenal bulb 0.5–2 cm distally from the pylorus (Fig. 18.4).

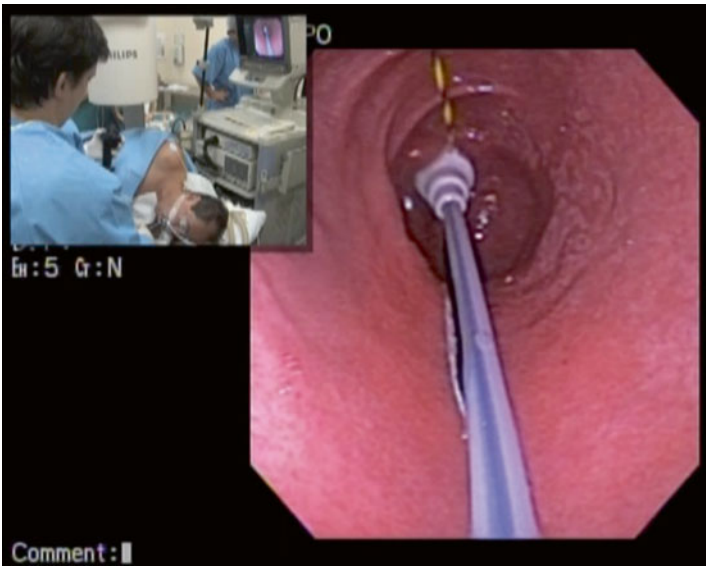

Fig. 18.2 Proper position of the capsule inside duodenal bulb and about to begin the sleeve expansion

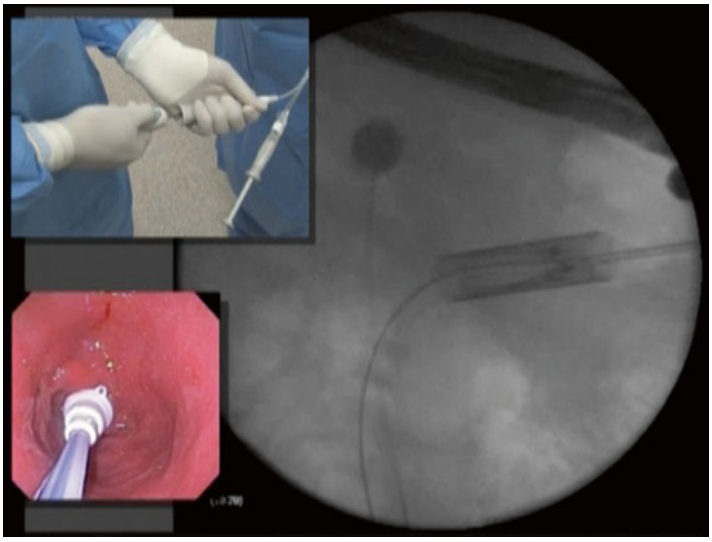

Fig. 18.3 Ball with the sleeve being extended into duodenum and proximal jejunum up to 60 cm with X-ray guidance

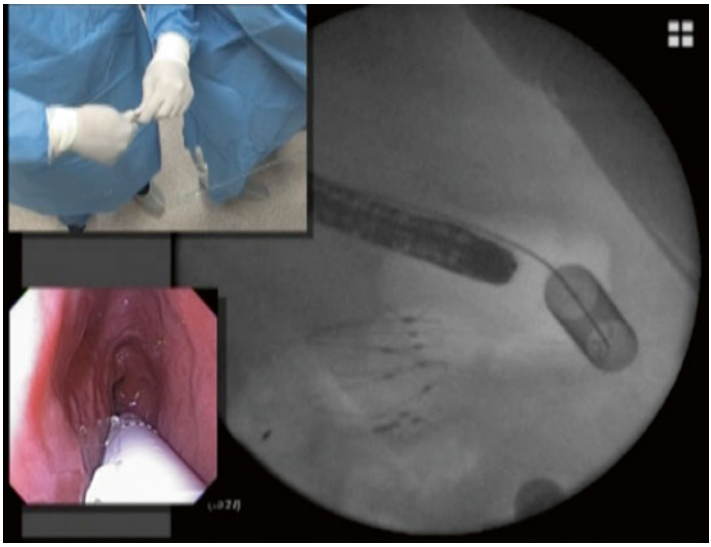

Fig. 18.4 After full extension of the sleeve, the ball is released and the anchor deployed in the duodenal bulb 0.5–2 cm distally from the pylorus

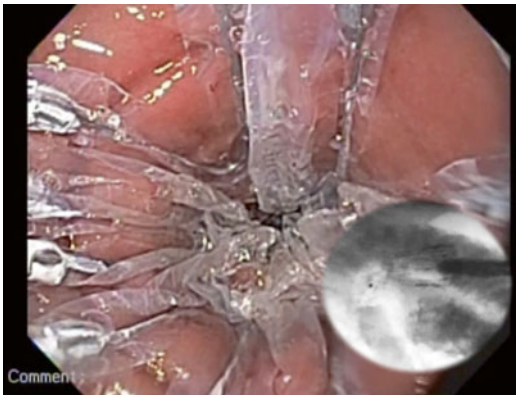

Fig. 18.5 Endoscopy view confirms a proper opening of the stent

– The anchor is self-expanded, and has barbs that will penetrate the tissue to prevent movement. To confirm correct positioning of the sleeve and patency, 60 ml of contrast is flushed.
– The catheter is detached form the sleeve and removed from the bowel, leaving the implant in place. Endoscopy view confirms a proper opening of the stent (Fig. 18.5). Figure 18.6 explains the implant in a graphic way.
– After implant, the liner (the sleeve) will prevent the ingested food to get in touch with the proximal bowel mucosa like a biliopancreatic limb of a gastric bypass (Figs. 18.7 and 18.8)

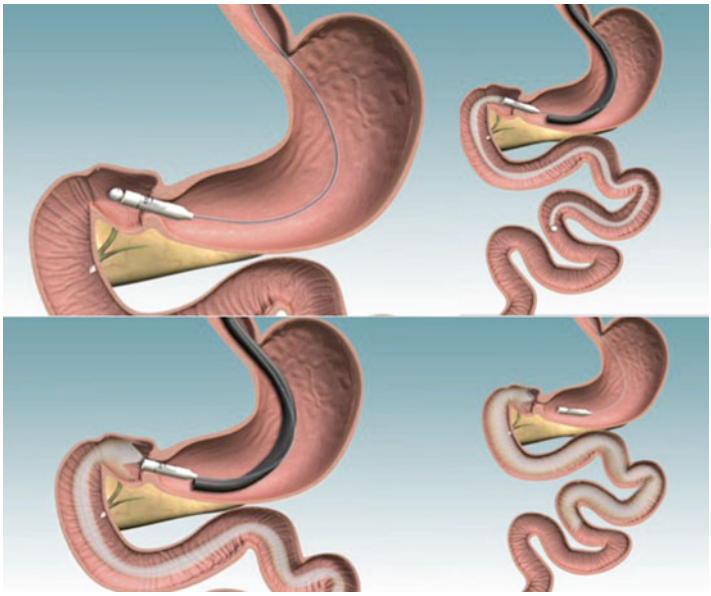

Fig. 18.6 Graph illustration of the Implant

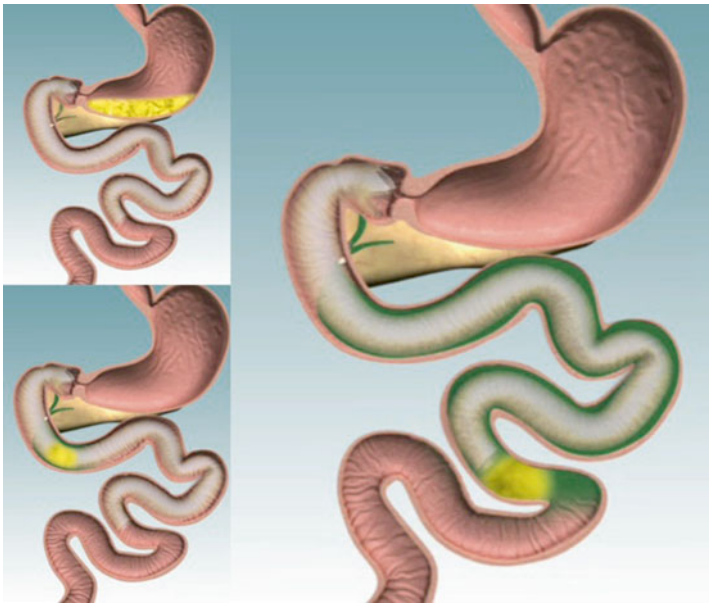

Fig. 18.7 Graph illustration on how the device prevents the food to reach the duodenum and proximal jejunum wall

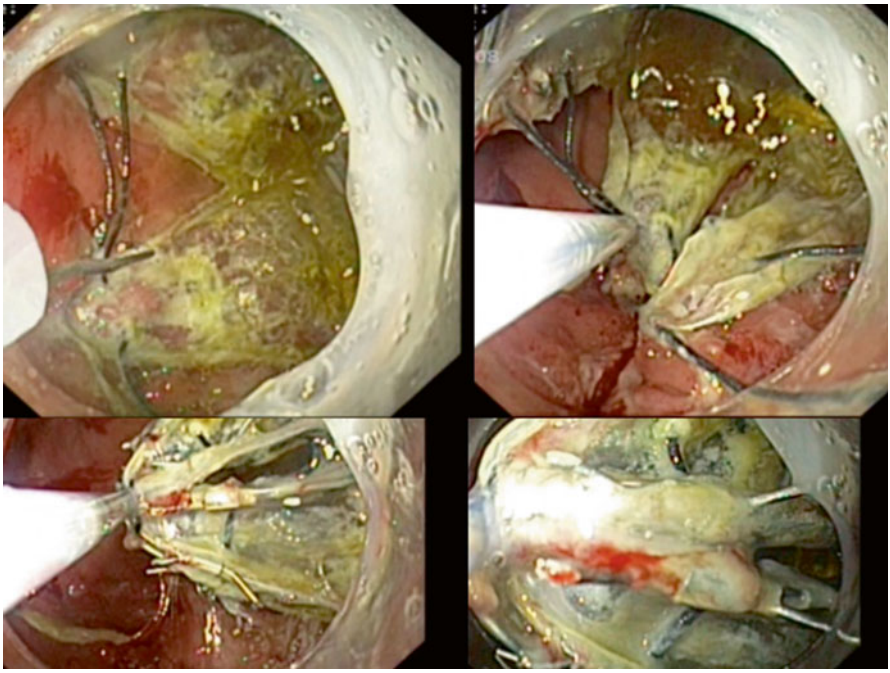

Fig. 18.8 Graph illustration on how the device compares with a biliopancreatic limb of a gastric bypass

- Retrieval at 1 year is accomplished by means of attaching a flexible hood on the endoscope tip and positioning it inside the duodenal bulb. Then, the anchor is collapsed by grabbing one of the proximal drawstrings using a custom grasper (Fig. 18.9)
- The collapsed anchor is then withdrawn into the protective hood, and the entire device withdrawn from the GI tract along with removal of the endoscope [4] (Fig. 18.10). A second-look confirms that there is no active bleeding or damage to the mucosa or perforation of the duodenal bulb, stomach, and esophagus

18.3 Results

The first case series on the use of this device was published by Rodriguez-Grunet L, Galvao Neto et al. in Chile. It included 12 patients, with successful implants in all cases, and a mean implant time of 26.6 min (range 20–51). Mean explant time was 43.3 min (range 17–182), successful in all cases. Premature removal was necessary in two patients, due to persistent abdominal pain, attributed to device misplacement. No major complications were reported, and EWL was 23.6 % after 12 weeks. Four patients were initially diabetic, and blood glucose levels were normal in three patients within a 24-h period, remaining for the study period [5]. Similar results were found in subsequent studies.

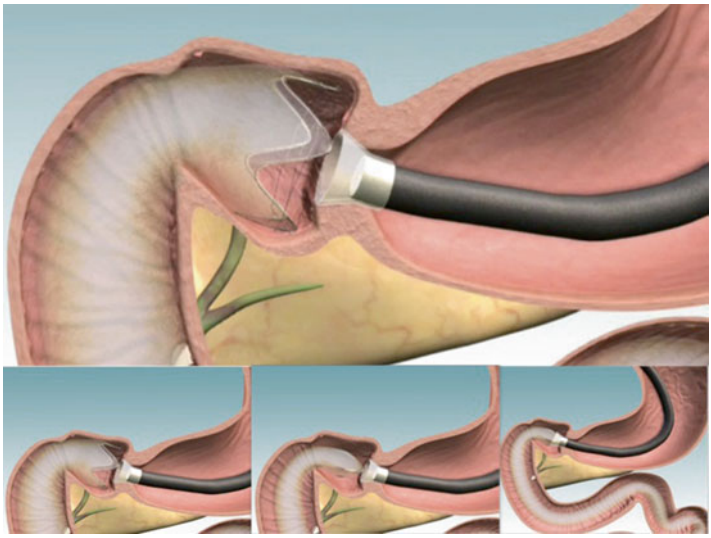

Fig. 18.9 Retrieval by means of attaching a flexible hood on the endoscope tip and positioning it inside the duodenal bulb. Then, the anchor is collapsed by grabbing one of the proximal drawstrings using a custom grasper

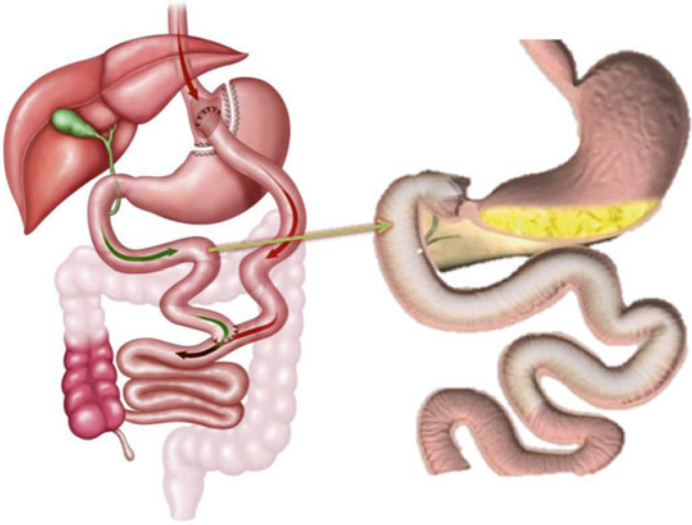

Fig. 18.10 Graph demonstration on how the collapsed anchor is withdrawn into the protective hood, and the entire device is removed from the GI tract along with the endoscope

Tarnoff M and Rodriguez L et al. also in Chile reported in their 12 week open-label prospective randomized controlled trial an excess weight loss (EWL) of 22.1 % and 5.3 %, respectively, for implanted participants and participants treated with a low-calorie diet [6]. Another randomized sham-controlled trial in US showed EWL of 11.9 % and 2.7 %, respectively, for the device group and the sham group. Eight of 21 subjects in the DJBS group had early explants, due to mild GI bleeding ($n=3$), abdominal pain ($n=2$), nausea and vomiting ($n=2$) and unrelated preexisting illness ($n=1$) [7].

The first study on Type 2 Diabetes was reported in a small but elegantly designed prospective randomized sham-controlled trial comparing Endobarrier™ against a sham endoscopy in a 24 week trial on morbid obese diabetic subjects [8]. In the completed population by week 1, change in fasting glucose in the DJBL arm was −55 ± 21 mg/dL versus +42 ± 30 mg/dL in the sham arm ($p \leq 0.05$; ±SE); the seven-point glucose profiles were reduced in the DJBL arm but not in the sham arm. Mean postprandial glucose area under the curve was reduced in the DJBL arm by 20 % and increased 17 % in the sham arm ($p=0.016$). At week 12, HbA(1c) change was −1.3 ± 0.9 % in the DJBL arm and −0.7 ± 0.4 % in the sham arm ($p>0.05$), and at 24 weeks, values were −2.4 ± 0.7 % in the DJBL arm and −0.8 ± 0.4 % in the sham arm ($p>0.05$).

In a modified and more durable version of the device, 22 morbidly obese diabetic subjects had an Endobarrier™ implanted in Brazil, 13 of those completed the 52-week study, and mean duration of implant period for all subjects was 42 weeks. Statistically significant reductions in fasting blood glucose, fasting insulin, and HbA1c were observed. Reductions in FPG were seen as early as week 1 and reached statistical significance at week 24. Mean HbA1c was statistically significantly decreased at week 24, and remained significantly decreased thereafter. At the end of the study, 16 of the 22 subjects had an HbA1c < 7 %, compared with only one of 22 at baseline [9].

Metabolic improvements were evaluated in 39 patients, after DJBS implant. The 52-week follow-up was completed by 64 % of subjects. Statistically significant reductions were seen in waist circumference, systolic and diastolic blood pressure, cholesterol, triglycerides and fasting glucose. The prevalence of metabolic syndrome was reduced from 83.3 to 41.6 %, and %EWL was 47.0. Subjects regained a mean of 4.4 kg after 6 months following the removal of the DJBS without any kind of maintenance program. This represents a change of −17.7 kg from baseline to 18 months in subjects who completed the 52 weeks of implantation [10].

Progressing on Type 2 diabetes research Choen RV, Galvao Neto MP et al. published a series [11] on non-morbid obese diabetic patients with a mean BMI of 30.0 ± 3.6. FPG levels dropped from 207 ± 61 mg/dL at baseline to 139 ± 37 mg/dL at 1 week and remained low throughout the study. Mean body weight also declined, but the change in body weight was not significantly associated with change in FPG at 52 weeks. HbA1c declined from 8.7 ± 0.9 % at baseline to 7.5 ± 1.6 % at week 52. For adverse events, gastrointestinal disorders were reported by 13 subjects, and metabolic or nutritional disorders occurred in 14 subjects. All were mild and transient especially in the first 2 weeks.

18.4 Adverse events

Endobarrier™ has been proving to be a safe device and as any implantable device, adverse events such as nausea, vomiting and abdominal pain are present and more often occur on the first weeks. Infection, bleeding, obstruction of the prosthesis, anchoring migration and possibility of perforation are less common complications rated around 5 %. Some of the devices had a surgical removal due to different reasons including team experience, acute bleeding and difficulties at removal. Factors implicated in premature removal are: abdominal pain, bleeding, anchor dislocation, sleeve migration, and rarely intestinal obstruction. No mortality was reported.

18.5 Final Comments and Conclusion

Endolumenal Bariatric Surgery is a promising field on less invasive techniques, and the Endobarrier device is safe and effective for T2DM in a short-term follow-up. Furthermore, when compared with the clinical treatment (diet), the device promotes a greater weight loss, reaching between the loss of 30–40 % of the excess. In two trials published on the use of Endobarrier for T2DM, there was no influence in weight loss on glucose homeostasis amelioration. This, therefore, brought up the possible role of the Endobarrier in treating type 2 diabetes mellitus independently of weight loss [5].

Besides the favorable short-term results, there is still a lack of knowledge concerning the mechanisms of weight loss and better assessment for the future clinical applications of this novel technique. This new procedure seems to be promising as it helps patients regain metabolic control of type 2 diabetes and aids in weight loss.

References

1. Kethu SR, Banerjee S, Barth BA, et al. Endoluminal bariatric techniques. Gastrointest Endosc. 2012;76(1):1–7.
2. Patel SR, Hakim D, Mason J, et al. The duodenal-jejunal bypass sleeve (EndoBarrier Gastrointestinal Liner) for weight loss and treatment of type 2 diabetes. Surg Obes Relat Dis. 2013;9(3):482–4.
3. Rohde U, Hedback N, Gluud LL, et al. Effect of the EndoBarrier Gastrointestinal Liner on obesity and type 2 diabetes: protocol for systematic review and meta-analysis of clinical studies. BMJ Open. 2013;3(9):e003417.
4. Schouten R, Rijs CS, Bouvy ND, et al. A multicenter, randomized efficacy study of the EndoBarrier Gastrointestinal Liner for presurgical weight loss prior to bariatric surgery. Ann Surg. 2010;251(2):236–43.
5. Rodriguez-Grunert L, Galvao Neto MP, Alamo M, et al. First human experience with endoscopically delivered and retrieved duodenal-jejunal bypass sleeve. Surg Obes Relat Dis. 2008;4(1):55–9.

6. Tarnoff M, Rodriguez L, Escalona A, et al. Open label, prospective, randomized controlled trial of an endoscopic duodenal-jejunal bypass sleeve versus low calorie diet for pre-operative weight loss in bariatric surgery. Surg Endosc. 2009;23(3):650–6.
7. Gersin KS, Rothstein RI, Rosenthal RJ, et al. Open-label, sham-controlled trial of an endoscopic duodenojejunal bypass liner for preoperative weight loss in bariatric surgery candidates. Gastrointest Endosc. 2010;71(6):976–82.
8. Rodriguez L, Reyes E, Fagalde P, et al. Pilot clinical study of an endoscopic, removable duodenal-jejunal bypass liner for the treatment of type 2 diabetes. Diabetes Technol Ther. 2009;11(11):725–32.
9. de Moura EG, Martins BC, Lopes GS, et al. Metabolic improvements in obese type 2 diabetes subjects implanted for 1 year with an endoscopically deployed duodenal-jejunal bypass liner. Diabetes Technol Ther. 2012;14(2):183–9.
10. Escalona A, Pimentel F, Sharp A, et al. Weight loss and metabolic improvement in morbidly obese subjects implanted for 1 year with an endoscopic duodenal-jejunal bypass liner. Ann Surg. 2012;255(6):1080–5.
11. Cohen RV, Neto MG, Correa JL, et al. A pilot study of the duodenal-jejunal bypass liner in low body mass index type 2 diabetes. J Clin Endocrinol Metab. 2013;98(2):E279–82.

Intragastric Balloon

19

Nicole Pena Sahdala

Obesity is a serious, complex disease and both its treatment and management have remained a global medical challenge. It has been proven that obesity reduces the quality of life as well as life expectancy in patients and is associated with numerous comorbidities including but not limited too diabetes mellitus, obstructive sleep apnea, hypertension, lipid disorders, hepatic steatosis, ischemic heart disease, certain cancers amongst other illnesses.

Body Mass Index (BMI) is used to classify weight, with overweight BMI 25.0–29.9 kg/m^2, obesity as class I BMI 30–34.9 kg/m^2, obesity class II BMI 35–39.9 kg/m^2, and obesity class III BMI > 40 kg/m^2. Based on data obtained from the National Health and Nutrition Examination Survey 2007–2008, 68 % of adults over the age of 20 years in the USA are overweight or obese; 33.8 % are Class I or above. 14.3 % having Class II and 5.7 % have Class III obesity (1, 2). The World Health Organization projects that by 2015, approximately 2.3 billion adults will be overweight and >700 million will be obese (3).

To date surgical therapies has been the only effective sustained option to treat obesity, efficiently reducing not only body weight and weight related comorbidities in up to 80 % but also aiding in the maintenance of weight loss (4, 5).

The World Health Organization has recommended a decrease of 5–15 % of total body weight maintained throughout time to reduce the incidence of morbidities related to obesity (6–8). The National Institute of Health recommends lifestyle changes remain the first line of therapy for successful weight loss, these include healthy eating habits, increased physical activity with exercise, as well as psychotherapeutic support (9) possibly supplemented by medication as second line therapy (10, 11). Unfortunately multiple studies report that these noninvasive therapeutic

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approaches have limited sustainability for the vast majority (>90 %) of those attempting these lifestyle modifications, resulting in frustration at not losing the amount of weight desired and after a variable amount of time an increase back to their original weight.

So to those many patients who have failed these conservative therapeutic methods but who are not yet ready or may not even qualify for a more aggressive surgical approach, what can we offer them? Ideally a less invasive option, with a lower risk profile and reduced costs, we offer them an endoscopic option.

Endoluminal therapies have the potential to extend treatment options to those patients with multiple comorbidities, older age, and those who do not qualify for surgical interventions such as type I obesity (BMI 30–35 kg/m^2) or even overweight patients (BMI 25–29.9). They can also supply a possibly reversible treatment modality avoiding committing to permanent surgical modifications of the gastrointestinal (GI) tract; this can be particularly attractive to a certain patient population (12).

One of the endoluminal/endoscopic bariatric therapeutic options is space occupying devices, which take form of a temporarily placed prosthetic balloon. The intragastric balloon is one of the earliest devices placed endoscopic as a weight loss intervention and continues to date as the most common endoscopic bariatric procedure performed worldwide, because of this it is the most widely studied of the minimally invasive endoscopic therapies for obesity.

The effect is intake restriction by mechanical space occupying artifact; this enhances satiety and instigates weight loss (13). The intragastric balloons are placed perorally as an outpatient procedure, with endoscopic assistance both for insertion and removal.

So how do these intragastric balloons actually work? Conceptually, they function on a mechanical basis, although other mechanisms of action may include delayed gastric emptying, hormonal modulation, neuronal effects, and behavior modification (14). Other non-balloon space-occupying technologies being developed include polymer pills that expand and later degrade in the stomach thereby eliminating the need for endoscopic insertion and removal (15).

In 2011, an ASMBS Task Force determined that the primary goal of endoluminal/endoscopic bariatric therapies (EBT) was to induce enough weight loss to decrease obesity related metabolic comorbidities and improve quality of life. Endoluminal therapies, such as the intragastric balloon, have many potential applications as primary, early intervention/preemptive therapy, bridge therapy, adjunctive, or revisional bariatric procedures (16).

Although various novel endoscopic interventions and endoscopically placed devices have been described over the past decade, and several such transoral endoluminal procedures are currently under investigation in the USA, none of them have been formally approved for use in the USA (11). Until formally approved by appropriate regulatory authorities, their use remains limited to clinical trials (16).

19.1 History of the Intragastric Balloon

Nieben proposed in 1982 the use of a gastric balloon for control of obesity after having observed that a gastric bezoar (space occupying intragastric mass) had been well tolerated for a long period of time and produced significant weight loss (17). And so the first artificial space occupying intragastric balloon for weight loss was used.

Theoretically the intragastric balloon affects both stretch receptors and gastric capacity, increasing satiety while decreasing residual volume available for food; therefore, this could be considered a non-surgical restrictive weight loss procedure.

In the early 1980s, several intragastric air-filled pouches with filling volumes of 20–500 ml were proposed. Amongst them the Garren–Edwards balloon required 220 ml, the Ballobes intragastric balloon inflated to 475 ml of room air and the Taylor intragastric balloon was smooth silicone pear-shaped filled with 550 ml of saline, were among those tried. Being that the cylinder shape devices were air filled and light, no weight effect was produced onto the stomach walls.

In 1985, the first widely used intragastric balloon, the Garren–Edwards Gastric Bubble (GEGB), was approved for use in the USA, as an adjunctive modality to a multifaceted approach to obesity. The GEGB was a polyurethane cylindrical device with a self-sealing valve through which a removable air-insufflation catheter was inserted, filled to 220 ml (unclear as to why this volume was chosen) then left to float freely in the stomach and was removed endoscopically after being punctured with a forceps.

In the late 1980s, several sham-controlled studies were published showing that diet and behavior modification were equally as efficacious as the GEGB in producing weight loss (18–20). Additionally these initial intragastric balloons had an elevated complications rate from: gastric erosion, 26 %; gastric ulcer, 14 %; Mallory–Weiss tears, 11 %; complete deflations, migrations, and intestinal obstructions. So after an initial enraptured period, a critical phase followed due to the failure and/or high complication rate of the Garren–Edwards, Ballobes, Taylor and Wilson–Cook balloons (21–25). More than 25,000 GEGB were placed before its withdrawal from the market. In addition, several polyurethane balloons (kept in place by a nasogastric catheter taped to the nose) were tried, with similar results (43, 44). None of these renditions were widely used in clinical practice. Other balloons used in the 1980s are now obsolete and had little controlled data, including devices produced by Wilson-Cook (Winston Salem, NC), Tremco (Cleveland, OH), and Dow-Corning.

In 1987, 75 international experts met and participated in a workshop on "Obesity and the Gastric Balloon" decided against a recommendation for removal of existing gastric balloons from the market but urged that their use be discouraged outside of controlled investigational trials. They also formulated and defined fundamental requirements for optimal, effective and safe intragastric balloon design. Years of research resulted in the development of a balloon that fulfilled the specified requirements: (1)

the balloon should be smooth, seamless, and constructed of long-lasting material, with a low ulcerogenic and obstructive potential; (2) incorporation of a radiopaque marker to allow appropriate follow-up in case of deflation; and (3) the ability to adjust the balloon to a variety of sizes and to fill it with fluid instead of air (26).

Today intragastric balloons are no longer available in the USA; a few newer intragastric balloons are under investigation for FDA approval.

19.1.1 Types of Balloons

19.1.1.1 Bioenterics Intragastric Balloon/Orbera

The Silicone Intragastric Balloon (SIB) was developed by Fred C. Gau in conjunction with INAMED Development Company (IDC) in 1986. In January 1996, the SIB IDE was transferred from IDC to BioEnterics Corporation (BEC) and the SIB was renamed the BioEnterics Intragastric Balloon (BIB). The BioEnterics Intragastric Balloon (BioEnterics Corp., Carpinteria, Calif.) meets the 1987 requirements (40).

The currently used Orbera™ intragastric balloon (Allergan Inc., Irvine, CA, USA) is a spherical, large capacity silicone polymer device. The deflated balloon comes preloaded on a catheter, which is blindly passed transorally into the esophagus then an endoscope is passed along side it to ensure accurate placement of the balloon in the fundus. Under direct endoscopic visualization, the device is inflated through the external port of the catheter with 400–700 ml saline and 10 ml methylene blue dye solution. In case of balloon rupture the dye is systemically absorbed and imparts a characteristic blue color to urine alerting the patient to contact the physician for urgent endoscopic removal of the device. The balloon is currently deployed for a maximum duration of up to 6 months, after this time there is a higher risk of spontaneous balloon deflation. When required the device can be safely deflated and extracted endoscopically using a snare or basket.

Other available IGBs include the Heliosphere (IHB) (Helioscopie, Vienne, France), Silimed (Silimed, Rio de Janeiro, Brazil), and Semi-stationary Antral Balloon (JP Industria Farmaceutica, Ribeirao Preto, Brazil).

19.1.1.2 Heliosphere

The placement of the Intragastric Heliosphere Bag (Helioscopie, Vienne, France) an intragastric device insufflated with air instead of fluid, introduced in 2004. The balloon is slowly inflated with 840–960 cm^3 of air, which gives the inflated final volume of 650–700 cm^3, as the air is compressed (27). Data regarding the efficacy and safety of IHB are limited.

19.1.1.3 Silimed

The Silimed Gastric Balloon (Silimed Silicone Instrumental Medical-Surgical Hospital Ltd., Rio de Janeiro, Brazil) is consists of a smooth and transparent silicone shell that acquires a round format when filled with saline solution, it is

supplied empty delicately rolled up inside a thin silicone sheath. During placement, the extremity of SGB's sheath, not of the shell, is carefully anchored to the endoscope extremity using a polypectomy snare then it is smoothly inserted into the stomach by traction under direct visual examination. When the device is near the pyloru it is released by the polypectomy snare and positioned in the gastric fundus by "J" maneuver, followed by SGB traction by the introduction catheter. After adequate placement in the gastric fundus and under continuous direct endoscopic visualization the SGB is filled with saline solution through a tube with a polytetrafluorethylene needle at its extremity, which is connected to a self-sealing valve attached to the device shell. The volumes of saline solution (mean of 632 ml), Iopamiron® contrast (20 ml), and 2 % methylene blue (10 ml) were fixed with the approximate final proportion of 65:2:1 (28).

The SGB removal procedure consists of first positioning a lubricated double silicon overtube in the patient's esophagus. Then under direct endoscopic observation, a hole is made into each SGB by a specially developed catheter containing a needle (Scorpion) to empty via the catheter the balloon. Then the emptied SGB is captured by a polypectomy snare and pulled until part of the SGB was held in the overtube. For the very flat balloons a double-hook endoscopic forceps can be used to bring the balloon partially inside the esophagus, the grasping it with the polypectomy snare, allowing the simultaneous removal of the balloon along with the whole endoscopic apparatus. Both the procedures are performed under usual sedation of diagnostic endoscopy (28).

Silimed Gastric Balloon has a radiopaque mark around the valve, using Iopamiron® in the filling solution of the device contributes to obtain more clearly defined images of the balloon to verify the correct placement, whenever necessary (28).

19.1.1.4 Reshape

From ReShape Medical (San Clemente, CA), the previously known ReShape Intragastric Balloon, now newly branded as the ReShape Duo is a unique dual-balloon filled with an evenly distributed 900 ml of saline. The proximal balloon sits high in the fundus, possibly contribute to increased satiety, the design conforms easily to the curvature of the stomach for stability and provides significant protection. The dual balloon design potentially reduces the undesirable risks of migration, obstruction, and perforation. In the case that one of the balloons deflates, because it is a dual-balloon device, the second balloon will maintain the ReShape Duo within the stomach, preventing migration and possible bowel obstruction. This enables the patient enough time to return to the physician for safe device removal (29).

The ReShape Duo is endoscopically delivered over a standard guidewire and automatically inflated with 900 ml sterile saline solution with a power pump delivering 450 ml to each balloon. The device is removed endoscopically after a controlled and rapid fluid evacuation with the ReShape Removal Catheter (29).

19.1.1.5 Obalon

The most recent addition to the intragastric balloon devices, commercially launched on a limited basis in Europe beginning in July 2012, is a novel swallowable gelatin capsule which dissolves inside the GI tract, that contains the balloon folded inside, attached to a miniature catheter via which the balloon is rapidly inflated and afterwards the catheter is easily removed without need of endoscopic assistance or sedation. The Obalon is a 250 ml gas filled balloon which resides in the fundus. The high buoyancy of the device allows it to occupy an area high in the gastric space perhaps allowing lower balloon volume to stimulate weight loss Additional balloons, up to three in total, can be swallowed and inflated to increase total resident volume throughout a 3-month treatment period to further stimulate weight loss. The swallowing and inflation of the balloons averaged 5 min. Balloons were removed via endoscopy using standard tools under light, conscious sedation and averaged 10 min. Minimal symptoms are reported, the ability to gradually add balloon volume appears to improve treatment and tolerability.

At the end of the 3 months, during a short endoscopy utilizing common standard tools, all balloons are removed. Safety and efficacy data were collected and reported on the first commercial product uses at 11 centers throughout Belgium, Germany, Italy, and Spain (30).

19.1.1.6 Adjustable Intragastric Balloon

The advantages of an adjustable balloon to provide improved patient comfort and hence offer greater efficacy are being investigated. The Spatz Adjustable Balloon system (ABS) has a migration prevention function to ideally enable safe prolonged implantation. Longer implantation duration could improve efficacy and weight maintenance post-extraction.

19.1.1.7 Mechanism of Action

Placement of an intragastric balloon results in a complex interplay of neurohormonal factors and changes in gastric motility, in addition to the obvious space-occupying effect. Several studies based on animal and human data, have shown that an effect on satiety and subsequent caloric intake is only seen after distention of the intragastric balloons to at least 400 ml (39).

A study done by Bonazzi et al. aimed to analyze the influence of an intragastric balloon on gastric emptying in obese patients. Twelve patients were included in the study, with BMI mean 38.51 SD ± 4.32 kg/m^2. The intragastric balloons inserted were BIB under light anesthesia, utilizing direct visualization via endoscopy they were inflated with 700 ml of saline and removed 6 months later.

The measurements obtained besides body weight for gastric emptying were T1/2 and Tlag using 13C-octanoic acid breath test. These were documented prior to balloon placement, during its permanence and 2 months after removal. Gastric emptying rates were significantly decreased in the first periods while the balloon was in the stomach, and these values returned to pre-implantation values after the IGB was removed. T1/2 was: 87 ± 32 min before BIB positioning, 181 ± 91 min after 1 month, 145 ± 99 min after 3 months, 104 ± 50 min after 6 months and 90 ± 43 min 2 months

after removal. T lag was 36 ± 18 min before BIB positioning, 102 ± 82 min after 1 month, 77 ± 53 min after 3 months, 59 ± 28 min after 6 months and 40 ± 21 min. Two months after removal (31).

So it appears that intragastric balloons in obese patients seem to aide patients in following the hypo caloric diet, especially during the first 3 months when the gastric emptying is slower and the sense of repletion is higher. Unfortunately after this period, the gastric emptying starts to return to normal maybe signaling that the stomach is adapting to intragastric balloon.

Ghrelin is an important gut hormone; a study led by Martinez-Brocca measured the effect of a BioEnteric Intragastric Balloon on the level of this hormone in morbidly obese patients who were considered treatment-resistant. Twenty-one participated in this randomized, double blind, sham controlled 4 month trial. Monthly anthropometric and biochemical parameters, estimation of energy intake, and preprandial and postprandial evaluation of satiety were required. Ghrelin response after a standard mixed meal was measured prior to BIB placement and 4 weeks after the endoscopic procedure (32).

There was no significant difference in weight loss between the Group Balloon and Group Sham at any time-point of the follow-up. Patients from Group Balloon did show a temporary increased preprandial and postprandial satiety, this was noted to have been maximal at 4 weeks after the intervention. Total area under the curve, fasting and postprandial plasma ghrelin were not significantly different between groups at inclusion or 4 weeks after follow-up. Therefore no correlation was found between any of the satiety scores at any time-point with their comparable ghrelin levels. From this study we can conclude though that BIB induces a temporary sense of satiety in morbidly obese patients, this is not mediated by modification of fasting or postprandial levels of plasma ghrelin (32).

Cholecystokinin (CCK), an important regulatory hormone involved in satiety, is produced in the duodenum and is stimulated by both the presence of digestion products in the stomach, mainly fats and proteins, and also by gastric distention/stretching. It acts not only on pancreatic enzyme secretion, gallbladder contraction, and increased gastric vagal afferent activity, CCK in addition delays gastric emptying and causes pyloric constriction. It has been shown that infusion of CCK, in combination with gastric distention, significantly reduces food intake in humans, and this effect is thought to be due to a CCK-mediated delay in gastric emptying. Knowing the effects of this regulatory hormone, we can imply it plays an important role in the physiologic effect of intragastric balloon placement (33, 34).

Short-term satiety is principally affected by gastric distention and gastric volume. In both animals and humans, short-term food intake is affected by the weight and volume of food more than its energy content or caloric value (35–37). Rolls et al. (38) showed that by infusing high-volume, low-calorie gastric feedings there was subsequently a decrease in caloric intake of a buffet meal, this was compared to similar degree with a high-volume, high-calorie gastric feeding. This volume regulated satiety is thought to result primarily from gastric distention. Mechanical gastric balloon distention to a volume greater than 400 cm^3 during meals significantly reduces oral intake, and even lesser volumes may have an effect in achieving satiety (39).

Results

In 2011, ASMBS joint Task force determined that the most commonly used endpoint in bariatric studies was percentage excess weight loss (%EWL). "Excess weight" being the difference between the patient's weight and the average weight of a standard individual with body mass index (BMI) of 25 kg/m^2. The weight loss achieved after bariatric intervention is calculated as a percentage of pre-intervention excess weight, this is the %EWL (16).

BIB

Of all the available intragastric balloons, the BioEnteric Intragastric Balloon has been the most widely used since 1995 in well over 20 countries worldwide, particularly in Europe, South America, and Asia (35). Probably because of this widespread use it has the highest number of publications than any other intragastric device. The indications for BIB use may be summarized as the following: (1) preoperatory weight loss in a patient candidate to bariatric surgery with high anesthesiological risk, (2) temporary weight loss treatment in a patient with body mass index (BMI) in the range of bariatric surgery (>35) who refuse surgery or has possible low compliance to surgery or in case of very long waiting list, and (3) temporary weight loss treatment for a patient with no indications to surgery in the context of an integrate medical approach to obesity (BMI < 35).

To be able to clearly advise a patient on weather or not an intragastric balloon will be helpful in their situation, we must first evaluate all the possibilities. Are intragastric balloons better than lifestyle modifications of diet and exercise alone for weight loss?

A study by Genco et al. (41) compared in a retrospective manner 130 patients with BIB placement with a 130 patients who underwent structured diet therapy with simple behavioral modifications for 6 months. A caloric restricted diet of 1000–1200 cal/day using an approximate macronutrient distribution, comparable to the "Mediterranean diet," including 25 % protein (at least 60 g/day), 20–25 % lipids, and 50–55 % carbohydrates. In the BIB group, patients received just generic counseling for eating behavior. In both groups considered weight loss parameters (kilograms, percentage of excess weight loss [%EWL], body mass index [BMI], percentage of excess BMI loss [%EBL]) at 6 and 24 months from baseline and comorbidities at baseline and after 24 months.

At 6 months time, BIB was removed significantly better results in terms of weight loss in kilograms 16.7 ± 4.7 vs. 6.6 ± 2.6; $p < 0.01$, BMI 35.4 ± 11.2 vs. 38.9 ± 12.1; $p < 0.01$, %EBL 38.5 ± 16.1 vs. 18.6 ± 14.3; $p < 0.01$, and %EWL 33.9 ± 18 vs. 24.3 ± 17.0; $p < 0.01$ were documented in patients treated by intragastric balloon as compared to diet-treated patients. All these parameter findings were statistically significant.

At 24 months from baseline, patients treated with intragastric balloon have tended to regain weight, whereas diet-treated patients have already regained most of lost weight. But we can state that in the short-to-medium term, BIB is significantly superior to diet in terms of weight loss.

The BIB has been compared with surgical treatment, specifically the sleeve gastrectomy, in two nonrandomized studies. At 6 months, one study showed no difference in mean weight loss, although the surgical procedure was shown to be superior at the 12-month follow-up (42). The second study of superobese patients (BMI > 50) found that sleeve gastrectomy patients lost significantly more weight at 6 months (45.5 kg vs 22.3 kg) as compared to the intragastric balloon (43).

So we now have the data to prove that intragastric balloons are not comparable to a surgical intervention for weight loss, but are statistically better at promoting weight loss when compared to diet and exercise alone.

In the largest reported retrospective study using intragastric balloon, 2515 patients were analyzed (44). The aim of the study was the evaluation of the efficacy of the BIB in a large population, specifically in terms of weight loss and its influence on comorbidities. Data were retrospectively recruited from May 2000 to September 2004, 2515 patients from the database of the Italian Collaborative Study Group for Lap-Band and BIB (GILB). Patients were discharged with diet counseling (~1000 kcal) and medical therapy for the post procedure symptoms. The BIB was removed after 6 months. Endoscopic positioning and removal were both performed under conscious or unconscious sedation. Technical success was achieved in 99 % of cases, and the authors reported five cases of gastric perforation (0.19 %), of which two were fatal, it was noted that previous gastric surgery is a contraindication to BIB placement.

Preoperative comorbidities were diagnosed 56.4 % of patients, 44.3 % of these comorbidities resolved, 44.8 % improved requiring less pharmacological dosage or shift to other therapies, and 10.9 % were unchanged. After 6 months %EWL was 33.9 ± 18.7 and BMI loss was 4.9 ± 12.7 kg/m^2, this along with the concomitant improvement in hypertension and diabetes values achieved significant correction in blood pressure and glycemic control.

In Brazil, Sallet et al. (45) conducted a study from November 2000 to February 2004, where 483 overweight and obese patients were treated with the BIB®. Of these 483 patients only 323 completed a 6-month follow-up, and 85 of them completed a 1-year follow-up. A multidisciplinary program involving clinical, psychiatric, physical training, and dietary approaches was part of the required guidelines for every patient.

At the 6-month follow-up subjects measurements were compared to their baseline values, and statistically significant reductions were observed in weight (15.2 ± 10.5 kg), percent excess weight loss (48.3 ± 28.1), and BMI (-5.3 ± 3.4 kg/m^2) ($p < 0.000$). There results are similar to other studies of the BioEnteric Intragastric Balloon (40). At the 1-year follow-up, 85 patients had maintained more than 90 % of their BMI reduction.

In a meta-analysis done by Imaz et al. (46) a Methods Systematic literature review of Medline, Embase, and other information sources from inception to March 2006 was done to perform the evidence-based systematic review of the published literature, afterwards the quality of the selected studies was assessed, 15 articles were pooled (3608 patients). Meta-analysis of weighted mean difference was made using the inverse variance method.

The estimates for weight lost at balloon removal for BIB® were the following: 14.7 kg, 12.2 % of initial total body weight, 5.7 kg/m^2 in BMI, and 32.1 % of excess weight. Efficacy at balloon removal was estimated with a meta-analysis of two randomized controlled trials (75 patients) that compared intragastric balloon versus placebo, the results indicated the balloon group lost more weight than the placebo group. These differences in weight lost were 6.7 kg, 1.5 % of initial weight, 3.2 kg/m^2, and 17.6 % of excess weight.

This meta-analysis did make note of the scant data available after balloon removal.

So what happens to these post BIB patients 6 months or a year after the balloon is removed? Is this short time period sufficient to change patients' lifestyle, modify their eating habits and exercise practices to maintain the weight reduction achieved with the BIB after its removal?

In a study published in 2005, Herve et al. (47) tried to answer just that. Hundred patients who received a BIB were included in a prospective study and followed for 1 year after BIB removal. The patients assisted to monthly post-implantation follow-up visits during which they were seen by the surgeon, dietitian, and if necessary, the psychologist.

The results upon BIB® removal were mean weight loss for the group of 12.0 kg. Mean percent excess weight loss (%EWL) was 39.8 %. A year after removal of the BIB® the documented mean weight loss was 8.6 kg and mean %EWL was 26.8 % for the group as a whole.

The results 1 year after removal of the BIB were found to be encouraging, specially considering it is a temporary non-surgical and non-pharmaceutical treatment for obesity that is totally reversible and repeatable. The authors recommend it for patients who have previously failed traditional methods of weight reduction. They do note that careful patient follow-up is of primary importance in avoiding complications and supporting efficacy of the treatment because concurrent behavior modification is essential for durable weight loss.

A second 1 year post BIB a randomized, double-blind trial of balloon or sham treatment of 3 months' duration consisting of 43 patients. A preset weight-loss goal was set and if the patients (sham- and balloon-treated groups) achieved this weight they were given an additional 9 months of balloon treatment. The patients were continued to be followed for a second year post balloon (48).

The mean body mass index at enrollment was 43.3 kg/m^2 were enrolled. Five patients did not meet the preset weight-loss goal and were considered nonresponders 11.6 %. Three patients were unable to tolerate the balloon 7.0 %, at the time of the endoscopy severe esophagitis was diagnosed.

In the intention-to-treat analysis, sham- and balloon-treated groups had overall weight loss of 20 kg (16.1 %) and 16.7 kg (13.4 %) after 6 months in the sham/balloon and in the balloon/balloon treated groups which was not shown to be statistically significant. After 1-year of balloon treatment, a mean weight loss of 21.3 kg (17.1 %) was achieved in all patients, 12.6 kg (9.9 %) was maintained at the end of the second balloon-free year. Forty-seven percent of patients sustained a greater than 10 % weight loss, with considerably reduced comorbidity. In those 33 patients

who completed the study per protocol, the weight loss at 1 year was of 25.6 kg (EBW 20.5 %) and 14.6 kg (EBW 11.4 %) after 2 years; 55 % maintained a weight loss of greater than 10 %.

In this study the conclusion was that for patients with treatment-resistant obesity, the intragastric balloon appeared to be safe, an independent benefit of balloon treatment beyond diet, exercise, and behavioral therapy with balloon treatment for 1 year resulted in substantial weight loss, the greater part of which was maintained during the balloon-free second year.

More recently, Angrisani et al. [49] observed the almost total regain of excess weight 1 year after BIB removal in 82 patients who had refused any other kind of treatment—surgical, pharmacological, or dietetic. On the other hand, Sallet et al. [45] observed 90 % weight loss maintenance in a subset of 85 (from the total of 323) patients at 1-year follow-up. Weight loss was noted to be significantly higher in BIB-treated patients both at 6 and 18 months follow-up. Additionally, the dropout rate was significantly lower in BIB-treated patients (1 % vs. 18 %, $p<0.001$).

Seeing that the data is unclear at 1 year post BIB removal and stabilization of weight is uncertain, Kotzampassi et al. (50) published a study on 500 enrolled patients, who were followed post 6 months of BIB® induced weight reduction for up to 5 years. All patients were contacted for follow-up at 6, 12, and 24 months post-removal and then yearly thereafter. Twenty-sex patients had to be excluded because of treatment protocol interruption, thus remaining 474, of these at the time of BIB® removal 79 were excluded because of %EWL less than 20 %; thus remaining 395 patients had weight loss of 23.91 ± 9.08 kg, BMI reduction of 8.34 ± 3.14 kg/m^2, and percent EWL of 42.34 ± 19.07. At 6 months and 12 months, 387 (98 %) and 352 (89 %) presented with percent EWL of 42.73 ± 18.87 and 27.71 ± 13.40, respectively. At 12 and 24 months, 187 (53 %) and 96 (27 %) of 352 continued to have percent EWL of >20. Finally, 195 of 474 completed the 60-month follow-up 23 % retained the percent EWL at >20. It was observed that those who in general lost 80 % of the total weight during the first 3 months of treatment succeeded in maintaining a percent EWL of >20 long term after. Speaking in percentages of EWL > 20, we can state from this publication that from the total of 500 obese subjects, EWL > 20 % was achieved in 83 % at the time of removal, in 53 % at the time of the 12-month follow-up, in 27 % at the time of the 24-month follow-up, and in 23 % at the time of the 60-month follow-up.

In search of improving the weight loss outcomes of the patients undergoing BIB® placement, various studies have introduced the notion of sequential IGB placements.

In 2010, a study by Dumonceau et al. (51) aimed at assessing the potential benefits of repeating IGB therapy, with a prospective non-randomized multicenter trial. Hundred and eighteen consecutive patients with a BMI 34 kg/m^2 were included. Nineteen patients (16 %) underwent repeat IGB placement as requested by them, 8 to prolong the first treatment and 11 after a IGB free trial.

Higher weight loss 3 months after first IB insertion independently predicted repeat therapy ($p=0.008$). Median weight loss in subjects who had repeat therapy was lower with second vs. first IGB 9.0 kg vs. 14.6 kg; 30.4 % vs. 49.3 % excess

weight loss; this achieved statistical significance $p=0.003$. Compared to subjects with single treatment, those with repeat treatment had greater weight loss at first IGB extraction 14.6 kg vs. 11.0 kg; 49.3 % vs 30.7 % EWL and 1 year later 12.0 kg vs 6.0 kg but the difference became less than 2 kg starting at 3 years.

At final follow-up at 4.9 years approximately, the whole subject population had lost a median of 2.0 kg or 6.2 % EW and identical proportions of subjects with single/repeat treatment had ≥10 % baseline weight loss (26 %) or bariatric surgery (32 %) which was delayed in subjects with repeat vs those with single IB therapy.

In Spain, Lopez-Nava et al. [52] evaluated a population of 714 consecutively placed BIB® which were removed after 6 months, between June 1, 2005 and May 31, 2007. These patients were discharged post BIB® with drug therapy and 1000 kcal diet. Of the initial patient population 112 patients underwent a second consecutive balloon positioning, a month after the removal of the first BIB during which they received medical therapy, the second BIB® was also removed at 6 months. Consequently patients were followed up in a weekly basis. After 6 months of BIB mean %EWL was 41.6 ± 21.8, mean BMI loss was 6.5 ± 12.7. After the second balloon removal, mean BMI was 30.3 ± 7.2, mean %EWL was 31.5 ± 23.2; mean BMI loss was 2.5 ± 18.2. After 24 months of follow-up, 22 (%) patients regained the pre-BIB weight, 61 (%) regained the 45–50 % of their pre-BIB weight, and 45 remain at the weight level after BIB removal ±2 kg. Considering the current experience, the support for this sequential approach should be in patients who require a continuous weight loss, even if not significant, to avoid the patients regain weight while waiting for definitive bariatric surgery.

The consideration in obtaining satisfactory basic results in terms of resolution of comorbidities is relevant, taking into account that the risk of death from cardiovascular disease, cancer, diabetes and other diseases increases throughout the range of moderate and severe overweight to obesity.

In this Spanish series (52), the improvement or resolution of preoperative comorbidities was obtained in 140/162 (86.4 %) patients. Many prior studies have confirmed the importance of these results demonstrating the benefit of 10 kg weight loss in terms of comorbidities (diabetes, blood pressure, lipids, etc.) and the related mortality (53–55).

The conclusion of these authors is that a second balloon can be positioned without difficulties, achieving good results after 12 months of treatment (52).

Both prior studies have shown that although patients who underwent a second balloon insertion had greater initial weight loss, there was no statistically significant difference in %EWL at 3-year follow-up [51, 52]. Furthermore, the placement of a second balloon was linked with a trend towards greater procedure- and device-related complications (52).

A prospective study by Forlano et al. [56] analyzed the metabolic benefits of intragastric balloon placement in 130 patients with mean BMI of 43.1 kg/m^2 who were maintained on a 1000–1200-kcal diet for 6 months after balloon placement. Hepatic steatosis was followed by ultrasound, and the frequency of sonographically detected advanced hepatic steatosis declined from 52 % at baseline to 4 % at the end of the 6 months. Comparable improvements were noted a well in blood glucose and

triglyceride levels, these corrections indicators of medical disease highlights the multifaceted role of intragastric balloon in patients with "metabolic syndrome."

A prospective study from November 2003 to April 2006 in the high risk superobese population examining the role of IGB as a bridge therapy prior to bariatric surgery (57). The BioEnterics intragastric balloon (BIB) was endoscopically placed in 26 high risk superobese patients preoperatively to induce weight loss to reduce the risk of surgery associated with morbid obesity. These patients had a mean body mass index of 65.3 ± 9.8 kg/m^2 and severe comorbidities. After 6 months the BIB® was endoscopically removed. The mean weight loss was 28.5 ± 19.6 kg, and clinical reevaluation revealed significant improvement in patient comorbidity status permitting bariatric surgery and reducing the perioperative morbidity and mortality rates associated with the superobese during bariatric surgical procedures. Post BIB® 20 patients underwent a primary bariatric surgical procedure the day after BIB removal; 2 patients were rejected for surgery because of inadequate weight loss. This study proves that BIB placement can be considered an effective first-stage treatment of high-risk superobese patients in need of surgical intervention.

These same findings were also corroborated by Zerrweck et al. (58) with a case control study between 2004 and 2009, where the records of 60 consecutive super-superobese patients (BMI 66.6 ± 3.4 kg/m^2), 23 cases with preoperative BIB® and 37 controls with no Balloon. The end point of significant adverse events was defined as the presence of at least one of the following conditions: conversion to open laparotomy, intensive care unit stay for more than 2 days, and overall hospital stay superior to 2 weeks. In the 23 cases IGB group, the intragastric balloon was maintained during 155 ± 62 days and induced a loss of 5.5 ± 1.3 kg/m^2. This weight loss manifested with clinical changes documented at the time of LGBP, and was associated with a decrease in systolic blood pressure and gamma-glutamyl transpeptidase level ($p < 0.05$ vs. baseline). Operative time was lower in the IGB group 146 ± 47 min vs. 201 ± 81 min in controls; $p < 0.01$ achieving statistical significance. Significant adverse events were also found to occur less frequently after LGBP in the BIB® group (2 vs. 13 in controls; $p < 0.05$).

We can now state that evidence favors that in super-superobese patients a pre surgical intragastric balloon should be considered, since this has been shown to reduce excess BMI which is associated with improved clinical measurements prior to bariatric surgery and overall decrease risk of significant adverse surgical outcomes.

Since BIB® affects patients with very elevated BMI in a positive way, what evidence exists that patients with lower BMIs can benefit from this intragastric device. A study published in 2012 (59) evaluated the effect of an intragastric balloon in patients with different BMI as part of the treatment for their obesity and overweight status. Two-hundred and fifty-one obese patients treated with liquid-filled BIB® in a center between 2005 and 2010, of these only 220 obese patients had balloons which were removed after 180 days. Data at the day of insertion, at the day of removal and at sixth month of the removal were collected and compared, according to the patient's BMI indexes.

The total weight losses, EWL%, and EBMIL% according to BMI index groups were significantly decreased at removal compared to the beginning ($p < 0.01$). This

significance is more prominent for patients with BMI 27–35 kg/m^2. In the BMI group <35 kg/m^2 the statistical work shows that the percent of loss of extra weight in this group is remarkable, as well as the fact that there is less weight regain and that the weight loss is greater at a the end of the year when compared to the groups of patients with BMI > 35 kg/m^2. The results in this study reiterate the findings of Mui et al. [60] where BIB® has excellent result in lower BMI patients where the percentage of excess body weight loss in BMI < 30 group is 87 % in contrast to 27.4 % in BMI > 40 group. Both these publications suggest that BIB® can be used alone for patients with BMI < 35 kg/m^2 to overcome obesity as a successful single stage procedure. Herve et al. (47) also documented of the 15 patients in his study that reached a BMI < 25 kg/m^2 (normal weight) all of these patients had a BMI < 35 before implantation BIB®.

In contrast those patients with BMI > 35 kg/m^2 were found to be less successful in terms of weight loss than the patients with lower BMIs, possibly inferring that combined therapy with another bariatric measure such as surgery may help to achieve the desired sustainable weight loss (59, 60).

Multidisciplinary Team

It is clear from the evidence presented until this point that the use of an intragastric balloon must be integrated into a weight-care program, and this should be continued after balloon removal to maintain the weight reduction. BIB® seems to be effective for significant weight loss and maintenance for a long period thereafter, under the absolute prerequisite of patient compliance and behavior change from the very early stages of treatment (50).

Mazure et al. (61) described the results of enhancing the importance of a Multidisciplinary Team (MT) taking part in the treatment of a BIB® patient.

Retrospectively 119 BIB®'s were reviewed from May 2001 until August 2006. Recommendation for follow-up with a MT in a physical unit, at least every 15 days during 6 months were given to 49 patients; 67 subjects followed by other medical professional without MT assistance. Concerning MT followed patients, an average decrease of weight excess was 31, 85 % (–4, 45–80, 4 %), and the BMI diminished 5.3 points. Treatment failure was documented in 34.6 % of the MT patients as compared with 53 % in the other treatment group. Physical exercise was markedly enhanced in the MT group as compared with patients who did not follow the program. The result of maintenance was obtained in 40 % of patients 1 year later. So even though BIB® can be an effective method to achieve a short term weight loss goal in obese patients, to achieve adequate, long lasting results depends on the modification of lifestyle obtained and fortified by a multidisciplinary approach (61).

Complications

Complications of IGBs reported in a large case series and a meta-analysis include esophagitis (1.27 %), gastric perforation (0.19–0.21 %) higher incidence post gastric surgery, gastric outlet obstruction (0.76 %), gastric ulcer (0.2 %), balloon rupture (0.36 %), and death (0.07 %). Overall complication rate was of 2.85 %.

BIB® is relatively safe, the majority of complications reported were mild and the early removal rate was 4.2 % (44, 46, 62).

Other reported complications of the BIB® include esophageal perforation (63), small-bowel obstruction requiring surgery (64–66), and two reports of cardiac arrest after BIB placement, one case which was thought to be secondary to vagal nerve activation caused by stretching of the gastric wall (67) and a second patient classified as superobese died of cardiac arrest after aspiration on the first post-insertion day as a direct result of BIB placement, 3.8 % incidence in this study (57).

Currently common postprocedure complications include nausea, vomiting, heartburn, and abdominal cramping, which rarely necessitate device removal.

In a large cohort from Brazil (45) the main side-effects were nausea/vomiting (40 %), and epigastric pain (20 %), requiring removal of the BIB® in 3.4 % of the patients (45).

To diminish complications during the removal of the BIB® a clear-fluid diet should be started 2 to 3-days prior, in order to minimize the risk of residual food tracheal aspiration. Deep intravenous anesthesia without tracheal intubation has been used although experts recommend tracheal intubation during the removal endoscopy, placing the patient in a left lateral decubitus position. A double-channel endoscope and two long-jaw rat-tooth forceps may help facilitated the extraction procedure (50).

Complications after a second BIB placement tended to be more frequent compared to the deployment of the first device. These complications consist of esophagitis and digestive intolerance that was treated by early IB extraction (50). In a second group of patients with sequential BIB® placement gastroduodenal ulcer, gastric perforation, gastric and intestinal obstructions, and balloon rupture were absent.

Partial balloon deflation was observed in 0.4 % of cases, esophagitis in 0.9 %, and acute mucosal gastroduodenal lesions in 3.1 % (52).

Improving Comorbidities

In a large study of 714 patients one or more preoperative comorbidities were diagnosed in 22.7 % patients: hypertension 13.6 %, type II diabetes 9.8 %, respiratory disorders 19.1 %, osteoarthropathy 8.6 %, and others 46.9 %. Comorbidities were resolved in 39.5 % and improved (lower pharmacological dosage or shift to other therapy) in 46.9 % (52).

Role of BIB® in Specific Cases: The Benefits

The data regarding the multiple benefits obtained from the BIB® has not been limited to weight loss investigations. In a case report published in the Annals of Thoracic Surgery a 68 year old male with a BMI > 50 kg/m^2 was treated prior to a triple bypass with a BIB® placement for weight loss. The patient lost 40 kg during the 6 months and his BMI decreased to 38, allowing for a successful coronary artery bypass graft surgery, with an unremarkable postoperative recovery and discharge (68). Lorenzo et al. (69) explored the effects of early myocardial pattern changes in 15 patients who underwent BIB® placement in patients with BMI between 40 and 50 kg/m^2 who had diagnosed cardiac hypertrophy and hypertension. Echocardiography and cardiac

Doppler examinations were performed preBIB® and post removal. The results after IGB was decrease in BMI to 34.2 ± 4.9 kg/m^2, both mean systolic and diastolic blood pressures improved, as well as did left ventricular mass all achieving statistical significance. Eighty percent of the patients were either able to stop or decrease the dose of their antihypertensive medications (69).

BIB® induced weight loss has been shown not only to improve cardiac function but also lung function. An investigation (70) regarding the use BIB® induced weight loss and lung function showed that obesity, specially truncal obesity, changes the mechanics of respiration, reducing its function by the deposition of subcutaneous adipose tissue, which results in a mechanical disadvantage for the respiratory muscles and possibly causes "chest strapping" (71, 72) all this is associated with increased pulmonary diffusion. BIB® induced weight loss determined an increase in lung volumes and a reduction in the inspiratory muscle strength. Another study focused on patients with obstructive sleep apnea, attributed to a reduction in pharyngeal cross-sectional area due to peripharyngeal fat deposition. Seventeen patients with morbid obesity were evaluated including a cardiorespiratory sleep study before and after weight loss obtained by BIB® placement. With documented statistically significant weight loss achieved 6 months after balloon insertion, values of waist circumference, sagittal abdominal diameter, and neck circumference were all reduced significantly. This achieved weight loss, about 15 % of baseline body weight, induced a nearly complete resolution of OSA score which was found to be statistically significant (73).

There exists a strong association between obesity and female infertility. In a retrospective study, the charts of 27 females diagnosed with infertility who underwent BIB® placement were reviewed. After IGB aided weight loss (7.5 ± 1.1 BMI units) 83.3 % of these patients were able to achieve pregnancy, carry it fully to term without any complications and end with a live birth (74).

The psychological impact of obesity on patients has also been very well documented; nowadays a complete psychological evaluation is warranted prior to most bariatric surgical interventions. Deliopoulou et al. (75) completed a 6-month prospective study to evaluate the evolution of depression status and its relation to weight loss, in morbidly obese patients utilizing an intragastric balloon to achieve the decrease in BMI. One-hundred females met the criteria for balloon treatment were assessed for depression 65 were diagnosed with depressed, 35 were non-depressed. Obesity-related parameters in both groups were comparable. During the treatment period, the depression status of the mildly, moderately, and severely depressed patients improved from 40 %, 32.3 %, and 27.7 % to 20 %, 7.7 %, and 1.5 %, respectively, with 70.8 % finally exhibiting no depression at all. There was a significant [percentage of EWL > 30] weight loss difference in favor of those who were less severely depressed initially. The conclusion of the authors was that the degree of weight loss observed in obese depressed females, comparable to that achieved by non-depressed females, after intragastric balloon insertion was found to positively affect their depression status.

Research indicates that females appear more vulnerable to the psychosocial impact of obesity as compared to men. In a smaller prospective study, including 27

obese females, the effect of intragastric balloon on controlling body weight and improving psychological functioning and QOL were evaluated using Psychological functioning (HADS) and QOL (SF-36) were assessments both at baseline and follow-up (6 months). Post BIB® removal patients' mean body weight was significantly decreased ($p<0.001$) with a mean (SD) loss of 15.7 (7.8) kg. Furthermore, patients reported a significant reduction in anxiety ($p=0.018$) and depression ($p=0.045$) symptoms scores and significant improvement in all SF-36 subscales including physical functioning, role functioning due to physical or emotional problems, bodily pain, vitality, social functioning, general health, and mental health (75, 76).

BIB in Adolescents

Unfortunately the obesity epidemic is not limited to the adult population, more and more we have evidence that adolescent and pediatric age groups are being afflicted with the consequences of increased BMI. The intragastric balloon being a noninvasive, reversible procedure that does not disrupt the continuity of the digestive tract can be considered a safer and less invasive option for this young patient population. There is a limited experience of the BIB® use in pediatric patients, and earlier reports of IGB application in pediatric patients were not encouraging (77).

A study conducted in Brazil, which includes 21 adolescents treated by IGB (45) suggests that obese adolescents patients can be considered as possible indication for the IB, arguing that because of the shorter duration of obesity a greater possibility exists for them to change their eating behavior and lifestyle to achieve and maintain the weight loss. Another study supports the theory that morbidly obese teenagers with no satisfactory results on clinical management for weight loss are the ideal candidates for IGB treatment (78).

A prospective clinical study of 14 obese adolescents with BMI 39.8 ± 5.8 kg/m^2 was to investigate the effectiveness of intragastric balloon on obese adolescents, data was collected monthly for the 6 month treatment period. Just prior to removal of the balloon, all measured parameters exhibited a statistically significant reduction including the BMI and %EWL; the loss of excessive weight was not as high as expected, compared to that of adults treated by the same medical group (80, 81). Appetite related sensation score was unchanged and poor compliance was seen in this group of adolescent patients. Improving the pre-procedure screening for the appropriate adolescent candidates prior to BIB® treatment as well as a better scheduled approach by a multi disciplinary group, should be considered mandatory in this patient population (79).

Heliosphere Balloon

Placement of the Intragastric Heliosphere Balloon is very similar to that of the BIB®, the intragastric balloon is inflated with air instead of fluid. Data regarding the efficacy and safety of IHB are limited.

A preliminary study published in 2006 (82) the safety and efficacy of the Heliosphere device was evaluated in ten patients, selected according to the guidelines for obesity surgery. On the first and second post-treatment day, intravenous saline (30–35 ml/kg/day) with omeprazole (20 mg/day), ondansetron (8 mg/day)

and butylscopolamine bromide (20 mg t.i.d.) were given to all patients and not until day 3 were the patients allowed to start a liquid diet and discharged home on day 4 with 1000 kcal diet. The investigators noted that the positioning of the Heliosphere Bag was quite difficult in all patients due to low pliancy and large size of the bag, this was associated to patient discomfort. System failure at time of Heliosphere Bag deployment was observed in 50 % of cases and in one patient at time of removal, the Heliosphere Bag was not found in the stomach and in three other patients, the balloon was found partially deflated.

At the time of balloon removal after 6 months %EWL was 29.1 ± 20.1 with a mean weight loss was 17.5 ± 16.2 kg. Taking into consideration the findings of this publication, even though weight loss was satisfactory, the Heliosphere Balloon had some instrumental and technical problems which required attention: high rate of system failure at positioning, high rate of spontaneous deflation, absence of a marker such as methylene blue, and large size with low pliability which caused patient discomfort (82).

Giuricin et al. (83) published the results of their experience with Heliosphere® BAG between 2006 and 2010, in 32 patients who completed a 6-month treatment and 16 patients an 18 month follow-up. At 24 weeks the device was removed and the data showed a mean weight loss of 13.62 kg and 26.14 %, at 18 months post Heliosphere® BAG, the a mean weight loss of 9.8 kg or 18.2 % was documented.

This group demonstrated that the Heliosphere® BAG can enable modest short-term weight loss with few reported side effects. As with other intragastric balloon data partial weight gain at mid/long-term follow-up was seen.

In a cases series of 50 using Heliosphere® balloon in Italy, early removal was required in 4 % for acute intolerance of the device and another 4 % premature radiologically confirmed desufflation. Of the patients that completed the 6 month treatment, BMI decreased 5.9 %, weight loss was 16.8 kg. Device tolerance was very good, limited to occasional dyspeptic symptoms during the first days after insertion.

The intragastric air filled balloon proved to be an acceptable profile of efficacy and good tolerance (84).

A smaller series reported one severe adverse event at the time of insertion, acute coronary syndrome in a patient with known chronic coronary artery disease, otherwise no other serious adverse effects. Device insertion was uncomplicated but removal of the Heliosphere® was technically more challenging with one distal migration and one balloon fragmentation requiring surgery (85). Weight loss was equivalent to other types of intragastric balloons.

A prospective, double-blind study comparing the fluid filled BIB® and air fluid Heliosphere® intragastric balloons was done in 33 patients with BMI 35–45.

18 Heliosphere® bag and 15 Bioenterics-BIB were placed with conscious sedation and removed under general anesthesia 6 months later. Patients were discharged a 1000-kcal diet, oral proton pump inhibitors and monthly follow-ups. At 6 and 12 months mean weight loss, BMI loss, and percent excess weight loss showed no significant differences between both groups. At removal, two Heliosphere® bags were not found in the stomach, and four patients required extraction of the balloon by rigid esophagoscopy or surgery, confirming the need for technical improvements for the Heliosphere® (87).

Silimed Balloon

Carvalho GL et al. (28) published preliminary results for the Silimed Gastric Balloon to treat 16 pre-obese patients body mass index (BMI) < 30, as a part of a multidisciplinary program involving clinical, psychological, and behavioral approaches. After the IGB treatment BMI values decreased significantly from overweight to normal range 24.5 kg/m^2. Only minor complications of nausea and vomiting were noted, two cases of spontaneous deflation of the devices which were safely removed by gastric endoscopy. Both the procedures were performed under usual sedation of diagnostic endoscopy.

An interventional study done in 30 overweight patients with metabolic syndrome aimed to evaluate the changes in lung function resulting from Silimed balloon use and to correlate the pattern of body fat distribution with changes in lung function.

During the initial evaluations, the main pulmonary function abnormalities observed were decreased expiratory reserve volume (ERV), decreased total lung capacity (TLC), and increased diffusing capacity of carbon monoxide (DLCO), which occurred in 56.7 %, 40 %, and 23.3 % of patients, respectively. Three months after Silimed Balloon placement a significant reduction in the body mass index was noted along with drop of the maximal inspiratory pressure, and a significant increase in the forced vital capacity, TLC, and ERV (88). Balloon removal rate was of 12.2 % mostly due to gastric intolerance (88).

Regarding the use of other intragastric balloons in the study of obese patient for weight loss, a comparative prospective study of 50 patients concluded that both the BIB® and Silimed intragastric balloon were equally safe and effective reducing weight measurements in morbidly obese patients. In this particular study, the application of Silimed Balloon was found to be technically more convenient and simple (89).

Reshape Duo Balloon

This uniquely shaped device, in contrast all other single balloon devices consists of dual balloons and it is design to maximize space occupation within the gastric fundus and body, conforming easily to the greater curvature (90). The benefit of a dual balloon against deflation related complications, such as migrations and obstruction decreases the severe adverse effects as seen in single balloon devices (91).

Seven feasibility studies, accounting for 155 subjects implanted with the ReShape Duo Intragastric Balloon System, have been conducted in Europe (unpublished data). These studies have aided in modifying and refining the Duo device design and procedure, demonstrating that Duo treatment facilitated clinically meaningful weight loss with a proven excellent safety profile (91). European clinical experience (unpublished data) with the ReShape Duo balloon has demonstrated similar weight loss results at 6 months and suggests improved gastrointestinal tolerance compared with single balloon devices.

The REDUCE study (phase 1 registered with http://ClinicalTrials.gov; number NCT 01061385), was a prospective, randomized, multicenter trial held in three Bariatric Surgery Centers of Excellence. The phase 1 portion of the study was found unlikely to achieve the primary effectiveness endpoint, after recommendations to the Food and Drug Administration as well as the sponsor the trial was halted and

intention to redesign. The 30 adult patients with a body mass index (BMI) of 30–40 kg/m^2 that had already been enrolled in a random 2:1 ratio after institutional review board approval, where the treatment group had the ReShape Duo device placed ($n=21$) and the control group did not ($n=9$) where followed for 48 weeks. Both groups followed up monthly for the first 24 weeks, then biweekly after that, and received similar diet and exercise counseling (91).

The ReShape Duo was well tolerated post implantation, secondary to nausea four patients required readmission, and during explantation one patient required transient endotracheal intubation. No patient deaths, bowel obstruction or perforation, balloon deflations, device malfunctioning requiring early removal or migration occurred.

No statistically significant difference was found in number of patients achieving EWL $\geq$ 25 %, 19 % of the TG and 7.7 % of the CG, although a positive trend was noted in favor of the TG. At device explanation, 62 % of the ReShape Duo subjects had lost $\geq$ 25 % of their excess weight. At 48 weeks of follow-up, 6 months post ReShape Duo removal, the TG subjects had maintained 64 % of their weight loss. The recommendation is that patients continue a supervised weight loss program after balloon removal.

Investigators rated after each device placement and removal procedure the complexity of using the device. The Duo device was reported to be easy to both place and remove by the researchers operating the device during the study.

Obalon

The novel prospect of an intragastric balloon that does not require endoscopy or sedation is a very alluring one. The Obalon, swallowable gelatin capsule which contains a folded balloon that once a patient has ingested it can be promptly filled with gas via a miniature capsule was commercially launched on a limited basis in Europe beginning in July 2012.

Up to three balloons can be swallowed and inflated throughout a 3 month period to increase total resident and stimulate further weight loss. At the termination of the treatment period (12 weeks) during a short endoscopy all balloons are removed.

The safety and efficacy data on this device were collected and reported on the first commercial product uses at 11 centers throughout Europe including Belgium, Germany, Italy, and Spain (30).

A 10-patient pilot study was conducted at the Obesity Control Center (Tijuana, Mexico) using Obalon gas filled gastric balloon with a single balloon placed for 1 month. The mean BMI was of 37.5 + 6.9 kg/m^2. No diet or plan for caloric restriction was provided. At the end of 1 month, mean excess weight loss was 11.8 ± 9.7 %, weight loss was 3.0 + 1.7 kg. All balloons were easily removed endoscopically and no serious or unexpected adverse events including balloon or system malfunctions were reported (93).

A 3-month feasibility study conducted by Martinez et al. (92) in a total of ten patients, mean baseline BMI of 33.5 ± 3 kg/m^2, weight of 92.3 ± 8.8 kg. A single 250 cm^3 balloon was initially given to each patient, by the second month all patients

received a second balloon and only two patients received a third balloon during the third month. Mean excess weight loss at the end of 12 weeks was 34.5 ± 16.9 % kg, mean weight loss was 7.9 + 4.4 kg, and mean reduction in BMI was 2.9 ± 1.6 kg/m^2. No unexpected or adverse events were reported including vomiting, nausea, or requests for early removal. Additionally a favorable trend toward improved metabolic value was identified.

Another 28 patients with a mean BMI 34.8 were enrolled in three trials lasting one, two, and 3 months. In this series position of the balloon capsule was confirmed under fluoroscopy prior to inflation with gas. Additional balloon placements were based on patient weight loss progress and reported satiety levels. Consistent monthly weight loss was reported in all three studies. Treatment with a second balloon added in the second month was associated with greater weight loss as compared to the single balloon treatment. The studies verified favorable tolerability and safety from progressively utilizing up to three swallowable 250 cm^3 gastric balloons, producing consistent weight loss and encouraging metabolic improvement. The ability to easily add balloon volume during the treatment period appears to improve treatment, weight loss and minimize patient symptoms (94).

A prospective pilot study of 17 overweight or obese patients, up to three balloons were ingested under fluoroscopic control. All balloons were removed 12 weeks after the ingestion of the first balloon. Ninety-eight percent attempts to swallow a balloon were successful. Nausea and stomach pain were the most frequent side effects, Weight loss was significant at weeks 4, 8, and 12 (95).

From the Obera website, the accumulative data of 119 patients from the first commercial uses of Obalon after CE Mark approval, were evaluated a baseline BMI of 33.0 ± 5.5 kg/m^2 received a single 250 cm^3 balloon. 47.9 % of patients received a second balloon and 5.0 % received a third balloon during the treatment period. Hundred and ten patients completed at least 8 weeks of treatment with mean excess weight loss of 50.2 ± 72.5 % and total weight loss 8.0 ± 5.8 kg. All these results were found to be statistically significant ($p < 0.001$). Excess weight loss of 25 % or greater was seen in 68.2 % of patients and 76.4 % had percent of total body weight loss of 50 % or greater in only 3 months of treatment. Nausea (10.1 %) and vomiting (6.7 %) were the most commonly reported adverse events (30).

With a very low adverse event rate, good tolerability even in patients with multiple balloons and a high responder rate with adequate 3-month weight loss results the initial results are encouraging for use of the Obalon in weight loss treatments (30).

Adjuvant Therapy: Sibutramine

As weight loss with intragastric balloons is not always optimal, considering adjuvant medical therapy may be an option. In multicentric studies, sibutramine has been used as a single treatment agent a large patient series for up to 24 months. Bray et al. (96) published a study on 1047 patients treated with this medication for a 6-month period where they found 5 % reduction of weight in 67 % of the patients, and 10 % reduction in 35 % of the patients. In a meta-analysis of 12 studies where sibutramine was used, authors reported a 3.4- to 6.0-kg weight loss in 16–24 weeks (97).

Coskun et al. (98) compared a group treated with BIB + sibutramine (a pharmacologic agent is a selective reuptake blocker of serotonin and norepinephrine) and a group treated only with BIB®, and reported that the dual modality treatment group lost more weight than the BIB® group alone, this was statistically significant. So compared to using an intragastric device alone, using BIB® together with specially in patients with plan surgical interventions, provides more effective weight loss.

Combination of IB therapy with weight loss drugs is another option to help maintaining weight loss: a 6-month course of sibutramine following IB extraction has allowed to decrease weight regain at 1 year by 5 kg compared to controls ($p < 0.001$).

19.1.2 Spatz Adjustable Balloon System (ABS)

The first implantations in 18 patients with a mean BMI of 37.3 kg/m^2, of an adjustable balloon with an attached migration prevention anchor lasting 12 months were reported. Balloon volumes were adjusted for intolerance or weight loss plateau, 16 adjustments were successfully performed, 37.5 % were downward adjustments to alleviate intolerance and this yielded an additional mean weight loss of 4.6 kg. 62.5 % were upward adjustments because of weight loss plateau; this modification yielded a mean additional weight loss of 7 kg. Mean weight loss at 24 weeks was 15.6 kg with 26.4 % EWL, at 52 weeks results were of 24.4 kg with 48.8 % EWL (99).

Complications necessitating early removal of seven balloons included valve malfunction (1), gastritis (1), Mallory–Weiss tear (1), NSAID perforating ulcer (1), and balloon deflation (1). Two incidents of catheter shear from the chain: one passed uneventfully and one caused an esophageal laceration without perforation during extraction (99).

Brooks et al. (100) published a study on 73 patients with a mean BMI 36.6 kg/m^2 scheduled for 1-year implantation with Spatz balloon. Three patients failed insertion, 21 underwent early removals for intolerance refusing adjustment, deflations and unsatisfied patients. Forty nine patients completed the 12 months, of these ten intolerant patients had balloon adjustments with additional mean 13.2 kg weight loss. Other patients who required adjustments these failed in 6 and non-response in 7. The successfully adjusted 38 patients lost an additional mean 9.4 kg and at extraction had mean 40.9 % EWL. Surgical excision was required for three catheter impactions; three balloons were deflated but did not migrate beyond the stomach. The failure rate was reported at 4.1 %, major complications occurred in 4.1 %.

In a comparative case–control study was done between ABS and the BIB, 40 patients were matched with 80 controls. The 12 month duration of the ABS was matched with sequential BIB® placements. The Spatz ABS balloon was adjusted with inflation of 200 cm^3 of saline 22.5 % patients for poor weight loss after first 6-months treatment. At the end of the study, the weight loss parameters were similar

between both groups, even though extraction and positioning complications as well as mortality was absent. There were seven Spatz device linked complications requiring removal in 85.7 % of the cases (101).

The introduction of an adjustable balloon with a migration prevention function, safely enabling prolonged implantation and possibly improve efficacy and weight maintenance post-extraction, is very appealing but warrants further research and device modification to improve safety and decrease device malfunction.

References

1. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. JAMA. 2010;303(3):235–41.
2. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. JAMA. 2006;295(13):1549–55.
3. World Health Organization Web site. Obesity and overweight. 2006. Available from http://www.who.int/mediacentre/news/releases/2005/pr44/en/. Accessed on September 18, 2010.
4. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, et al. Bariatric surgery: a systematic review and metaanalysis. JAMA. 2004;292(14):1724–37.
5. Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, Pories WJ, et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. Am J Med. 2009;122(3):248–56.e5.
6. WHO. Obesity: preventing and managing the global epidemic. Report of a WHO consultation on obesity. Geneva: WHO; 1998.
7. Allison DB, Fontaine KR, Manson JE, et al. Annual deaths attributable to obesity in the United States. JAMA. 1999;282:1530–8.
8. Health benefits of weight loss. Available from www.maso.org.my/spom/chap4.pdf.
9. National Institutes of Health. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—the evidence report. National Institutes of Health. Obes Res. 1998;6:51S–209.
10. Bays HE. Current and investigational antiobesity agents and obesity therapeutic treatment targets. Obes Res. 2004;12:1197–211.
11. Waseem T, Mogensen KM, Lautz DB, et al. Pathophysiology of obesity: why surgery remains the most effective treatment. Obes Surg. 2007;17:1389–98.
12. Coté GA, Edmundowicz SA. Emerging technology: endoluminal treatment of obesity. Gastrointest Endosc. 2009;70:991–9.
13. Imaz I, Martinez-Cervell C, Garcia-Alvarez EE, Sendra-Gutierrez JM, Gonzalez-Enriquez J. Safety and effectiveness of the intragastric balloon for obesity. A meta-analysis. Obes Surg. 2008;18(7):841–6.
14. Konopko-Zubrzycka M, Baniukiewicz A, Wroblewski E, Kowalska I, Zarzycki W, Gorska M, et al. The effect of intragastric balloon on plasma ghrelin, leptin, and adiponectin levels in patients with morbid obesity. J Clin Endocrinol Metab. 2009;94(5):1644–9.
15. Martin CK, Bellanger DE, Rau KK, Coulon S, Greenway FL. Safety of the Ullorex oral intragastric balloon for the treatment of obesity. J Diabetes Sci Technol. 2007;1(4):574–81.
16. ASGE/ASMBS Task Force on Endoscopic Bariatric Therapy. A pathway to endoscopic bariatric therapies. Surg Obes Relat Dis. 2011;7:672–82.
17. Nieben OG, Harboe H. Intragastric balloon as an artificial bezoar for treatment of obesity. Lancet. 1982;1:198–9.
18. Hogan R, Johnston J, Long B, et al. A double-blind, randomized, shamcontrolled trial of the gastric bubble for obesity. Gastrointest Endosc. 1989;35:381–5.
19. Benjamin S, Maher K, Cattau Jr E, et al. Double-blind controlled trial of the Garren-Edwards gastric bubble: an adjunctive treatment for exogenous obesity. Gastroenterology. 1988; 95:581–8.

20. Mathus-Vliegen E, Tytgat G, Veldhuyzen-Offermans E. Intragastric balloon in the treatment of super-morbid obesity. Double-blind, shamcontrolled, crossover evaluation of 500-milliliter balloon. Gastroenterology. 1990;99:362–9.
21. McFarland RJ, Grundy A, Gazet JC, et al. The intra- gastric balloon: a novel idea proved ineffective. Br J Surg. 1987;74:137–9.
22. Ramhamadany EM, Fowler J, Baird IM. Effect of the gastric balloon versus sham procedure on weight loss in obese subjects. Gut. 1989;30:1054–7.
23. Mathus-Vliegen EMH, Tytgat GNJ. Intragastric balloons for morbid obesity: results, patient tolerance and balloon life-span. Br J Surg. 1990;77:77–9.
24. Hogan RB, Johnston JH, Long BW, et al. A double blind, randomised, sham controlled trial of the gastric bubble for obesity. Gastrointest Endosc. 1989;35:381–5.
25. Meshkinpour H, Hsu D, Farivar S. Effect of gastric bubble as a weight reduction device: a controlled, crossover study. Gastroenterology. 1988;95:589–92.
26. Schapiro M, et al. Obesity and the gastric balloon: a comprehensive workshop. Tarpon Springs, Florida, March 19–21, 1987. Gastrointest Endosc. 1987;33(4):323–7.
27. Forestieri P, De Palma GD, Formato A, et al. Heliosphere Bag in the treatment of severe obesity: preliminary experience. Obes Surg. 2006;16:635–7.
28. Carvalho GL, et al. The use of an improved intragastric balloon technique to reduce weight in pre-obese patients—preliminary results. Obes Surg. 2011;21:924–7.
29. Ponce J, et al. Prospective, randomized, multicenter study evaluating safety and efficacy of intragastric dual-balloon in obesity. Surg Obes Relat Dis. 2013;9:290.
30. Obalon website: www.obalon.com.
31. Bonazzi P, Petrelli MD, Lorenzini I, Peruzzi E, Nicolai A, Galeazzi R. Gastric emptying and intragastric balloon in obese patients. Eur Rev Med Pharmacol Sci. 2005;9(5 Suppl 1):15–21.
32. Martinez-Brocca MA, et al. Intragastric balloon-induced satiety is not mediated by modification in fasting or postprandial plasma ghrelin levels in morbid obesity. Obes Surg. 2007;17(7):996.
33. Kissileff HR, Carretta JC, Geliebter A, Pi-Sunyer FX. Cholecystokinin and stomach distension combine to reduce food intake in humans. Am J Physiol Regul Integr Comp Physiol. 2003;285:R992–8.
34. Lal S, McLaughlin J, Barlow J, et al. Cholecystokinin pathways modulate sensations induced by gastric distension in humans. Am J Physiol Gastrointest Liver Physiol. 2004;287:G72–9.
35. Evans JT, DeLegge MH. Intragastric balloon therapy in the management of obesity: why the bad wrap? JPEN J Parenter Enteral Nutr. 2011;35(1):25–31.
36. Phillips RJ, Powley TL. Gastric volume rather than nutrient content inhibits food intake. Am J Physiol Regul Integr Comp Physiol. 1996;271:R766–9.
37. Bell EA, Roe LS, Rolls BJ. Sensory-specific satiety is affected more by volume than by energy content of a liquid food. Physiol Behav. 2003;78:593–600.
38. Ello-Martin JA, Ledikwe JH, Rolls BJ. The influence of food portion size and energy density on energy intake: implications for weight management. Am J Clin Nutr. 2005;82(1 suppl):236S–41.
39. Geliebter A, Westreich S, Gage D. Gastric distention by balloon and test-meal intake in obese and lean subjects. Am J Clin Nutr. 1988;48:592–4.
40. ASGE. Endoluminal bariatric techniques. Report on emerging technology. Gastrointest Endosc. 2012;76(1):1.
41. Genco A, Balducci S, Bacci V, et al. Intragastric balloon or diet alone? A retrospective evaluation. Obes Surg. 2008;18:989–92.
42. Genco A, Cipriano M, Materia A, et al. Laparoscopic sleeve gastrectomy versus intragastric balloon: a case-control study. Surg Endosc. 2009;23:1849–53.
43. Milone L, Strong V, Gagner M. Laparoscopic sleeve gastrectomy is superior to endoscopic intragastric balloon as a first stage procedure for super-obese patients (BMI > or = 50). Obes Surg. 2005;15:612–7.

44. Genco A, Bruni T, Doldi SB, et al. BioEnterics intragastric balloon: the Italian experience with 2,515 patients. Obes Surg. 2005;15(8):1161–4.
45. Sallet JA, Marchesini JB, et al. Brazilian multicenter study of the intragastric balloon. Obes Surg. 2004;14(7):991–8.
46. Imaz I, Martinez-Cervell C, Garcia-Alvarez EE, et al. Safety and effectiveness of the intragastric balloon for obesity. A meta-analysis. Obes Surg. 2008;18(7):841–6.
47. Herve J, Wahlen CH, Schaeken A, et al. What becomes of patients one year after the intragastric balloon has been removed? Obes Surg. 2005;15(6):864–70.
48. Mathus-Vliegen EMH, Tytgat GNJ. Intragastric balloon for treatment-resistant obesity: safety, tolerance, and efficacy of 1-year balloon treatment followed by a 1-year balloon-free follow-up. Gastrointest Endosc. 2005;61(1):19–27.
49. Angrisani L, Lorenzo M, Borrelli V, Giuffré M, Fonderico C, Capece G. Is bariatric surgery necessary after intragastric balloon treatment? Obes Surg. 2006;16:1135–7.
50. Kotzampassi K, Grosomanidis V, Papakostas P, Penna S, Eleftheriadis E. 500 Intragastric balloons: what happens 5 years thereafter? Obes Surg. 2012;22:896–903.
51. Dumonceau J, et al. Single vs repeated treatment with the intragastric balloon: a 5-year weight loss study. Obes Surg. 2010;20:692–7.
52. Lopez-Nava G, Rubio MA, Prados S, et al. BioEnterics® intragastric balloon (BIB): single ambulatory center Spanish experience with 714 consecutive patients treated with one or two consecutive balloons. Obes Surg. 2011;21:5–9.
53. Deitel M. How much weight loss is sufficient to overcome major co-morbidities? Obes Surg. 2001;11:659.
54. Pasulka PS, Bistrian BR, Benotti PN, et al. The risks of surgery in obese patients. Ann Intern Med. 1986;104:540–6.
55. Pinkey JH, Sjostrom CD, Gale EA. Should surgeons treat diabetes in severely obese people? Lancet. 2001;1:357–9.
56. Forlano R, Ippolito AM, Iacobellis A, et al. Effect of the BioEnterics intragastric balloon on weight, insulin resistance, and liver steatosis in obese patients. Gastrointest Endosc. 2010;71:927–33.
57. Spyropoulos C, Katsakoulis E, Mead N, et al. Intragastric balloon for high-risk superobese patients: a prospective analysis of efficacy. Surg Obes Relat Dis. 2007;3(1):78–83.
58. Zerrweck C, et al. Preoperative weight loss with IGB decreases the risk of significant adverse outcomes of laparoscopic gastric bypass in super-super obese patients. Obes Surg. 2012;22:777–82.
59. Bozkurt S, Coskun H. The early results of intragastric balloon application of different BMI groups. Eur Surg. 2012;44:383–7.
60. Mui WL, et al. Impact on obesity-related illnesses and quality of life following intragastric balloon. Obes Surg. 2010;20:1128–32.
61. Mazure RA, Culebras JM, et al. Intragastric balloon and multidisciplinary team. Nutr Hosp. 2009;24(3):282–7.
62. Dumonceau JM. Evidence-based review of the Bioenterics intragastric balloon for weight loss. Obes Surg. 2008;18:1611–7.
63. Nijhof HW, Steenvoorde P, Tollenaar RA. Perforation of the esophagus caused by the insertion of an intragastric balloon for the treatment of obesity. Obes Surg. 2006;16:667–70.
64. Zdichavsky M, Beckert S, Kueper M, et al. Mechanical ileus induces surgical intervention due to gastric balloon: a case report and review of the literature. Obes Surg. 2010;20:1743–6.
65. Oztürk A, Akinci OF, Kurt M. Small intestinal obstruction due to self deflated free intragastric balloon. Surg Obes Relat Dis. 2010;6:569–71.
66. Vanden Eynden F, Urbain P. Small intestine gastric balloon impaction treated by laparoscopic surgery. Obes Surg. 2001;11:646–8.
67. Cubattoli L, Barneschi C, Mastrocinque E, et al. Cardiac arrest after intragastric balloon insertion in a super-obese patient. Obes Surg. 2009;19:253–6.

68. Mumbi C, et al. Role of intragastric balloon in cardiac surgery: an adjunct to preoperative optimization for morbid obesity. Ann Thorac Surg. 2011;92:1517–8.
69. Lorenzo M, et al. The effect of intragastric balloon on left ventricular function in morbidly obese with hypertension. The XVIth World Congress of the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO 2011), Aug 31–Sep 3, 2011, Hamburg, Germany.
70. Mafort TT, et al. Intragastric balloon for the treatment of obesity: evaluation of pulmonary function over a 3-month period. Lung. 2012;190:671.
71. Barreto SSM. Volumes pulmonares. J Bras Pneumol. 2002;28 Suppl 3:S83–94.
72. Unterborn J. Pulmonary function testing in obesity, pregnancy, and extremes of body habitus. Clin Chest Med. 2001;22:759–67.
73. Busetto L, Enzi G, Inelmen EM, Costa G, et al. Obstructive sleep apnea syndrome in morbid obesity. Effects of intragastric balloon. Chest. 2005;128(2):618–23.
74. Musella M, et al. The potential role of intragastric balloon in the treatment of obese-related infertility: personal experience. Obes Surg. 2011;21:425–30.
75. Deliopoulou K, et al. The impact of weight loss on depression status in obese individuals subjected to intragastric balloon treatment. Obes Surg. 2013;23:669.
76. Karaivazoglou K, et al. The effect of intragastric balloon on female obese patients' weight, psychological function and quality of life: a prospective study. Abstracts. J Psychosom Res. 2011;70:580–623.
77. Vandenplas Y, Bollen P, De Langhe K, Vandemaele K, De Schepper J. Intragastric balloons in adolescents with morbid obesity. Eur J Gastroenterol Hepatol. 1999;11:243–5.
78. Inge TH, Xanthakos SA, Zeller MH. Bariatric surgery for pediatric extreme obesity: now or later? Int J Obes (Lond). 2007;31:1–14.
79. Karagiozoglou-Lampoudi T, Papakostas P, et al. Effective intragastric balloon treatment in obese adolescents. Ann Gastroenterol. 2009;22(1):46–51.
80. Kotzampassi K, Eleftheriadis E. Intragastric balloon as an alternative restrictive procedure for morbid obesity. Ann Gastroenterol. 2006;19:285–8.
81. Lampoudi T, Apostolou A, Lampoudi S, Kotsani C, Savvidou A, Kotzampassi K. Ghrelin levels and Appetite Related Sensations are suppressed in parallel in obese patients treated by Intragastric Balloon (IB) until they reach extreme weight loss. JPEN J Parenter Enteral Nutr. 2007;31:S1–70.
82. Forestieri P, De Palma GD, Formato A, et al. Heliosphere Bag in the treatment of severe obesity: preliminary experience. Obes Surg. 2006;16:635–7.
83. Giuricin M, et al. Short- and long-term efficacy of intragastric air-filled balloon (Heliosphere® BAG) among obese patients. Obes Surg. 2012;22(11):1686–9.
84. Sciumè C, et al. Role of intragastric air filled balloon (Heliosphere Bag) in severe obesity. Personal experience. Ann Ital Chir. 2009;80(2):113–7.
85. Trande P, et al. Efficacy, tolerance and safety of new intragastric air-filled balloon (Heliosphere BAG) for obesity: the experience of 17 cases. Obes Surg. 2010;20(9):1227–30.
86. Castro D, et al. Efficacy, safety, and tolerance of two types of intragastric balloons placed in obese subjects: a double-blind comparative study. Obes Surg. 2010;20:1642–6.
87. Castro D, et al. Efficacy, safety, and tolerance of two types of intragastric balloons placed in obese subjects: a double-blind comparative study. Obes Surg. 2010;20:1642–6.
88. Mafort TT, et al. Intragastric balloon for the treatment of obesity: evaluation of pulmonary function over a 3-month period. Lung. 2012;190:671.
89. Bozkurt S, et al. Normal 0 21 analysis of safety and effectiveness of two different liquid-filled intragastric balloon (Bioenterics® Vs Silimed®). The XVIth World Congress of the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO 2011), Aug 31–Sep 3, 2011, Hamburg, Germany.
90. Evans JT, et al. Intragastric balloon therapy in the management of obesity: why the bad wrap? JPEN J Parenter Enteral Nutr. 2011;35:25–6.

91. Ponce J, et al. Prospective, randomized, multicenter study evaluating safety and efficacy of intragastric dual-balloon in obesity. Surg Obes Relat Dis. 2013;9:290.
92. Martinez A, et al. Weight loss and metabolic improvement using a swallowable, volume-titratable gastric balloon system. ASMBS – 28th Annual Meeting, Oralndo, FL, June 12–17, 2011.
93. Ortiz A, et al. Novel swallowable, gas-filled intragastric balloon – results of a pilot study IFSO – European Chapter Congress, Barcelona, April 26–28, 2012.
94. Martinez A, et al. A less invasive gastric volume reduction with safe and effective titration IFSO – European Chapter Congress, Barcelona, April 26–28, 2012.
95. Mion F, et al. Swallowable Obalon® gastric balloons as an aid for weight loss: a pilot feasibility study. Obes Surg. 2013;23(5):730–3.
96. Bray GA, Blackburn GL, Ferguson JM, et al. Sıbutramine produces dose-related weight loss. Obes Res. 1999;7:189–98.
97. Li Z, Maglione M, Tu W, et al. Meta-analysis: pharmacologic treatment of obesity. Ann Intern Med. 2005;142:532.
98. Coskun H, et al. Assessment of the application of the intragastric balloon together with sibutramine: a prospective clinical study. Obes Surg. 2010;20(8):1117–20.
99. Machytka E, et al. Adjustable intragastric balloons: a 12-month pilot trial in endoscopic weight loss management. Obes Surg. 2011;21(10):1499–507.
100. Brooks J, et al. One-year adjustable intragastric balloons: results in 73 consecutive patients in the UK. Obes Surg. 2014;24(5):813–9.
101. Genco A, et al. Adjustable intragastric balloon vs non-adjustable intragastric balloon: case-control study on complications, tolerance, and efficacy. Obes Surg. 2013;23(7):953–8. doi:10.1007/s11695-013-0891-5.

Index

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