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OTHER

Bariatric Surgery in Class I Obesity

A Position Statement from the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO)

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Abstract Class I obesity conveys an increased risk of comorbidities, impairs physical and mental health-related quality of life, and it is associated to an increased psychosocial burden, particularly in women. The need for effective and safe therapies for class I obesity is great and not yet met by nonsurgical approaches. Eligibility to bariatric surgery has been largely based on body mass index (BMI) cut points and limited to patients with more severe obesity levels. However, obese patients belonging to the same BMI class may have very different levels of health, risk, and impact of obesity on quality of life. Individual patients in class I obesity may have a comorbidity burden similar to, or greater than, patients with more severe obesity. Therefore, the denial of bariatric surgery to a patient with class I obesity suffering from a significant obesity-related health burden and not achieving weight control with nonsurgical therapy simply on the basis of the BMI level does not appear to be clinically justified. A clinical decision should be based on a more comprehensive evaluation of the patient's current global health and on a more reliable prediction of future morbidity and mortality. After a careful review of available data about safety and efficacy of bariatric surgery in patients with class I obesity, this panel reached a consensus on ten clinical recommendations.

Keywords Class I obesity · BMI · Eligibility

The Position Statement has been written by a working group formed by members of the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO)-The Position Statement has been discussed and approved by the Executive Board of the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO).

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Executive Summary and Final Recommendations

Class I obesity [body mass index (BMI) 30–35 kg/m^2] conveys an increased risk of comorbidities, impairs physical and mental health-related quality of life, and it is associated to an increased psycho-social burden, particularly in women. The need for effective and safe therapies for class I obesity is great and not yet met by nonsurgical approaches.

Eligibility to bariatric surgery has been largely based on BMI cut-points and limited to patients with more severe obesity levels (BMI > 40 kg/m^2 or BMI 35–40 kg/m^2 with obesity-related comorbidities). However, obese patients belonging to the same BMI class may have very different levels of health, risk, and impact of obesity on quality of life. Individual patients in class I obesity may have a comorbidity burden similar to, or greater than, patients with more severe obesity. Therefore, the denial of bariatric surgery to a patient with class I obesity suffering from a significant obesity-related health burden and not achieving weight control with

nonsurgical therapy simply on the basis of the BMI level does not appear to be clinically justified. A clinical decision should be based on a more comprehensive evaluation of the patient's current global health and on a more reliable prediction of future morbidity and mortality.

After a careful review of available data about safety and efficacy of bariatric surgery in patients with class I obesity, this panel reached a consensus on these recommendations:

(1) The impact on health of class I obesity varies greatly between subjects. However, the physical, psychological and social health burden imposed by class I obesity may be great at an individual level.
(2) Nonsurgical therapies may achieve a clinically meaningful weight loss in a significant number of patients with class I obesity, but this weight loss is maintained in the long term only in a smaller proportion of them.
(3) Bariatric surgery is a highly effective weight loss strategy in patients with class I obesity at least in the medium term. Adverse event's rate in class I obese patients appears to be the same than in morbid obesity.
(4) Access to bariatric surgery should not be denied to a patient with class I obesity associated to significant obesity-related co-morbidity simply on the basis of the BMI level, which alone is an inaccurate index of adiposity and a poor health risk predictor. Patients with class I obesity who are not able to achieve adequate weight loss after a reasonable period of nonsurgical therapy should be considered for bariatric surgery.
(5) Bariatric surgery should be considered in patients with class I obesity on an individual basis and after a comprehensive clinical evaluation of the patient's global health and a prediction of its future disease risk. The use of bariatric surgery in patients with class I obesity should be considered only after failure of proper nonsurgical therapy.
(6) Indication to bariatric surgery in class I obesity should be based more on the comorbidity burden than on BMI levels. Comorbidities should be evaluated considering their likely response to surgery and in relation to how they can be treated by established medical therapies.
(7) The use of bariatric surgery should be avoided in patients with class I obesity and advanced obesity-related or obesity-unrelated comorbidities (frailty patients), in which intentional weight loss may not have any beneficial effect on prognosis or may be harmful.
(8) The use of bariatric surgery cannot be currently recommended in children/adolescents or in elderly obese patients with class I obesity.
(9) National and regional health providers need to consider the current evidences favoring the application of bariatric surgery in class I obesity in the context of local health resources and deliver services that are locally appropriate.
(10) Published literature on bariatric surgery in class I obesity is small and hampered by many factors related to poor study design, short follow-up, and diversity of clinical definitions. Accrual of controlled long-term data is strongly advised. The introduction in clinical practice of novel procedures and new devices should be guided by the results of appropriately designed research protocols conducted with the highest levels of ethical behavior.

Position Statements

Introduction

The Global Pandemic

The global pandemic of obesity continues to progress globally. The causes of this pandemic are complex. To date, any attempts to control the trends of the pandemic appear ineffective.

Achieving and Sustaining Weight Loss is Difficult

Regulatory processes that maintain body fatness are highly efficient and any increase in weight is defended physiologically. Multiple interventions assist in inducing and maintaining weight loss including lifestyle changes, specific diets, medications, devices, and surgery. The extent to which sustained weight loss can be achieved varies with the intervention.

Need for Effective Treatment

Obesity is a chronic disorder requiring a chronic disease model of care. Combining interventions and scaling-up therapy for serious or resistant disease are usual parts of chronic disease models of care.

Responsibility

The International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) recognizes its responsibility in developing evidence-based position statements regarding new and emerging areas related to bariatric and metabolic surgery. This draft position statement examines the use of bariatric surgery in the class I obesity range (BMI 30–35 kg/m^2).

Impact of Class I Obesity on Health

Mortality

Most recent epidemiologic data suggest that the BMI range with the lowest mortality is in the overweight range, with the risk for the normal weight and that of class I obesity being similar. Mortality rates are increased only in patients with BMI > 35 kg/m^2. The effect of intentional weight loss on mortality is unclear for patients with class I obesity.

Risk of Comorbidity

The risk of developing type 2 diabetes, hypertension, dyslipidemia, metabolic syndrome, obstructive sleep apnea, polycystic ovary syndrome, depression, osteoarthritis, and nonalcoholic fatty liver is increased in class I obesity. Class I obesity is clearly associated with an increased risk of many cancers. Class I obesity impairs physical and mental health-related quality of life and it is associated to an increased psychosocial burden, particularly in women.

Nonsurgical Therapy for Class I Obesity

Treatment Goals

The objective of nonsurgical obesity therapy is to achieve and sustain a weight loss of as much as 10 % of initial body weight. This degree of weight loss is considered to be safe and sufficient to obtain a significant improvement of general health in patients who are overweight or have class I obesity.

Lifestyle Modification Programs

Randomized controlled trials (RCTs) demonstrated that lifestyle modification programs may achieve a weight loss of 5–7 % in approximately half of the patients. This modest weight loss is only partly maintained over time, but may convey important health benefits such as diabetes prevention in at-risk populations and improved metabolic control in patients with type 2 diabetes. Prevention of cardiovascular events was not achieved.

Meal replacements and Very Low Calorie Diets

The use of meal replacement programs and very low energy diets may induce greater weight loss than conventional diets in the short term. However, it is not clear whether the initial weight loss advantage obtained would result in a better weight loss maintenance over the long term.

Current Pharmacologic Approaches

Pharmacotherapy of obesity is rapidly evolving, with many new drugs or combination drugs moving closer to clinical use. Many of these drugs seem to have the capability to potentiate significantly the effects of life-style modifications, with 25–50 % of patients achieving the 10 % weight loss target. Weight maintenance seems also to be facilitated. However, long-term results (>2 years) are currently available only for orlistat. Long-term efficacy, tolerability, and adverse events of new combination and single drug regimens remain to be established.

Endoscopic Procedures

The intra-gastric balloon, several forms of transoral/endoscopic gastric partitioning, and novel endoscopic devices mimicking the effect of the exclusion of the proximal intestine have been proposed as less invasive alternatives to bariatric surgery. The efficacy, safety, durability, and long-term clinical utility of these procedures remain to be established.

The Current Position of Bariatric and Metabolic Surgery for Class I Obesity

International Diabetes Federation

The International Diabetes Federation (IDF) experts suggested that diabetic patients with class I obesity may be eligible, but not prioritized, for surgery if they have poorly controlled diabetes despite fully optimized conventional therapy, especially if their weight is increasing or other weight-responsive comorbidities are not achieving targets on conventional therapy.

American Society for Metabolic and Bariatric Surgery

The American Society for Metabolic and Bariatric Surgery (ASMBS) Clinical Issue Committee stated that bariatric surgery should be an available option for suitable patients with BMI 30–35 kg/m^2 who do not achieve substantial and durable weight and comorbidities improvement with nonsurgical methods.

Beyond BMI in the Selection/Prioritization of Obese Patients for Surgery

BMI Alone is a Poor Index of Adiposity

BMI is used in epidemiological and clinical practice to diagnose and categorize obesity. Eligibility to bariatric surgery has been based so far largely on BMI cut-offs. However, the use of BMI as a proxy for adiposity, the true determinant of the obese

state, is misleading, giving that its value is influenced also by skeletal muscle and organs mass.

Beyond BMI in the Definition of Cardiometabolic Risk in Obesity

Patients in class I obesity may have very different levels of health and risks at the same BMI level. Visceral fat accumulation and the presence of ectopic fat deposition in relevant organs are the most important determinants of cardiometabolic risk in class I obesity. BMI does not convey any information on these biological body components.

Beyond BMI in Phenotyping Obese Patients

The use of only BMI in the selection of obese patients for surgery should be abandoned. A clinical decision should be based on a more comprehensive evaluation of the patient's global health and on a more reliable prediction of its future disease risk.

Obesity Scoring Systems

The use of a score that could quantitatively represent the actual and future health burden that obesity induces in the individual patient would be an important tool for clinicians for phenotypization beyond BMI levels and for guiding therapeutic choices. The validation and application of obesity scoring systems or algorithms should be implemented.

Surgery in Class I Obesity: "What Do We Know" and "Identify Gaps"

Randomized Controlled Trials

Four RCTs evaluated the results of bariatric surgery in samples including patients with class I obesity and one was specifically conducted in patients with class I obesity. All the studies reported consistent weight loss and comorbidities improvements.

Meta-Analysis and Systematic Reviews in Patients with Type 2 Diabetes

Comprehensive reviews evaluated nonrandomized prospective and retrospective studies in patients with type 2 diabetes and BMI < 35 kg/m^2. Both traditional and experimental procedures were included. Weight loss, diabetes remission rates, and improvements in lipids and metabolic syndrome were judged to be as good as in morbid obese patients.

Prospective Observational Studies and Retrospective Studies

Multicenter or single-site, observational, prospective, or retrospective studies analyzed the outcome of class I obese patients sorted out from general bariatric surgery series and reported satisfactory weight loss, with resolution or improvements of comorbidities.

Final Summary

A comprehensive evaluation of the randomized control trials, meta-analysis, and prospective or retrospective studies demonstrated that overall weight loss was excellent in patients with class I obesity after all the most established bariatric procedures, with some studies reporting better excess weight loss in this group of patients compared to patients with morbid obesity. Adverse event's rate in class I obese patients appears to be the same than in morbid obesity, with some studies reporting serious adverse events.

Limitations

RCTS are few and observational studies contain several methodological deficiencies, with lack of control data, propensity to bias, and lack of information. Length of follow-up is short (<2 years) in most of the studies in patients with class I obesity. Shortness of follow-up limits our knowledge on the long-term risk / benefit ratio of surgery in this subset of patients. In particular, potentially serious effects of the profound weight loss produced by surgical procedures on nutritional status and body composition cannot be evaluated. Finally, reliable information about the effects of bariatric surgery on longevity in patients with class I obesity remains completely lacking.

Special Considerations Regarding Patient Selection

Ethnicity

The risk of metabolic syndrome and type 2 diabetes varies with ethnicity. Adjusted BMI action cut points for Asians or other high-risk ethnic groups are recommended.

Age

The use of surgery should not be extended in children and adolescents with BMI < 35 kg/m^2 as long as its efficacy and safety would be not more firmly proved in adults. Data about efficacy and safety of surgery in class I obese adolescents are lacking. The optimal weight for lowest mortality appear to be in the overweight/class I obesity range in the elderly and there is no clear guidance regarding intentional weight loss in older adults, as it is unclear that benefits outweigh risks. The use of

bariatric metabolic surgery cannot be currently recommended in older adults with a BMI < 35 kg/m^2.

Regional, Economic, and Equity Considerations

There are regional variations in access to bariatric metabolic surgery and regional differences in the regulatory and economic conditions that may limit the direction of surgery for patients with class I obesity. National and regional health services providers need to consider the evidence and deliver services that are locally appropriate.

Comorbidity

Metabolic, mechanical, and psychological comorbidities of obesity often cluster and are associated with increased risk of morbidity and mortality that is poorly related to BMI. In indicating bariatric metabolic surgery in patients with class I obesity, comorbidities should be evaluated considering their likely response to surgery and in relation to how they can be treated by established medical therapies.

Low BMI as a Consequence of Previous Medical or Surgical Therapy

BMI criterion for election to bariatric metabolic surgery should be the current BMI or a documented previous BMI of this severity. Surgery may be indicated at low BMI levels in patients who exhibited a substantial weight loss in a conservative treatment program but started to gain weight again or in bariatric patents having reached a low BMI after a first intervention, but requiring redo surgery for complications or side effects.

Research Gaps and Priorities

Long-Term Outcomes

One of the biggest deficiencies of the prevailing literature concerning both conventional and nonconventional surgical procedures for BMI < 35 kg/m^2 is the lack of long-term outcome data. It would be reasonable to suggest that adequate postoperative follow-up for the sake of investigational data collection and procedure evaluation should be no less than 3 years and preferably 5 years.

How to Assess new Procedures, Devices, and Techniques

All new procedures, devices, and techniques mandate rigorous assessment before being offered to patients. To minimize harm, new procedures should undergo extensive preclinical investigation. After demonstration of efficacy and safety, the procedure should be rigorously evaluated in carefully designed clinical human trials, with small open-label feasibility trials performed first and larger-scale investigations with sufficient follow-up thereafter. If feasible, a randomized sham-controlled trial should be performed. Each procedure or device, having different safety profiles, degree of complexities, and outcome results, should be judged by its own defined set of criteria. Procedures that are less radical, less complex, and/or less risky can be acceptable even if they result in significantly less benefit than more complex procedures that have higher complication profiles.

Reporting Weight Loss Outcomes

There is still no scientifically validated and universally accepted method for measuring and recording weight loss outcomes. Professional medical societies and medical journals still differ on the preferred method.

Measuring and Reporting Comorbidity Outcomes

Universal standard definitions for comorbidity outcomes need to be instituted for clinical practice and research protocols. This would include a uniform acceptance of the definition of each disease state, a uniform definition of the chemical markers used to label a patient with suffering from a particular disease, a uniform terminology for determining the severity of the disease, uniform and scientifically based criteria for the various outcomes after surgery, and consensus on what constitutes “best” medical therapy.

Is There a Need for a Large RCT Looking at Hard Outcomes?

RCTs represent the highest standard in clinical investigation. Randomizing patients to different study groups dramatically reduces differences, inequalities, and biases between study and control subjects. However, RCTs are difficult to conduct in the field or bariatric surgery and large long-term RCTs present formidable challenges.

Ethics of Surgery for BMI < 35 kg/m^2

The ethical behavior for studying or treating patients whose BMI < 35 kg/m^2 by surgical interventions should be rigorous. While there is an overwhelming body of evidence that concludes that bariatric surgery is safe and effective for patients whose BMI ≥ 35 kg/m^2, it cannot be assumed that the results would be the same for patients with BMIs < 35 kg/m^2. Novel metabolic operative procedures and devices are still investigational and must be treated as such. Standard rules of ethical research needs to be applied to patients in class I obesity.

Introduction

Global Pandemic—Complex Determinants—Obesity Prevention

The global pandemic of obesity with its associated comorbidity has progress steadily and inexorably since the late 1970s and foreseeably the most serious and costly health issue for this century. The magnitude of rise has varied with region, country, and with gender; however, stabilization of the obesity prevalence is rare, and of great concern, the rise has accelerated globally over the last decade. The global age-standardized prevalence of obesity [body mass index (BMI) ≥ 30 kg/m^2] nearly doubled from 6.4 % in 1980 to 12.0 % in 2008. Half of this rise occurred in the 20 years between 1980 and 2000 and half occurred in the 8 years between 2000 and 2008 [1]. With increasing levels of obesity we see an exponential rise in class III obesity (BMI > 40 kg/m^2). In the US between 2000 and 2005, the prevalence of obesity increased by 24 %, class III obesity by 50 % and BMI > 50 kg/m^2 increased by 75 %, two and three times faster, respectively [2]. The resultant exponential increase in class III obesity and super obesity is an expected trend as the mean BMI for a community steadily increases. Sadly, no part of the globe is protected from the obesity pandemic, and the transition from undernourished to overnourished occurs with alarming speed in developing countries in both urban and rural regions [3].

The causes of this pandemic are complex and extend beyond the relevant, but overly simplistic, view that it is driven by western fast food diets and sedentary nature of modern living. Genetics, metabolic programming, epigenetic changes, increasing maternal age, and assertive mating set the baby born today up for an aberrant interaction with today's environment generating an almost inevitable problematic weight trajectory for the majority. Arguably the most important 4 years for an individual weight trajectory for life are the 4 years prior to their third birthday. In addition many aspects of modern living imperceptibly and passively contribute to the issue: shorter sleeping hours, increase screen time, temperature-controlled environments, endocrine modifiers, and medications for many chronic conditions increasing weight.

The complexity of the determinants of this pandemic generate major challenges in prevention and arguments regarding the degree of personal responsibility and blame vs. the need for a widespread environmental makeover with greater regulation lead to philosophical stalemates, commercial conflicts, and systematic inertia. To date, any attempts to control the trends of the pandemic appear piecemeal, tokenistic, and ineffective.

Achieving and Sustaining Weight Loss is Difficult

Regulatory processes that maintain body weight and body fatness are highly efficient and physiologically critical for protecting life in a similar way to maintaining blood pressure, temperature, and blood glucose. It is extraordinary how accurate regulation is for body weight and what drives the dysregulation that leads to a tiny but regular increase in weight in obese individuals is poorly understood. Unfortunately, any increase in weight is defended physiologically in a similar way in which a person with hypertension defends and inappropriately high blood pressure and therapy needed. Multiple interventions assist in generating and maintaining weight loss including lifestyle changes, specific diets, physical activity, medications, devices, and surgery. The extent to which sustained weight loss can be achieved varies with the intervention used, and there is also great variability within interventions suggesting individual differences in response are important.

Need for Effective Treatment

Obesity and related disorders that it generates are chronic conditions requiring a chronic disease model care. As for any chronic disorder, a cure of the condition is an ultimate goal, but difficult to achieve. Obesity is no exception. We can manage obesity, but to date have no cure and we need a range of effective therapies. As for all chronic disease management, we engage the informed patient actively in the management decision-making process for long-term care with the ultimate aim of using evidence-based interventions to improve long-term outcomes. Combining interventions and scaling-up therapy for serious or resistant disease are usual parts of this continuum of care.

All interventions have a range of benefits and risks, and this need to be balanced for each individual. Medications used to treat diabetes and cardiovascular risks sometimes appear to have benefits beyond their initial primary target: metformin an effect beyond glycemic control, statins effects beyond an influence on LDL-cholesterol, and angiotensin-converting-enzyme inhibitors beyond blood pressure. Similarly bariatric procedures originally designed primarily for weight loss have effects beyond that weight loss. These additional benefits may alter the indications for therapy, but can also come at a cost with unexpected downsides. One only needs to look at the medications used for weight management and to treat type 2 diabetes for unexpected downsides, and it would be naive to expect that interventions targeting the GI tract using surgery or devices and having effect on complex biological systems would be exempt from similar unfavorable downsides.

The International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) recognizes its responsibility in developing evidence-based position statements to guide its members, and health services providers generally, regarding new and emerging areas related to bariatric and metabolic surgery. Extending the indications for bariatric–metabolic surgery beyond traditional boundaries defined by age, body mass

index, level of comorbidity, and operative risk is such an area. This position statement examines the use of bariatric–metabolic surgery and devices in the class I obesity range (BMI 30–35 kg/m^2) with the appropriate adjustment for ethnicity.

The process, led by IFSO president-elect Luigi Angrisani in 2013–2014, commenced with the development of an expert working group:

(1) To critically review the current knowledge regarding the epidemiology, health risks, and current therapies for those with class I obesity;
(2) To review the evidence for bariatric metabolic surgery in those with class I obesity: efficacy and safety, relative risk and benefit, and effect on obesity-related comorbidity;
(3) To examine the broader issues involved from a health care prioritization and delivery perspective in of extending bariatric–metabolic surgery to the class I obese range;
(4) To develop practical recommendations for clinicians;
(5) To identify gaps in our present knowledge and identify priorities for clinical research in using established bariatric–metabolic procedures; and
(6) To provide guidance regarding development and introduction of novel procedures and devices for bariatric metabolic surgery.

Impact of Class I Obesity on Health

To assess the place of bariatric–metabolic surgery in those with class I obesity (BMI 30–35 kg/m^2), we need to understand the risk associated with this BMI range. It is also important to consider that the great majority of obese individuals are in the class I obese category with considerable public health and health economic impact. In the US Centers for Disease Control and Prevention (CDC), data indicate that approximately 2/3 of obese men are in the class I obese range, and 50 % of obese women are in the class I obese range.

Mortality

Most recent epidemiologic data suggest that the BMI range with the lowest mortality is actually the overweight range (BMI 25–30 kg/m^2) with the risk for the normal weight range (BMI 18.5–25 kg/m^2) and that of class I obesity range similar [4]. Mortality rates are increased in those with a BMI of 35 kg/m^2 or greater. These findings are common across multiple countries and ethnic groups. This data comes from 97 studies providing a combined sample size of more than 2.88 million individuals and more than 270,000 deaths. When examining years of life lost related to obesity, overweight and class I obesity are not associated with a reduced life expectancy [5]. In those of East Asian ethnicity, there was an increased mortality with class I obesity, but in South Asians, there does not appear to be an increase [6]. However, action BMI cut points for Asia are reduced by 2.5 kg/m^2 to BMI 27.5, 32.5, and 37.5 kg/m^2, respectively [7]. There are difficulties looking at specific causes of mortality as obesity is often not split into BMI subclasses. As class I obesity is not associated with a major overall increased mortality risk, then are there subgroups that are at increased risk?

Type 2-diabetes is often the disease that generates interest in lower BMI bariatric–metabolic surgery, however, those with diabetes and a BMI in the class I obese range may have the lowest risk of mortality. The weight status at the time of diabetes diagnosis was examined in relation to mortality in five major longitudinal studies. Overweight and obese had lowered all cause, cardiovascular, and noncardiovascular hazard ratios. These were not altered after adjustment for demographics, smoking, and cardiovascular risk factors [8]. Two additional studies have demonstrated a nadir of mortality in class I obese individuals [9, 10]. Data from the PROactive study, a randomized trial using pioglitazone, demonstrated an increased mortality with weight loss and a reduction with weight gain [10]. A follow-up study of men with diabetes attending US Veteran Affairs clinic found an inverse association between BMI and mortality [11]. This pattern extends to Taiwan where there was also an inverse relationship between BMI and mortality in those with type 2 diabetes [12]. It is of note that this mortality data in those with diabetes has largely been published since 2011 and therefore represent a recent clinical consideration. In addition, the early cessation of the Look Ahead study for failing to demonstrate hard cardiovascular and mortality advantage in overweight and obese participants to an intensive lifestyle program including intentional weight loss [13] raises questions about the value of intentional weight loss in overweight and obese (class I) individuals with type 2 diabetes. Of course bariatric surgery has demonstrated a mortality advantage in severely obese patients with and without diabetes, but these studies were all restricted to those with conventional BMI indications for surgery (BMI > 35) and where an increased overall mortality is demonstrated [14].

The last decade has seen a puzzling array of data demonstrating a mortality advantage in overweight and obese patients with cardiac failure, myocardial infarction, coronary artery disease, post-coronary bypass surgery, and renal failure compared with those of normal weight [15, 16]. Indeed there appears to be a U-shaped relationship between BMI and mortality with the nadir shifted up in BMI with many diseases and with aging [17].

In summary, mortality risk for those with class I obesity may be higher than for overweight individuals, but similar to those of the normal weight range, when all of the adult studies are combined. However, with aging and in many disease

states, the nadir for mortality risk increases to a higher BMI level, and under these circumstances, mortality risk of those with class I obesity may appear to be lower than those in the normal weight range. Many issues may confound these results, for example, smoking and issues related to illness and unintentional weight loss. The effect of intentional weight loss on mortality is unclear for those in the class I obese range and requires careful research. From a mortality perspective, the risk with surgery vs. the benefit with surgery is shifted toward risk, when compared with those with classes II and III obesity, as surgery itself is always associated with risk, and any additional benefits and risks of surgery are unknown. Bariatric–metabolic surgery in patients in the class I obese range generates major improvements in diabetes and cardiovascular risk factors, however, this may not translate to mortality benefit and there is the potential that intentional weight loss may increase mortality risk for some patient groups.

Risk of Comorbidity

The risk of developing type 2 diabetes increases progressively with increasing BMI. The adjusted relative risk of developing type 2 diabetes is 93 times higher in women with BMI 35 kg/m^2 than in women with normal BMI, and 42 times higher in men with BMI 35 kg/m^2 than in women with normal BMI, but a significant increase in prevalence is observed also in class I obesity [18, 19]. There is also consistent and impressive data from lifestyle programs and bariatric surgery that weight loss reduces the risk of developing type 2 diabetes [20–22]. The risk of developing hypertension also increases progressively with BMI and the prevalence is 18 % in those with a normal BMI and 39 % in those with class I obesity [23]. Dyslipidemia has a complex association with BMI, with the highest risk in the BMI 30–40 kg/m^2 range and a reduction in risk at greater BMI levels [24]. These risk prevalence data would suggest that cardiovascular mortality would be considerably increased in the class I obese population but the risk, if any, is modest when looking at epidemiological data. The risk of obstructive sleep apnea, polycystic ovary syndrome, metabolic syndrome, depression, osteoarthritis, and nonalcoholic fatty liver are all increased with class I obesity when compared with a normal weight population [25].

BMI is linked in a positive way to the risk of many cancers, and cancer incidence increases progressively with increasing levels of obesity. In men, a 5 kg/m^2 increase in BMI is strongly associated with esophageal adenocarcinoma and with thyroid, colon, and renal cancers. In women, strong associations are with endometrial, gallbladder, esophageal adenocarcinoma, and renal cancers. Other cancers have weaker associations with obesity [26]. However, class I obesity is clearly associated with an increased risk of many cancers.

Quality of Life, Psychosocial Burden, and Costs

There is consistent evidence that obesity impairs physical and mental aspects of health-related quality of life. The effect is graded with increasing levels of obesity, and utility-based quality of life measures are important when wanting to perform health economic studies of cost effectiveness [27]. Patients seeking bariatric–metabolic surgery report poorer health-related quality of life than matched controls not seeking a surgical solution [28].

There are many psychosocial demographic factors associated with obesity and these can vary with ethnicity. Depression, low self-esteem, binge-eating disorder, lower employment opportunity, and stigmatization and discrimination all tend to have greater impact on women and all increase with increasing levels of obesity. Obesity, diabetes, and depression are conditions that all cluster together in low socioeconomic groups [29]. Levels of conditions such as depression and binge-eating disorder are higher in those seeking surgery than those of the same BMI in the general community [30, 31]. Taken together, these issues raise concern about equity of access to bariatric–metabolic surgery and are important considerations to those providing national health care service delivery.

The overall health costs related to obesity are estimated to be 4–8 % of health budgets and growing. The personal costs to the individual are considerable and include additional health costs, reduced employment, employment opportunity, employment discrimination and lower income, and increased disability, injury, and likelihood of requiring social support through pensions [32]. These costs are partly borne by the community, and in addition, lost productivity related to obesity through absenteeism and presenteeism are considerable and also grade up with increasing BMI and especially in the classes II and III obese categories [33].

Conclusion

The impact of class I obesity on mortality is considerably less than that of classes II and III obesity and the benefit of bariatric metabolic surgery in terms of longevity may be far more difficult to define. The role of substantial intentional weight loss on total mortality, while providing a logical therapy, is yet to be determined in the overweight and class I obese range. Class I obesity conveys an increased risk of comorbidities, impairs physical and mental health-related quality of life, and it is associated to an increased psychosocial burden, particularly in women.

Nonsurgical Therapy for Class I Obesity

Introduction

Current treatment guidelines set the objective of nonsurgical obesity therapy to achieve and sustain a weight loss of as much as 10 % of initial body weight for a period of time [34, 35]. This degree of weight loss is considered to be safe and sufficient to obtain a significant improvement of general health in patients who are overweight or have class I obesity. More ambitious levels of weight loss are generally required for patients with class II or class III obesity, the population in which bariatric surgery is currently recommended [34, 35].

A systematic review of randomized controlled trials (RCTs) conducted with traditional diet programs tends to demonstrate that the mean weight loss obtained in the first year of treatment is generally inferior to the abovementioned therapeutic objectives, and this weight loss is rarely maintained over time [36]. The adherence of obese patients to dietary regimens tends to reduce after the first 6 months, and a total or partial weight regain was usually observed thereafter. However, some patients were able to achieve and maintain a 10 % weight loss [36]. Additionally, some health benefits were observed at even less than a 10 % body weight loss. In this chapter, we briefly review the results of current nonsurgical treatment options for class I obesity including long-term lifestyle modification programs, meal replacements, very low calorie diets, current pharmacologic approaches, and novel endoscopic procedures.

Lifestyle Modification Programs

Two large seminal randomized control trials (RCTs) tested the efficacy of lifestyle modification programs for the prevention of type 2 diabetes in high-risk populations [37, 38]. These trials were not specifically conducted in the overweight or patients with class I obesity, but were instead conducted on participants whose mean baseline BMI was in the 30–35 kg/m^2 range [4, 5]. In the Finnish Diabetes Prevention Study [37], 523 overweight or obese patients with impaired glucose tolerance (BMI ≥ 25 kg/m^2; mean BMI in the intervention group: 31.3±4.6 kg/m^2) were randomly assigned to standard care or to an intensive lifestyle intervention with specific dietary and physical activity goals including the achievement and maintenance of a weight loss of at least 5 % of initial body weight. During the first year of the study, body weight decreased by a mean of 4.7 % in the intervention group. However, only 43 % of patients in the intervention group had a weight loss greater than 5 % of initial body weight and in the second year of the study, weight regain was observed. On a positive note, the study did demonstrate that the 4-year cumulative incidence of diabetes was 58 % lower in the intervention than in the control group ($p<0.001$) [37]. Moreover, a prolonged protective effect of lifestyle modifications on diabetes was observed years after the termination of the trials, when most of the effects of the intervention program on body weight were no longer evident [21]. In the Diabetes Prevention Program (DPP) [38], 3,234 overweight or obese patients with impaired glucose tolerance (BMI ≥25 kg/m^2; mean BMI 34.0±6.7 kg/m^2) were randomly assigned to standard care, to standard care plus metformin, or to an intensive lifestyle intervention program. The goals for the participants assigned to the intensive lifestyle intervention were to achieve and maintain a weight reduction of at least 7 % of initial body weight through a healthy low-calorie, low-fat 4diet and to engage in physical activity of moderate intensity for at least 150 min/week. Only half of the participants in the lifestyle intervention group achieved a 7 % weight loss during the program and this weight loss was only partly maintained over the 4-year follow-up. However, the incidence of diabetes was again 58 % lower in the lifestyle intervention group than in the placebo group and also 39 % lower than in the metformin group [38]. Additionally, the DPP population has been followed beyond the 4 year initial study period and continues to demonstrate an advantage in diabetes prevention with life-style modification at even 6 years out [22]. A broad range of diabetes prevention studies have been conducted in developing countries in high-risk populations and all have been shown to be effective [39].

The Look AHEAD study was a very large RCT that also examined the effects of an intensive lifestyle intervention on the incidence of major CVD events in 5,145 overweight or obese individuals with type 2 diabetes (BMI ≥25 kg/m^2; mean BMI in the intervention group: 36.3±6.2 kg/m^2 in women and 35.3±5.7 kg/m^2 in men) [40]. Patients were randomly assigned to conventional diabetes support and education or to an intensive lifestyle intervention program with a 10 % weight loss goal. Over the first year, the intensive lifestyle intervention group lost an average of 8.6 % of initial body weight, with 37.8 % of participants having a greater than 10 % weight loss, and 55.2 % of subjects achieved a greater than 7 % weight loss [40]. Participants in the intensive lifestyle intervention maintained a mean weight loss of 4.7 % at year 4 of the study [41]. This moderate but sustained weight loss was associated to improvements in fitness, glycemic control, and CVD risk factors [41] and to very small rates of complete diabetes remission [42]. However, the National Institutes of Health decided to prematurely halt the Look AHEAD trial because of a failure to achieve a significant reduction in the occurrence of cardiovascular events in the intervention group [13].

In summary, RCTs demonstrated that lifestyle modification programs may achieve a modest weight loss of 5–7 % but only in approximately half of the patients. This modest weight loss is only partly maintained over time, but may still convey important health benefits, such as diabetes prevention in at-risk populations and improved metabolic control in patients with type 2 diabetes.

Meal Replacements and Very Low Calorie Diets

Meal replacement programs are low-calorie diet plans whereby one or two meals of the day are replaced by commercially available, energy-reduced products that are vitamin- and mineral-fortified. These programs have been proposed as more effective weight reduction strategies in obese patients than conventional diets. A meta-analysis that analyzed six short-term studies of liquid meal replacements indicated that weight loss was greater in the meal replacement groups when compared to the calorie equivalent traditional diets, with an average 7–8 % body weight loss in the meal replacement group compared with an average 3–7 % body weight loss in the conventional diet group [43]. However, it is not clear whether the initial weight loss advantage obtained by meal replacement strategy would result in a better weight loss maintenance over the long term.

Very low energy diets (VLEDs) are defined as diets that provide less than 800 kcal/day. They are usually prescribed as a synthetic or food-based formulation of 450–80 kcal/day, provided high levels of protein, and supplemented with vitamins, minerals, electrolytes, and fatty acids. VLEDs are second to surgery in generating weight loss and the ketosis generated by low carbohydrate intake and in utilizing stored fat for energy provides suppression of appetite by altering some of the physiological changes to weight loss [44]. VLEDs have been proposed as a more effective method for weight loss in obese patients. The efficacy and safety of modern VLEDs in obese patients [45] and in obese patients with type 2 diabetes [46] have been recently revisited. In summary, the use of a course of VLED may safely produce a large initial weight loss, in the order of 1.5–2.5 kg/week. Obese patients treated by VLEDs may have better long-term weight maintenance than patients treated by more conventional diet [47], and even a more effective weight maintenance may be observed in those obese subjects with higher initial weight loss results [48]. In summary, VLEDs require careful physician supervision, but generally provide better sustained weight loss than other dietary methods and can be used intermittently or on demand to maintain weight loss [49]. VLCDs have an important role in reducing liver size prior to bariatric surgery [50].

Current Pharmacologic Approaches

The history of drug treatments for obesity has been one of recurrent optimism followed by failure, with many promising drugs coming into clinical practice only for being subsequently withdrawn for unexpected side effects [51]. Currently, the only drug worldwide approved for weight loss treatment with a 15-year-long clinical experience is orlistat, a gastrointestinal lipase inhibitor [52]. In the XENDOS study, the longest duration RCT published thus far with orlistat, 3,505 obese patients (BMI $\geq$ 30 kg/m^2; mean BMI in the intervention group: 37.4±4.5 kg/m^2) were randomly assigned to orlistat plus lifestyle changes or to placebo plus lifestyle changes [53]. Mean weight loss was significantly greater for the orlistat group than the placebo group at 1 year (10.6 vs. 6.2 kg) and remained significantly greater at the end of the 4-year study (5.8 vs. 3.0 kg). Significantly more orlistat patients (41.0 %) than placebo patients (20.8 %) achieved a weight loss greater than or equal to 10 % after 1 year of treatment and for those patients who completed 4 full years of treatment, 26.2 and 15.6 %, respectively, lost greater than or equal to 10 % of baseline body weight [53]. Additionally, a 37.3 % decrease in the risk of developing diabetes was observed in the orlistat group as compared to placebo [53].

Apart from orlistat, many new drugs or combination of drugs are now in advanced phases of clinical research and/or entering clinical practice. Lorcaserin, a selective serotonin 2C receptor agonist, has been tested against placebo in the Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) trial, a 2-year RCT that enrolled 3,182 obese patients with BMI of 30–45 or 27–45 kg/m^2 with at least one coexisting condition [54]. At the end of the first year of the study, patients in the lorcaserin group lost an average of 5.8 % of the baseline body weight, as compared with 2.1 % in the placebo group ($P<0.001$). In addition, a greater percentage of patients lost 10 % or more of their baseline body weight in the lorcaserin group (22.6 %) than in the placebo group (7.7 %). For year 2, patients who had been receiving placebo continued to receive it, whereas patients who had been receiving lorcaserin were again randomly assigned either to continue to receive lorcaserin or to begin to receive placebo. Among patients in the lorcaserin group who had weight loss of 5 % or more at year 1, the loss was maintained in a greater proportion of patients who continued to receive lorcaserin in year 2 compared with those who were reassigned to receive placebo (67.9 % vs. 50.3 %) [54]. Lorcaserin was approved for clinical use in the US by the Food and Drug Administration (FDA) in 2012.

In the CONQUER study, a combination drug regimen with low dose of phentermine and topiramate was tested for two different formulations (7.5 mg phentermine/46 mg controlled release topiramate or 15 mg phentermine/92 mg controlled release topiramate) against placebo in 2,487 subjects with a BMI greater than or equal to 27 and less than or equal to 45 kg/m^2 as well as suffering from more than two weight-related comorbidities [55]. Phentermine is a central norepinephrine-releasing drug approved in some countries for short-term treatment of obesity as monotherapy and topiramate is an anticonvulsant that has shown unexpected weight-loss properties. After 56 weeks, the change in body weight was −1·4, −8·1, and −10·2 kg in the patients assigned to placebo, phentermine 7.5 mg plus topiramate 46 mg, and phentermine 15 mg plus topiramate 92 mg, respectively. The percent of

patients achieving a weight loss greater than or equal to 10 % was 7, 37, and 48 %, respectively [55]. Of the 866 completers of the CONQUER study, 676 was subsequently enrolled in an extension SEQUEL study and continued receiving their blinded treatments for an additional 52 weeks [56]. In this extension trial, the difference in weight loss observed in the three treatment arms in the first year was maintained even in the second year [56]. In 2012, the combination drug phentermine/topiramate was approved for limited clinical use in the US by the FDA. This combination medication was rejected by the EMA for use in Europe because further evidence of cardiovascular safety was required.

Finally, the efficacy and safety of a combined treatment with sustained–released naltrexone and bupropion was tested in patients with BMI 30–45 kg/m^2 and uncomplicated obesity or with BMI 27–45 kg/m^2 and controlled hypertension or dyslipidemia. In two independent 56-week RCTs (COR-I and COR-II) [57, 58], weight loss was significantly higher in the combination therapy groups than in the placebo groups. Weight loss greater than or equal to 5 % was achieved by 16 % participants assigned to the placebo group and 48 % assigned to naltrexone 32 mg plus bupropion in COR-I [57] and in 17.1 and 55.6 %, respectively, in COR-II [58]. This combination preparation was rejected by the US FDA because further evidence of cardiovascular safety was required.

Liraglutide is a glucagon-like peptide-1 (GLP-1) analog with a 97 % structural homology to human GLP-1. Native GLP-1 has a short elimination half-life of 1–2 min, whereas liraglutide has a much longer half-life and can be administered once daily by subcutaneous injection. Liraglutide was initially developed for the treatment of type 2 diabetes mellitus as it was shown to decrease glycosylated hemoglobin and, at the same time, to reduce body weight [59, 60]. The weight loss observed by liraglutide treatment in patients with type 2 diabetes supported the investigation of the drug as an anti-obesity treatment, for overweight and obese subjects without type 2 diabetes. Astrup and coworkers [61] randomized 563 obese patients (BMI 30–40 kg/m^2) without type 2 diabetes to liraglutide (1.2, 1.8, 2.4, or 3.0 mg once a day by subcutaneous injection), placebo or orlistat for a 20-week trial. Participants on liraglutide lost significantly more weight than did those on placebo and orlistat. Additionally, a greater number of individuals lost more than 5 % weight with liraglutide 3·0 mg (76 %) than with placebo (30 %) or orlistat (44 %). Completers of this first short study entered an extension 2-year RCT, continuing on randomized treatment for 1 year, after which liraglutide- or placebo-treated individuals switched to liraglutide 2.4–3.0 mg and orlistat was continued as the only comparator. At the end of the trial, 52 % of the patients on liraglutide 3.0 mg had a weight loss greater than 5, and 26 % of subjects had a weight loss greater than 10 %, while corresponding figures in the orlistat group was 29 and 16 %, respectively [62].

On the basis of this short overview of recent anti-obesity drugs RCTS, we can conclude that pharmacotherapy of obesity is now rapidly moving forward, with many new drugs or combination drugs with a very diverse spectrum of mechanisms of action moving closer to clinical use. Many of these drugs seem to have the capability to potentiate significantly the effects of lifestyle modifications on body weight, whereas 25–50 % of patients can achieve the 10 % weight loss target. Weight maintenance seems also to be facilitated. However, long-term results (>2 years) are currently known only for orlistat (the least potent of the medications described above). Long-term efficacy, tolerability, and adverse events of these new combination and single drugs regimens remain to be established.

Endoscopic Procedures

The intra-gastric balloon, a temporary 6-month endoscopic gastric restriction procedure where an inflatable balloon is endoscopically inserted into the stomach, has been widely used for weight loss purposes in some countries for patients with class I obesity [63]. However, no prospective controlled observations have supported the hypothesis that intra-gastric balloon treatment would achieve better weight loss than diet in the long term and the procedure itself is invasive and not free from side effects and mortality [63]. Several forms of transoral/endoscopic gastric partitioning using various locations, techniques, and devices have been proposed as less invasive alternatives to surgical gastric restriction [64]. There are also under development novel endoscopic [65] or mixed endoscopic laparoscopic [66] devices meant to mimic the effect of the exclusion of the proximal intestine as achieved with bariatric surgical procedures such as the gastric bypass. However, the development of these techniques has been hampered by technical problems and side effects and long-term durability and sustainability remain completely undetermined [64].

In summary, the results of weight loss endoscopic procedures to date have been mixed, with some devices providing inadequate weight loss and others promising results. In addition, there are only limited published studies, most being small series with short follow-up. These are considered less invasive than most conventional bariatric surgical procedures but more invasive than medical therapies. However, while there is excitement in the novel medical device area, the efficacy, safety, durability, and clinical utility of many of these procedures in the management of obese people diabetes is still to be established and the procedures need to be considered still investigational at this stage.

Combining Therapies

As obesity is a chronic condition, selectively combining the therapies listed above may provide a more logical and

sustained approach to therapy. Lifestyle modification forms the basis for all weight management including bariatric surgery. Achieving weight loss with low-calorie diets, meal replacements, VLEDs, and intra-gastric devices can be substantial and satisfactory for the class I obese range. However, all these approaches are followed by the challenge of weight regain. It is here that emerging pharmacotherapy may play its most significant role. By combining currently available therapy with medications expected in the near future, within a chronic disease framework, we may be on the verge of adequately treating large numbers of people in this BMI range.

Conclusion

According to the data revised here, we can conclude that the need for effective and safe therapies for class I obesity is great and not yet met by nonsurgical approaches. However, the field is rapidly evolving. Structured and feasible lifestyle modification programs may achieve modest weight loss in the range of 5–7 % of body weight in about half the patients and important health benefits. Established and novel pharmacologic treatments may significantly potentiate the effects of lifestyle modifications, in that 25–50 % of patients may obtain the 10 % weight loss target. Definitive conclusions about long-term efficacy and safety of new combination and single drugs remain pending. Endoscopic alternatives are underdevelopment but will need more study to better understand the safety and efficacy.

Current Position of Bariatric and Metabolic Surgery for Those with a BMI < 35 kg/m^2

In 1991, a panel of experts endorsed by the National Institutes of Health produced the first set of guidelines for the criteria for selecting obese patients for bariatric surgery [67]. At that time and without the support of evidence-based data, the panel decided to restrict the use of bariatric procedures to patients with severe obesity (BMI > 40 kg/m^2) or with less severe obesity (BMI 35–40 kg/m^2) accompanied by severe obesity-related comorbidities. This decision was driven by a prudent evaluation of the risk / benefit ratio of bariatric surgery in an era in which open surgery was the rule and procedures were limited to a very few options. However, the decision was subsequently supported by the accumulation of high-quality prospective data that confirmed that bariatric surgery resulted in an improvement of metabolic cardiovascular risk factors, a reduction of coronary events, a lower incidence of cancer, and a reduction of total mortality [20]. The support for offering surgery to patients with BMI > 35 kg/m^2 was subsequently endorsed by other independent entities [34, 35, 68].

The first significant attempts to consider bariatric surgery for patients with BMI < 35 kg/m^2 were stimulated by the increasing awareness of the effects of surgery on type 2 diabetes. In 2007, a multidisciplinary group of experts convened in Rome, Italy, for the first international Diabetes Surgery Summit [69]. After an extensive discussion on the evidences, the experts released a clear position statement supporting the role of surgery for the treatment of type 2 diabetes in acceptable surgical candidates with BMI ≥ 35 kg/m^2 not achieving adequate metabolic control by lifestyle and medical therapy and, for the first time, suggested that a surgical approach may also be appropriate as a nonprimary alternative to treat inadequately controlled type 2 diabetes in suitable surgical candidates with mild-to-moderate obesity (BMI 30–35 kg/m^2) [69]. Randomized controlled trials on the field were strongly encouraged [69]. The position statements released by the Diabetes Surgery Summit were endorsed by several scientific societies, including IFSO [69]. Shortly after, the "bariatric surgery" section of the clinical recommendations for the standard of care in diabetes released by the American Diabetes Association in 2009 recommended bariatric surgery for adults with BMI ≥ 35 kg/m^2 and type 2 diabetes, especially if the diabetes is difficult to control with lifestyle and pharmacologic therapy, but considered current evidences insufficient to recommend surgery in patients with BMI < 35 kg/m^2 outside of a research protocol [70]. Finally, the International Diabetes Federation (IDF) Taskforce on Epidemiology and Prevention of Diabetes in 2011, 20 years after the NIH guidelines, released an important document on this subject [71]. After reviewing the accumulating studies on the role of surgery on diabetes, a consensus working group of diabetologists, endocrinologists, surgeons, and public health experts concluded that there was clear evidence that bariatric surgery is a very effective therapy for obese patients with type 2 diabetes and attempted to position this therapeutic option in diabetes treatment algorithms [71]. According to IDF experts, while the indications for bariatric surgery typically classify those who are eligible for surgery, recommendations for surgical referral as best practice or prioritization has not been widely considered. IDF suggested that conditional eligibility or prioritization for surgery should be assessed by a team specializing in diabetes. Working on this framework, the IDF suggested the consideration for bariatric treatment for morbid obese patients (BMI > 40 kg/m^2) with type 2 diabetes not adequately controlled (HbA1c > 53 mmol/mol or 7 %) by lifestyle measures and metformin. Less severe obese diabetic patients (BMI 35–40 kg/m^2) should be eligible for surgery and may be prioritized if they have poorly controlled diabetes (HbA1c > 53 mmol/mol or 7.5 %) despite fully optimized conventional therapy, especially if their weight is increasing or other weight responsive comorbidities (blood pressure, dyslipidemia, and obstructive sleep apnea) are not achieving targets on conventional therapy. Finally, diabetic patients with class I obesity (BMI 30–35 kg/m^2) may be eligible, but not

prioritized, for surgery if they fall in the same metabolic and clinical conditions warranting prioritization in the 35–40 BMI class [71]. Australian clinical practice guidelines for the management of overweight and obesity also recently suggested that bariatric surgery may be a consideration for people with a BMI > 30 kg/m^2 who have poorly controlled type 2 diabetes and are at increased cardiovascular risk, taking into account the individual situation [72], and a similar position has been also included in the updated version of the clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient cosponsored by the American Association of Clinical Endocrinologists, the Obesity Society, and the American Society for Metabolic & Bariatric Surgery [73].

More recently, the American Society for Metabolic and Bariatric Surgery (ASMBS) issued a very relevant position statement in response to numerous inquiries made to the society by patients, physicians, society members, hospitals, and others regarding the safety profile and efficacy of bariatric surgery for patients with class I obesity (BMI 30–35 kg/m^2) [74]. By reviewing and summarizing available data, the ASMBS Clinical Issue Committee stated that class I obesity is a well-defined deserving treatment disease causing or exacerbating multiple other diseases, decreasing the duration and the quality of life. Current options of nonsurgical treatment for class I obesity were considered by the ASMBS to generally not be effective in achieving a substantial and durable weight reduction in the majority of patients treated by these measures. Therefore, the ASMBS concluded that bariatric surgery should be an available option for suitable patients with BMI 30–35 kg/m^2 who do not achieve substantial and durable weight and comorbidity improvement with nonsurgical methods [74]. The ASMBS document stressed the fact that the existing cut-off of BMI, which excludes those with class I obesity, was established arbitrarily nearly 20 years ago [67] and that on the basis of currently available data, there is no current justification on grounds of evidence of clinical effectiveness, cost-effectiveness, ethics, or equity that this group should be excluded from surgery [74]. The ASMBS Clinical Issue Committee indicated that gastric banding, sleeve gastrectomy, and gastric bypass have been shown in RCTs to be safe, well-tolerated and effective treatment for patients with BMI 30–35 kg/m^2 in the short and medium term [74]. Finally, the ASMBS statement concluded that, before considering surgical treatment for obesity for any individual, an adequate trial of nonsurgical therapy should always be required. If, however, the attempts at treating their obesity and obesity-related comorbidities have not been effective, we must recognize that the individual has a disease that threatens their health and life expectancy and therefore must seek an effective, durable therapy such as bariatric surgery [74].

Beyond BMI in the Selection/Prioritization of Obese Patients for Surgery

BMI Alone Is a Poor Index of Adiposity

Body mass index (BMI) is used in epidemiological and clinical practice to define underweight, normal weight, overweight and obesity [34]. Categorization of obese patients for the eligibility to bariatric surgery has been based so far largely on BMI cut-offs [67]. However, BMI is not a biological trait, but a calculated value based on body weight. The use of BMI as a proxy for adiposity, the true determinant of the obese state, may be misleading, given that body weight is the sum of individual organs and tissues, and therefore it includes adipose tissue, skeletal muscle mass, and organs mass. Moreover, BMI does not convey any information on fat distribution (e.g., visceral fat accumulation and fatty infiltrations in individual organs) that is now considered an important determinant of metabolic and cardiovascular risk [75].

On a population level, a strong positive correlation between BMI and overall body fat content has been extensively reported [76]. However, this can mask significant variations in the relationship between BMI and adiposity on an individual level. For instance, at a given BMI value (24 kg/m^2), the body fat content has been demonstrated to vary in male and female subjects from 7.8 to 38.3 % and from 29.9 to 44.2 %, respectively [77]. This large variability implies that an individual subject may have a BMI corresponding to an obese state (e.g., 32 kg/m^2) both having a low fat-free mass and a substantial fat accumulation or having a large skeletal muscle mass and normal fat mass. This latter condition typically occurs in athletes, in which high BMI may simply reflect increased muscle mass, which does not infer less favorable health [78]. The poor performance of BMI as a marker adiposity is further emphasized by the large differences in percentage body fat observed between men and women at almost every BMI point [77] and by the fact that a BMI of 20–25 kg/m^2, which would be considered lean and by inference "healthy" within a Caucasian population, may correspond to an elevated body fat content in other ethnic groups [79].

The deleterious and confusing consequences of the use of BMI as a simple clinical and epidemiological marker for obesity/adiposity may be better understood by considering the so-called "Obesity Paradox". The term Obesity Paradox refers to a body of epidemiological observations in which having a BMI level in the overweight or class I obesity range seems to confer a survival advantage with respect to normal weight and underweight patients in selected clinical situations. Indeed, a survival advantage in people with overweight or moderate obesity, when compared with underweight or normal weight subjects, has been described in patients with chronic heart failure [80–82]; in end-stage renal disease [83]; after major vascular surgery for peripheral arterial disease

[84]; in patients who underwent a percutaneous coronary intervention for coronary artery disease [85]; in patients who are medically treated for non-ST-segment elevation acute coronary syndrome [86]; and in the first 30 days after general non bariatric surgery [87]. Several complex possible explanations for the Obesity Paradox have been advocated, but one common suggestion is that the very concept of the obesity paradox may be driven by the deleterious effects of cachexia and not by salutary effects of obesity [16]. The protective effect of a relatively high BMI level in such stressful clinical situations may be therefore driven by having a good fat-free mass and a good nutritional status, instead of by a protective effect of adiposity alone. However, we must also accept that quality studies exclude early deaths to limit the effect of disease-driven cachexia, and that a higher BMI at a population level is largely associated with fatness and therefore, in some conditions, increased fatness may have mortality advantage. These considerations may stress the need for a more accurate description of body composition, fat distribution, and global health in patients with moderate obesity, which are considered to be candidates for bariatric surgery.

Beyond BMI in the Definition of Cardiometabolic Risk in Obesity

The use of only BMI and obesity-related comorbidity for the selection and prioritization of patients to surgery has been frequently criticized, but no alternative options have been proposed. This issue will become even more important if we move to include class I obesity in bariatric surgery. Indeed, patients in this class may have very different levels of health and risk even though at the same BMI level.

Evidence in favor of the use of body composition and fat distribution analyses in the categorization of metabolic risk comes from data on a subgroup of normal weight subjects with low subcutaneous but increased visceral fat mass. This thin-on-the-outside, fat-on-the-inside (TOFI) subphenotype has been observed in both male and female subjects and increases an individual's risk of metabolic disease [77]. The elevated visceral fat found in individuals classified as TOFI is accompanied by increased levels of ectopic fat deposition both in the liver and in the skeletal muscle. Lipid accumulation in nonadipose cells (ectopic fat) may impair the normal function of some tissues through a process known as "lipotoxicity" [85]. Ectopic storage of excess lipids in organs such as the liver, skeletal muscle and pancreatic beta-cells may be the causative link between fat distribution and the metabolic syndrome [88]. Ectopic fat deposition has also been shown to affect cardiovascular function and contribute to the development of cardiovascular diseases [89]. Similar findings have been already reported in obese individuals, where obese subjects with a disproportionate accumulation of visceral fat had increased incidence of metabolic disorders [90, 91].

In the opposite corner, even if obesity is known to be related to numerous metabolic disturbances, a substantial proportion of obese subjects appear to have a favorable metabolic profile: normal insulin sensitivity levels and blood pressure, high HDL, low plasma triglycerides levels, and absence of inflammation. These subjects have been referred to as "metabolically healthy obese" (MHO) [92]. The incidence of MHO varies according to the criteria used for its definition, but it is substantial, covering about 25–35 % of the obese population [92, 93]. This phenotype seems to be characterized by elevated fat content and subcutaneous adipose tissue, but reduced visceral and ectopic fat deposition.

These observations, coming from the characterization of "extreme" or "outlier" metabolic phenotypes, emphasizes once more the role of fat distribution in the determinism of the metabolic and cardiovascular complications of obesity. Visceral fat accumulation may, however, be difficult to quantify at a clinical level, and surrogate anthropometric indexes have been proposed. Waist circumference has been proposed as a reliable clinical indicator of visceral fat accumulation [34] and having a large waist is associated to a higher prevalence of metabolic disorders and cardiovascular diseases [34]. Therefore, the measurement of the waist circumference is suggested to determine cardiovascular risk of overweight and obese patients [34] and specific ethnic cut-off levels for waist circumference have been defined [94]. The simple measurement of waist circumference has replaced the use of the waist-to-hip circumference ratio (WHR), originally proposed as a powerful marker of fat distribution. More recently, on the basis of several epidemiological studies showing that having a large hip circumference may confer some BMI-independent protection from metabolic and cardiovascular diseases, particularly in women, a return to the measurement of hip circumference has been proposed [95]. The presence of ectopic fat deposition in the relevant organs may be even more difficult to quantify than visceral fat accumulation in clinical practice. However, liver fat infiltration (hepatic steatosis) may be roughly, albeit imprecisely, estimated by ultrasound [96] and precisely measured by more advanced imaging techniques [77]. Increased liver fat has been suggested to be a more crucial determinant of multiorgan insulin resistance than visceral fat [97]. An alternative approach to the quantification of ectopic fat accumulation may be represented by the ultrasonographic measurement of epicardial fat, which has been suggested as a further marker of metabolic and cardiovascular risk [98].

Beyond BMI in Phenotyping Obese Patients

The use of only BMI in the selection of obese patients for surgery appears now a clear oversimplification of the problem [99]. A clinical decision based on a more comprehensive evaluation of the patient's global health and on a more reliable prediction of its future disease risk may be more sensible than

neglecting or suggesting surgery to someone simply on the basis of the calculated ratio between body weight and squared height. On the basis of the above considerations, a more precise phenotypization of obese patients should include a determination of percentage body fat with reliable techniques (DEXA), particularly in cases where the BMI value may be misleading, and an estimation of fat distribution and ectopic fat deposition (waist circumference, hip circumference, hepatic steatosis, epicardial fat, etc.). Phenotyping should obviously be completed by the determination of cardiovascular risk factors and clinical status of obesity-related comorbidities [73], and a comprehensive medical history for those factors that may increase the risk of metabolic diseases in the future (family history of type 2 diabetes, gestational diabetes, polycystic ovary syndrome, impaired glucose tolerance, or impaired fasting glucose) or may represent early markers of atherosclerosis (plaques or increased intima-media thickness at carotid ultrasonography, low ankle-brachial index, and high coronary artery calcium score) or initial signs of organ damage (left-sided cardiac hypertrophy and microalbuminuria). Psychological issues, eating behavior disorders, and quality-of-life impairment should also probably be included. A list of clinical data that should potentially be integrated in the comprehensive evaluation of the obese patients beyond BMI values is reported in Table 1.

The integration of this large set of clinical information in a comprehensive picture would be highly facilitated by the adoption of an obesity scoring system. The use of a score that could quantitatively represent the actual and future health burden that obesity induces in every single patient would be an important tool for clinicians for the phenotypization of the patients beyond simple BMI level and for guiding therapeutic choices. A scoring system should also be helpful for prioritization and resources allocation in a health system with limited resources. However, at this stage, we do not have an obesity scoring system of this type already implemented and the relative weight to assign to each factor in the construction of this score would be largely arbitrary in the absence of reliable prognostic data. An alternative option would be the use of a more simple but integrated staging system. The Edmonton Obesity Staging System (EOSS) has been proposed by Sharma and Kushner [100] as a clinical staging system for obesity. EOSS classified obesity in five stages (0 to 4) accordingly to worsening clinical and functional status (Table 2) [100]. EOSS stage has been shown to be a more stringent predictor of total mortality than BMI levels in large epidemiological databases [101, 102], and its application for the selection/prioritization of obese patients to bariatric surgery has been suggested [103]. The validation and application of EOSS or other alternative staging systems for the selection/prioritization of obese patients to bariatric surgery beyond BMI values should be a focus of future clinical research in the field.

Table 1 A list of clinical factors that may potentially be integrated in a comprehensive evaluation system for the selection or the prioritization of obese patents for bariatric surgery

Body composition	BMI (% body fat, as determined by DEXA)
Fat distribution	Waist circumference
	Hip circumference
	Visceral fat accumulation
Ectopic fat deposition	Liver fat infiltration (hepatic steatosis)
	Epicardial fat
Cardiovascular risk factors	LDL-cholesterol, HDL-cholesterol, triglycerides
	Fibrinogen
	hs-PCR
Obesity-related comorbidities	Type 2 diabetes
	Hypertension
	Obesity-related cardiomyopathy
	Sleep apnea syndrome
	Obesity/hypoventilation syndrome
	Disabling weight-bearing joint disease
	Obesity-related infertility
	Urinary stress incontinence
	Severe gastro-esophageal reflux disease
High risk for type 2 diabetes	Family history of type 2 diabetes
	Previous gestational diabetes
	Polycystic ovary syndrome
	Impaired glucose tolerance/impaired fasting glucose
	Hyperinsulinemia/insulin resistance (HOMA)
Early markers of atherosclerosis	Plaques or increased intima-media thickness at carotid ultrasonography
	Low ankle-brachial index
	High coronary artery calcium score
Initial signs of organ damage	Left sided cardiac hypertrophy
	Micro-albuminuria/proteinuria
Socio and psychological issues	Depressive symptoms
	Eating behavior disorders
	Reduced work capacity
	Impaired quality of life

The application of a staging system for the selection/prioritization of obese patients to bariatric surgery beyond BMI values does not automatically imply that patients in the most advanced stages should represent the best candidates for surgical procedures. Patients in EOSS stage 4 have a poor prognosis, a very high surgical and anesthesiological risk, and disputable benefits from intentional weight loss. Even patients in stage 3, for instance, a patient with a recent myocardial infarction, may have clinical conditions that suggest surgery should be avoided or postponed. The clinical decision to indicate a bariatric procedure should obviously also take into account individual surgical risk. The surgical risk of bariatric procedures is generally low [104], but risk can be stratified by

Table 2 Edmonton obesity scoring system: a proposed clinical and functional staging of obesity (modified by Ref # [100])

Stage	Description
0	No apparent obesity-related risk factors (e.g., blood pressure, serum lipids, fasting glucose, etc., within normal range), no physical symptoms, no psychopathology, no functional limitations and/or impairment of well-being
1	Presence of obesity-related subclinical risk factors (e.g., borderline hypertension, impaired fasting glucose, elevated liver enzymes, etc.), mild physical symptoms (e.g., dyspnea on moderate exertion, occasional aches and pains, fatigue, etc.), mild psychopathology, mild functional limitations, and/or mild impairment of well-being
2	Presence of established obesity-related chronic disease (e.g., hypertension, type 2 diabetes, sleep apnea, osteoarthritis, reflux disease, polycystic ovary syndrome, anxiety disorder, etc.), moderate limitations in activities of daily living and/or well–being
3	Established end-organ damage such as myocardial infarction, heart failure, diabetic complications, incapacitating osteoarthritis, significant psychopathology, significant functional limitations and/or impairment of well–being
4	Severe (potentially end-stage) disabilities from obesity-related chronic diseases, severe disabling psychopathology, severe functional limitations, and/or severe impairment of well–being

a range of simple clinical factors [105, 106]. Recently, different scoring systems have been proposed for more accurately predicting surgical complications in bariatric surgery [106–109]. The integrated use of more accurate instruments for a more complete clinical description of the obese patient and for a more precise estimation of surgical risk may help clinicians to base the clinical decision on a more logical and appropriate basis than the simple BMI level.

Surgery in Class I Obesity: "What Do We Know" and "Identify Gaps"

To date, there is a robust body of literature to support safety, efficacy, and comorbidity benefits for patients with class I obesity. This chapter performs a review of current evidences on the role of bariatric surgery on class I obesity and one or more obesity-related comorbidities, including type 2 diabetes mellitus (T2DM), hypertension, hyperlipemia, obstructive sleep apnea (OSA), obesity-hypoventilation syndrome (OHS), Pickwickian syndrome (combination of OSA and OHS), nonalcoholic fatty liver disease (NAFLD), nonalcoholic steato-hepatitis (NASH), pseudotumor cerebri, gastro-esophageal reflux disease (GERD), asthma, venous stasis disease, urinary incontinence, debilitating arthritis, or considerably impaired quality of life.

Five randomized controlled trials (RCTs) have been conducted to evaluate the role of bariatric surgery on class I obesity with or without T2DM. The level of evidence from these trials is high and the importance of surgical operations to reduce weight and to treat comorbidities is critical. Additionally, two large meta-analysis/systematic reviews analyzed the outcomes of several prospective and retrospective studies conducted in patients with class I obesity and T2DM, showing that surgical treatment is able to determine significant changes in body weight, fasting plasma glucose, HbA1c, and lipid levels in diabetic patients with class I obesity. In the reviews, the rate of complications and adverse were also evaluated in studies with follow-up ranging from 6 months up to over 10 years. Finally, nine other observational studies, seven prospective, and four retrospective, evaluated the effects of bariatric surgery on class I obese patients with and without T2DM in terms of weight loss, diabetes remission, improvements in lipid and metabolic syndrome, and rate of complications.

Randomized Controlled Trials

Five RCTs evaluated the results of bariatric surgery in samples including patients with class I obesity. Four of these trials also included patients with higher BMI levels and one was specifically conducted in patients with class I obesity. Considered operations are gastric banding, gastric bypass, sleeve gastrectomy. and mini-gastric bypass. Primary endpoint was diabetic remission in four trials and weight loss in one. However, all the studies reported consistent weight loss and co-morbidity reduction data. The principal characteristics of these five RCTs are reported in Table 3.

In 2006, O'Brien et al. [110] randomized 80 patients with a BMI range of 30–35 to laparoscopic gastric banding or to medical weight loss therapy. Duration of the study was 2 years and follow-up rate was 97 %. The surgical group achieved greater weight loss than the medical group at 2 years (87.2 % EWL vs. 21.8 %; $p<0.001$). Mean BMI decreased from 33.7 to 26.4 in the surgical group and from 33.5 to 31.5 in the medical group ($p<0.001$). The metabolic syndrome, defined by the Adult Treatment Panel III Criteria, was initially present in 38 % patients in each group and was present in 3 % of patients of surgical group and 24 % of patients of medical group at the end of the study ($p<0.002$). Quality-of-life changes were measured with the Short Form 36 Health Survey (SF-36). Quality of life improved more in surgical group (eight of eight subscales of Short Form-36) than in nonsurgical group (three of eight subscales). The gastric banding group had significantly greater improvements than the nonsurgical group for physical functioning, vitality, and mental health. Four serious adverse event were reported in surgical group (10 %); these patients developed posterior gastric wall prolapse and needed revisional surgery [110].

After 2 years, in 2008, Dixon et al. [111] randomized 60 patients with a BMI range of 30–40 and recent-onset type 2 diabetes (<2 years duration) to laparoscopic gastric banding or

Table 3 Principal characteristics of randomized controlled trials including patients with class I obesity

Reference	Pts. no.	Pts. BMI/characteristics	Arms	FU length	FU rate
O'Brien et al. [110]	80	30–35	Adjustable gastric banding vs. medical weight loss therapy	2 years	97 %
Dixon et al. [111]	60	30–40 (BMI < 35 in 13 pts.) with type 2 diabetes	Adjustable gastric banding vs. conventional diabetes therapy	2 years	92 %
Lee et al. [112]	60	25–35 with type 2 diabetes	Mini gastric bypass vs. sleeve gastrectomy	1 year	100 %
Schauer et al. [113]	150	27–43 (BMI < 35 in 51 pts.) with type 2 diabetes	Roux-en-Y gastric bypass vs. sleeve gastrectomy vs. Intensive medical therapy	1 year	93 %
Ikramuddin et al. [114]	120	30–40 (BMI < 35 in 71 pts.) with type 2 diabetes	Roux-en-Y gastric bypass vs. intensive lifestyle-medical management	1 year	95 %

to conventional diabetes therapy focused mainly on weight management. Duration of the study was again follow-up 2 years and follow-up rate is 92 %. The surgical group achieved significantly greater weight loss at 2 years (20 % of baseline body weight vs. 1.4 %; $p<0.001$). Mean BMI changed from 36.9 to 29.5 in the surgical group and from 37.1 to 36.6 in the conventional diabetes therapy group ($p<0.001$). Moreover surgical group achieved greater results in terms of diabetes remission. Rate of diabetes remission in surgical group was 73 % (fasting glucose level <126 mg/dl and glycated hemoglobin (HbA1c) value <6.2 % while taking no glycemic therapy) compared with 13 % of the medical treatment group ($p<0.001$). There was a significant reduction in the use of drugs for glycemic control in the surgical group at 2 years and no decrease in the conventional managed group. Weight loss and diabetes remission results were not separately reported for patients with class I obesity and patients with class II obesity in this study. No serious adverse events were reported in either group [111].

In 2011, Lee et al. [112] randomized 60 patients with a BMI range of 25–35 and poorly controlled diabetes to laparoscopic mini-gastric bypass (LMGB) or to laparoscopic sleeve gastrectomy (LSG). There was no medical treatment arm in this study. The primary endpoint was diabetes remission (fasting glucose <126 mg/dl and HbA1c <6.5 % without glycemic therapy). Duration of the study was 1 year and follow-up rate 100 %. LMGB patients achieved 94 % EWL, LSG patients achieved 76 % EWL. BMI changes for LMGB and LSG were −7.2 (from 30 to 22.8) and −5.6 (from 30 to 24.4), respectively. Significantly more LMGB patients achieved diabetes remission compared to LSG patients (93 vs. 47 %, respectively; $p<0.02$). HbA1c decreased from 9.9 to 5.4 % for LMGB patients and from 10.2 to 7.2 % for LSG patients. LMGB patients achieved significantly greater improvements in lipids levels and metabolic syndrome than LSG patients. There were no serious adverse events in either group. Minor complications were recorded in 10 % of patients (three cases in LMGB group and three cases in LSG group) [112].

In 2012, Schauer et al. [113] randomized 150 patients with T2DM and a BMI range of 27–43 (34 % of patients with BMI < 35) to Roux-en-Y gastric bypass (LRYGB), sleeve gastrectomy (LSG) or intensive medical therapy (IMT). Duration of the study was 1 year and follow-up rate 93 %. EWL was 88 % in LRYGB patients, 81 % in LSG patients, and 13 % in IMT patients ($p<0.001$). BMI change was −10.2, −8.9, and −1.9, respectively. Remission of diabetes was the primary end point of this study. Baseline value of HbA1c was 9.3 % for LRYGB group, 9.5 % for SG group and 8.9 % for IMT group, while at 1 year, the values were 6.4 (change −2.9), 6.6 (change −2.9), 7.5 (change −1.4), respectively, ($p<0.001$). The reduction in prevalence of the metabolic syndrome was significantly greater in the two surgical group than in medical therapy group. Considering use of cardiovascular medications, lipid lowering drugs were required at baseline in 86 and 78 % of patients assigned to LRYGB and SG, respectively, but use declined to 27 and 39 % at 1 year, as compared with 92 % at 1 year for IMT group ($p<0.001$). There was no significant difference in systolic and diastolic blood pressure levels among the three groups at 1 year, but there was a significant reduction in the number of anti-hypertension medications after the two bariatric procedures. Weight loss, diabetes remission, and metabolic syndrome results were not divided for patients with BMI 27–35 and patients with BMI 35–43. In the surgical group, 15.5 % of patients had one or more than one serious adverse events requiring hospitalization including four cases (4 %) of revisional surgery. In the IMT group, hospitalization was required in 9 % of the patients [113].

Finally, in 2013, Ikramuddin et al. [114] randomized 120 patients with T2DM and a BMI range of 30–40 (59 % of patients with BMI < 35) to intensive lifestyle-medical management and Roux-en-Y gastric bypass (LRYGB) or intensive lifestyle-medical management alone. Medications for hyperglycemia, hypertension, and dyslipidemia were prescribed according to protocol. Duration of the study was 1 year and follow-up rate 95 %. Main outcome of the study was a composite goal of HbA1c less than 7.0 %, low-density lipoprotein cholesterol less than 100 mg/dl, and systolic blood pressure less than 130 mm Hg. After 12 months, 28 participants (49 %; 95 %CI: 36 %–63 %) in the gastric bypass group and 11 (19 %; 95 %CI: 10–32 %) in the lifestyle-medical management group achieved the primary end points (odds ratio: 4.8; 95 %CI: 1.9–11.7). Participants in the gastric bypass

group lost 26.1 vs. 7.9 % of their initial body weigh compared with the lifestyle-medical management group (difference: 17.5 %; 95 %CI: 14.2–20.7 %). There were 22 serious adverse events in the gastric bypass group, including one cardiovascular event, and 15 in the lifestyle-medical management group. There were four perioperative complications and six late postoperative complications. The gastric bypass group experienced more nutritional deficiency than the lifestyle-medical management group [114].

Metanalysis and Systematic Reviews in Patients with Type 2 Diabetes

Li et al. [115] recently published a large meta-analysis of prospective and retrospective non randomized studies on the metabolic effects of bariatric surgery in T2DM patients with class I obesity. A total of 13 studies, including 357 patients, were systematically evaluated. Both traditional and experimental bariatric/metabolic procedures were included. Laparoscopic Roux-en-Y gastric bypass was performed in four studies [116–119], duodenal–jejunal bypass in three studies [120–122], bilio-pancreatic diversion in three studies [123–125], laparoscopic mini-gastric bypass in two studies [126, 127] and laparoscopic ileal interposition with diverted sleeve gastrectomy in one study [128]. Nine studies were prospective and four studies were retrospective. Five studies were conducted in Brazil, three in Taiwan, three in Italy, one in India, and 1 in the US. The principal characteristics and the main results of the 13 studies included in this meta-analysis were reported in Table 4. Follow-up length ranged from 6 to 48 months for 11 studies, while the remaining two studies lasted more than 5 years, even 18 years in 1 study. The median duration of follow-up was 26.8 months. Total weight loss, as derived by the meta-analysis of the five studies reporting this outcome, was 17.23 kg ($p<0.00001$). Mean BMI reduction (data reported in 12 studies) was 5.18 kg/m^2 ($p<0.00001$). Resolution of diabetes was defined as a normal fasting plasma glucose (<100 mg/dl), a normal HbA1c (<6 %), and no need for diabetic medications. The majority of patients (80 %) reached a HbA1c value <7 % and these patients were off T2DM medications. Mean reduction in fasting plasma glucose levels was −4.4 mmol/L ($p<0.00001$) in 12 studies and mean reduction of HbA1c was 2.59 % ($p<0.00001$) in 11 studies. These important effects on glucose metabolism were accompanied by a significant reduction in LDL-cholesterol levels (−36.7 mg/dl in four studies; $p<0.00001$) and triglycerides levels (−56.7 mg/dl in five studies; $p<0.00001$) and by a nonsignificant increment in HDL-cholesterol levels (+5.37 mg/dl in six studies; $p=0.08$). Perioperative (<30 days) serious adverse events were recorded in 11 cases (3.2 % of patients). None resulted in late complications of the whole series [115].

Reis et al. [129] recently conducted a literature review on the role of bariatric–metabolic surgery in the treatment of obese type 2 diabetes with body mass index < 35 kg/m^2. A total of 29 studies, with 1,209 class I obese T2DM patients, were included. Twelve studies were from Brazil, five from Italy, two from the US, two 2 from China, two from South Korea, two from Chile, and one from Australia. Effects of laparoscopic ileal interposition were evaluated in nine studies, laparoscopic duodenal–jejunal bypass in five studies, laparoscopic gastric bypass in five studies, biliopancreatic diversion in four studies, laparoscopic adjustable gastric banding in three studies, laparoscopic mini gastric bypass in two studies, and laparoscopic sleeve gastrectomy (LSG) in one study. In the pooled analysis, BMI was reduced from 29.9 to 24.8 kg/m^2 ($p<0.001$). Fasting plasma glucose was reduced from 207.8 to 113.5 mg/dl ($p<0.001$) and Hb1Ac from 8.9 to 6.3 % ($p<0.001$). The withdrawal of T2DM medications was obtained in 84 % patients [129]. A more extended series of patients treated with stomach-sparing duodenal–jejunal bypass has been recently published [130].

In summary, the two systematic reviews [115, 129] evaluated 13 and 29 nonrandomized prospective and retrospective studies, with 359 and 1,209 diabetic patients, respectively. Both traditional (Gastric Banding, Gastric Bypass, Sleeve Gastrectomy, Biliopancreatic Diversion) and experimental (Duodeno Jejunal Bypass and Ileal Interposition) procedures were included. In the first meta-analysis, weight loss, diabetes remission and improvements in lipids and metabolic syndrome were analyzed and the results were judged to be as good as in morbid obese patients for all the four parameters [115]. Perioperative 30 days, complications rate was 3.2 % in the total series. Different complications rates were observed in different operations, but class I obesity surgical complications rate was considered, in general, lower than the complication rates observed in morbid obesity [115]. The second meta-analysis focused diabetic remission as the primary endpoint and reported for this specific outcome good results, as observed in morbid obesity [129]. Further systematic reviews and meta-analysis on the topic have been recently published [131, 132], and others will probably appear in the next future as new evidences are rapidly accumulating.

Prospective Observational Studies and Retrospective Studies

In 2009, Flum et al. [133] evaluated the 30-day outcomes in 623 patients with BMI 30–40 sorted out from 4,776 consecutive patients undergoing bariatric surgical procedure at ten clinical sites in the US from 2005 through 2007. Most of the procedures were represented by Roux-en-Y Gastric Bypass (GBP) (71.4 % of cases; laparoscopic GBP 87.2 % and open GBP 12.8 %) and by Laparoscopic Gastric Banding (LGB) (25.1 % of cases), with 3.5 % of the procedures represented by other techniques, mainly laparoscopic sleeve gastrectomy

Table 4 Principal characteristics and main results of the prospective and retrospective non randomized studies included in the Li et al. [115] meta-analysis on the metabolic effects of bariatric surgery in T2DM patients with class I obesity

Reference	Pts no.	BMI range	Type	FU length	FU rate	Main results
Roux-en-Y gastric bypass						
Shah et al. [116]	15	22–35	Prospective observational	9 months	100 %	BMI from 28.9 to 23.0. Fasting glucose from 233 to 89 mg/dl. HbA1c from 10.1 to 6.1 %. Off T2DM medication in 100 % of patients. Improvements in lipids and metabolic syndrome
Huang et al. [117]	22	25–35	Prospective observational	12 months	100 %	BMI from 30.8 to 23.7. Fasting glucose from 204 to 103 mg/dl. HbA1c from 9.2 to 5.9 %. Off T2DM medication in 90.9 % of patients
De Sa et al. [118]	27	30–35	Retrospective observational	20 months	100 %	BMI from 33.5 to 25.6. Fasting glucose from 176.1 to 93.9 mg/dl. HbA1c from 8.4 to 5.9 %. Off T2D medication in 74 % of patients
Cohen et al. [119]	66	30–35	Prospective observational	5 years	100 %	Total weight loss: 36 %. T2DM remission: 88 %, HbA1c from 9.7 to 5.9 %. Improvements in lipids and metabolic syndrome
Duodenal–jejunal bypass						
Ferzli et al. [120]	7	21–33	Prospective observational	12 months	100 %	BMI loss not recorded. Fasting glucose from 208 to 154 mg/dl. HbA1c from 9.4 to 8.5 %. Off T2DM medication in 14.2 % of patients. Reduction T2DM medication in 85.8 % of patients. Improvements in lipid and metabolic syndrome
Geloneze et al. [121]	12	25–29.9	Prospective nonrandomized case control	24 weeks	100 %	Surgical patients compared to 162 medically treated patients. HbA1c from 8.7 to 7.4 % in surgical, 8.9 to 8.7 % in control group. Reduction in insulin therapy in 93 % of surgical group and 29 % in control group
Ramos et al. [122]	20	20–30	Prospective observational	6 months	100 %	BMI from 27.1 to 24.4. Fasting glucose from 171.3 to 107.1 mg/dl. HbA1c from 8.8 to 6.8 %. Off T2D medication in 90 % of patients
Biliopancreatic diversion						
Scopinaro et al. [123]	7	32–34.6	Retrospective observational	13 years (10–18 years)	100 %	Body weight from 92 to 75 kg. 100 % of patients <125 mg/dl fasting glucose at 3 years. Off T2DM medication in 100 % of patients. Improvements in lipid and metabolic syndrome
Chiellini et al. [124]	5	27–33	Prospective observational	18 months	100 %	BMI from 30.9 to 25.1. HbA1c from 8.5 to 5.7 %. Off T2DM medication in 100 % of patients. Improvements in lipids and metabolic syndrome
Scopinaro et al. [125]	30	25–30 and 30–35	Prospective controlled		100 %	BMI from 28.1 to 24.6 (25–30) and from 33.1 to 27.4 (30–35). HbA1c from 9.1 to 6.9 % (25–30) and from 9.5 to 5.9 % (30–35). Off T2DM medication in 83.3 % of patients. Improvements in lipid and metabolic syndrome
Mini gastric bypass						
Lee et al. [126]	44	BMI < 35	Retrospective observational	12 months	100 %	Fasting glucose reached normal range in 89.5 % of patients. HbA1c < 7 % in 76.5 % of patients. Off T2DM medication in 90 % of patients. Improvements in lipids
Lee et al. [127]	62	23–35	Retrospective observational	2 years	100 %	BMI from 30.1 to 23. Fasting glucose from 195 to 106 mg/dl. HbA1c from 9.7 to 5.9 %. Off T2DM medication in 55 % of patients
Ileal interposition and diverted sleeve gastrectomy						
De Paula et al. [128]	69	21–29	Prospective observational	22 months	100 %	BMI from 25.7 to 21.8. Fasting glucose from 218 to 102 mg/dl. HbA1c from 8.7 to 5.9 %. Off T2DM medication in 95.7 % of patients. Improvements in lipid and metabolic syndrome

(LSG) and biliopancreatic diversion (BPD). In this large prospective multicenter observational study, perioperative complications were recorded in 23 out of 623 patients with BMI 30–40 (3.7 %), with no clear differences in adverse event rate comparing bariatric surgery in patients with BMI 30–40 and surgery in patients with BMI, with the exclusion of super-obese patients having a clearly higher adverse event's rate. In the general sample, predictors of adverse events were the presence of obstructive sleep apnea, a positive history for deep vein thrombosis and an older age. Patients treated with GBP reported more complications than patients treated with LGB. However, specific procedure-related adverse events were not separately reported for patients with class I obesity and patients with class II obesity [133].

A second large retrospective review multicentre study was published in 2010. De Maria et al. [134] evaluated the data from 66,264 patients with a primary bariatric surgery procedures belonging to the Bariatric Outcomes Longitudinal Database (BOLD). BOLD was created by Surgical Review Corporation as a tool to monitor and track outcomes of surgeries performed by participants of the American Society for Metabolic and Bariatric Surgery (ASMBS), Bariatric Surgery Centre of Excellence (BSCOE) program. Patients' recruitment started on June 2007 and ended on June 2009. Class I obesity patients with type 2 diabetes patients were specifically considered. A total of 235 patients met these inclusion criteria, with adjustable gastric banding (AGB) performed in 109 patients, gastric bypass (GBP) in 109 patients, sleeve gastrectomy (SG) in seven patients, biliopancreatic diversion (BPD) in one patient and other surgical operations in nine patients. Results at 1 year were evaluated and compared in the 109 AGB patients and the 109 GBP patients. One year follow-up was 62 % for AGB patients and 69 % for GBP patients. BMI levels were reduced from 33.9 to 30.9 kg/m^2 for AGB ($p<0.001$) and from 33.7 to 27.1 kg/m^2 for GBP ($p<0.0001$). Off 2DM medication was observed in 27.5 % for AGB patients ($p<0.05$) and in 55.2 % for GBP patients ($p<0.05$). Complication rate was 3.3 % in AGB patients and 18 % in GBP patients [134].

The results of other smaller and/or single site prospective observational studies conducted in patients with class I obesity [135–139] are summarized in Table 5 and the results of some retrospective studies specifically analyzing the outcome of class I obese patients sorted out from general bariatric surgery series [140–144] are reported in Table 6.

All the observational studies report satisfactory weight loss, resolution or improvements of type 2 diabetes mellitus, improvements in lipids and metabolic syndrome. The details regarding specific parameters were variable. Several studies focused primarily on the effects of surgery on type 2 diabetes and evaluated remission rates based on different definitions. However, all the observational studies reported positive effects on glycemic control and diabetes remission rate. These effects were higher in patients with higher BMI. Other cardiovascular risk factors, when reported, improved after bariatric surgery. The systematic reviews and the observational studies,

Table 5 Principal characteristics and main results of prospective observational single site studies on the role of bariatric surgery in patients with class I obesity

Reference	Pts N.	BMI range	Procedure	FU length	FU rate	Main results
Parikh et al. [135]	93	25–30	Adjustable gastric banding	8 years	89 %	%EWL: 53.8 at 3 years. BMI from 32.7 to 27.2 at 3 years. Significant improvements in lipids and metabolic syndrome
Sultan et al. [136]	53	28–35	Adjustable gastric banding	2 years	81 %	%EWL: 69.7. BMI from 33.1 to 25.8. Off T2DM medication in 50 % of patients. Significant improvements in lipids and metabolic syndrome. Major and minor overall complications rate: 13.2 %
Choi et al. [137]	66	30–40 (30–35 if comorbidities)	Adjustable gastric banding	18 months	100 %	%EWL: 42.2. T2DM resolution /improvement in 33.3 % of patients. Significant improvements in lipids and metabolic syndrome
Kakoulidis et al. [138]	23	30–35	Sleeve gastrectomy	6 months	100 %	%EWL: 100 %. BMI from 33.8 to 25.0. Significant improvements in lipids and metabolic syndrome. Quality of life excellent in 50 % of patients, very good in 16.6 %, good in 25 %, fair in 4 % and poor in 0 %.
Abbatini et al. [139]	9	30–35	Sleeve gastrectomy	1 year	100 %	9 surgical patients compared with 9 patients treated with conventional medical therapy. BMI from 32.7 to 21.1 in LSG group, and from 32.9 to 31.7 in medical group. HbA1c from 8.1 % to 5.9 % in LSG group, and from 7.5 to 8.2 in medical group. Off T2DM medication in 89 % of patients in LSG group and 0 % in medical group. Significant improvements in lipids and metabolic syndrome in LSG group, no changes in medical group

Table 6 Principal characteristics and main results of retrospective studies specifically analysing the outcome of class I obese patients sorted out from general bariatric surgery series

Reference	Pts N.	Procedure	FU length	FU rate	Main results
Angrisani et al. [140]	225 class I obese patients out of 3319 bariatric patients	AGB	5 years	72 %	%EWL at 5 years: 71.9 %. BMI from 33.9 to 28.2. T2DM remission in 100 %. Comorbidities reduction in 89.1 % of patients. Perioperative complication in 8.1 % of cases. Mortality in 1 case (0.4 %).
Serrot et al. [141]	17 patients with class I obesity and T2DM	GBP	1 year	100 %	17 surgical patients compared with 17 patients treated with medical therapy. BMI from 34.6 to 25.8 in GBP group and from 34 to 34.3 in medical group. HbA1c from 8.2 % to 6.1 % in GBP group and from 7.0 to 7.1 % in medical group. T2DM medications reduced in 71 % of patients in GBP group and in 6 % of patients in MT group. Significant improvements in lipid and metabolic syndrome.
Frenken et al. [142]	16 patients with BMI 26–34.5 and T2DM	BPD-DS in 7 pts. BPD in 5 pts. GBP in 4 pts.	1 year	94 %	HbA1c from 8.8 % to 5.6 % for BPD and BPD-DS and from 7.8 % to 6.7 % for GBP.
Gianos et al. [143]	42 patients with class I obesity	SG in 24 pts. GBP in 8 pts. AGB in 10 pts.	14 months	100 %	BMI from 33.9 to 26.5. T2DM resolution/improvement in 68 % of patients. Significant improvements in lipid and metabolic syndrome.
Angrisani et al. [144]	34 patients with class I obesity	AGB	7 years	100 %	%EWL: 70.9 % at 7 years. BMI from 32.6 to 27.4. T2DM medications reduced in 100 % of patients at 3 years. Significant improvements in lipid and metabolic syndrome.

AGB adjustable gastric banding, *GBP* gastric bypass, *BPD-DS* biliopancreatic diversion-duodenal switch, *BPD* biliopancreatic diversion, *SG* sleeve gastrectomy

prospective or retrospective, contain however several methodological deficiencies, related to the different study designs with different kinds of surgery, number of patients, lengths of follow-up, primary and secondary endpoints. Weight loss and rate of complications were considered in studies with different operations. Some studies report lack of control data, propensity to bias, and lack of information. There was also variability in the method of weight and co-morbidity reporting.

Final Summary

The comprehensive evaluation of the randomized control trials, meta-analysis and prospective or retrospective studies included in this short overview demonstrated that overall %EWL was excellent in patients with class I obesity after all the most established bariatric procedures, with the majority of the studies reporting no substantial differences in respect to the weight loss observed in patients with morbid obesity meeting the current BMI criteria. In studies considering gastric banding operation, EWL at 2 years was 87.2 % in the RCT reported by O'Brien et al. [110], Parikh et al. [135] reported a 57.9 % EWL at 1 year and a 53.8 % EWL at 3 years, Sultan et al. [136] reported a 69.7 % EWL at 2 years. Finally, the Italian Collaborative study with gastric banding reported a 71.9 % EWL at 5 years [140]. Kakoulidis et al. [138] reported a 100 % EWL in 23 patients who had reached 6 months of follow-up after sleeve gastrectomy. Schauer et al. [113] reported in their RCT a 81 % EWL at 1 year after laparoscopic sleeve gastrectomy and Lee et al. [112] 76 % EWL. Three other studies with small numbers of patients who received sleeve gastrectomy reported significant weight loss in class I obesity patients [128, 139, 143]. Schauer et al. [113] reported in their RCT a 88 % EWL at 1 year in patients underwent to gastric bypass. Data collected from the BOLD registry included 109 RYGB patients with BMI < 35 kg/m^2 who had 69 % EWL 1 year after surgery [134]. Other studies of weight loss after RYGB in this patient population consistently report BMI reduction 12–36 months after surgery [116–119, 141–143]. Lee et al. [112], in a RCT study, reported 94 % EWL in patients underwent to mini gastric bypass at 1 year. Two other studies with patients who received mini gastric bypass with a follow-up of 12–24 months reported significant weight loss [126, 127]. Finally, three studies reported excellent weight loss after biliopancreatic diversion or duodenal switch in patients with BMI < 35 kg/m^2. Importantly, patients did not have excessive weight loss after these procedures, and weight stabilized at a BMI around 25 kg/m^2 within a year after surgery [123–125].

In the five RCTs, in systematic reviews and in the observational studies above considered, resolution or improvements of type 2 diabetes and various comorbidities were analyzed. The level of detail regarding specific comorbidities was variable within studies, limiting the generalizability of the results. Several studies focused primarily on the effects of surgery on type 2 diabetes, but evaluated remission rates using variable definitions. However, in general, positive effects on glycemic control and diabetes remission rates were reported, as previously shown in patients with higher BMI levels. The

true effects of surgery on glycemic control and diabetes remission in patients with type 2 diabetes and class I obesity may be at present underestimated taking into account the fact that patients with maturity onset diabetes of the young (MODY), a group of inherited forms of beta-cell defect, and Latent Autoimmune Diabetes in the Adult (LADA), a late-onset form of type 1 diabetes, have a low probability to remit after surgery and have not been adequately screened and excluded before surgery in some studies [145, 146]. Metabolic syndrome, when reported, improved after bariatric surgery.

Adverse event's rate in class I obese patients appears to be the same than in morbid obesity, with some studies reporting serious adverse events. In the review of the BOLD database including 109 RYGB and 109 LAGB patients with BMI < 35 kg/m^2, complications rate was 18 % after gastric bypass and 3.3 % after gastric banding ($p<0.05$). Most complications were minor (nausea, vomiting), but serious complications, including anastomotic leakage, intraabdominal bleeding, and internal hernia, were reported in the gastric bypass group. One gastric banding patient developed a band slippage in this review [134]. In the Italian Collaborative study that retrospectively considered several class I obese patients treated with banding operated, one patient died 20 after surgery from sepsis after gastric perforation in association with a dilated gastric pouch. This study also reported a 8 % of late complications requiring reoperation for proximal gastric pouch, band erosion and leakage of the port [140].

Quality-of-life data were seldom reported in the studies included in this overview. However, quality of life was measured using the Short Form Health Survey (SF36) in one RCT and the patients treated with gastric banding group had significant improvements in all the eight domains of the SF-36, with significantly greater improvement than the nonsurgical group for physical functioning, vitality, and mental health [110]. Kakoulidis et al. [138] also reported good or excellent quality of life in 22 of 23 patients 6 months after sleeve gastrectomy.

Major limitation of current data on the use of bariatric surgery in patients with class I obesity is the short length of follow-up in most of the studies. All the RCTs and most of the observational studies were shorter than 2 years in follow-up and a more extended follow-up was available only in some prospective or retrospective uncontrolled studies. This problem limits our knowledge about the long-term risk / benefit ratio of surgery in this subset of patients. In particular, potentially serious effects of the profound weight loss produced by surgical procedures on nutritional status and body composition (loss of muscle mass and sarcopenia) cannot be evaluated. Finally, reliable information about the effects of bariatric surgery on longevity in patients with class I obesity remains completely lacking.

In conclusion, this review documents the effectiveness of bariatric surgery for patients with BMI 30–35. As outlined above, the BMI, with its failure to account for gender, fitness, age, ethnicity, and disease risk, is not a reliable and fair approach to the denial of surgery to patients for whom this is the only effective treatment. Instead, this decision should be guided, as for other diseases, by the patients' states of health and the risk/benefits of the operation.

Special Considerations Regarding Patient Selection

Ethnicity

BMI categories have been developed primarily in populations of mainly European ethnicity and often underestimate health risks in other populations. The risk and expression of metabolic syndrome features, and the risk of developing type 2 diabetes, vary with ethnicity [147]. Ethnicity rather than the country of residency is important, as often, obesity rates are higher for those of high-risk ethnicity when living in developed rather than developing countries. Adjusted BMI action cut points for with Asian or other high-risk ethnic groups are recommended to be reduced by 2.5 kg/m^2 to BMI 27.5, 32.5, and 37.5 kg/m^2, respectively [7, 148] (Table 7).

Age

Extremes of age present specific challenges when considering bariatric–metabolic surgery in those with a BMI < 35 kg/m^2. Bariatric metabolic surgery is only generally considered suitable for adolescents of developmental and physical maturity who are severely obese. Several position statements from Europe, the US, and Australia have emerged over the last decade and all made similar recommendations for suitable BMI, generally following traditional adult criteria of BMI > 40 kg/m^2 or BMI > 35 kg/m^2 with severe co-morbidities (including type 2 diabetes) [68, 149, 150]. While statements have varied in a minor way with youngest age and BMI, position statements have yet to recommend lowering the BMI to below 35 kg/m^2. This would appear to be in line with the principle of establishing efficacy, safety, and broad acceptability in adults before extending indications in children and adolescents and with lack of data about efficacy and safety of surgery in class I obese adolescents.

There are important considerations with increasing age as the effect of obesity on morbidity and mortality is attenuated and the NADIR for the optimal BMI with respect to mortality is in the overweight to class I obese range [17]. The optimal weight for lowest mortality appears to be between 25 and 35 kg/m^2 for those with an age of 70 years and older [17]. The effect of more severe forms of obesity on mortality after the age of 65 years is low. These effects are not restricted to the healthy older adults, but are similar in those with diabetes and established cardiovascular disease. Weight loss of 10 % in obese older patients can reduce functional capacity and

Table 7 The classification of weight category by BMI

Classification	BMI (kg/m^2)	
	Principal cut-off points	Cut-off points for Asians
Normal range	18.5 - 24.9	18.5 - 22.9
		23.0 - 24.9
Pre-obese	25.0 - 29.9	25.0 - 27.4
		27.5 - 29.9
Obese class I	30.0 - 34.9	30.0 - 32.4
		32.5 - 34.9
Obese class II	35.0 - 39.9	35.0 - 37.4
		37.5 - 39.9
Obese class III	≥40.0	≥40.0

For Asian populations classifications remain the same as the international classification but that public health action points for interventions are set at 23, 27.5, 32.5, and 37.5. We address eligibility and prioritization for bariatric surgery within the different gray shadowing. Source: Adapted from WHO [7, 148].

mobility [151]. Weight maintenance irrespective of BMI and improved fitness may be the appropriate focus in older adults. If intentional weight loss is desired than modest weight loss in association with exercise provides the best functional outcomes [152]. There is no clear guidance regarding intentional weight loss in older adults as it is unclear that benefits outweigh risks [153]. Weight loss trajectories in older people are associated with considerable risks of both morbidity and mortality [154], and while much research is needed into weight loss and weight gain in the later years of life, major weight loss in older adults with a BMI < 35 kg/m^2 cannot be currently recommended.

Regional, Economic, and Equity Considerations

There are regional variations in access, broad uptake, and type of bariatric metabolic surgery performed [155], and there are also regional differences in the regulatory and economic conditions that may limit the direction of surgery for patients with a BMI < 35 kg/m^2. Economic issues are a particular problem in emerging countries where rates of obesity and metabolic disease including diabetes are increasing rapidly and health care resources limited. Lowering the BMI threshold is likely to alter the overall risk to benefit and influence the health economics of bariatric metabolic surgery [156]. National and regional health services providers need to consider the evidence and deliver services that are locally appropriate.

Issues of equity of access to surgery are strongly influenced by socioeconomic circumstances. In the developed world, obesity and its related metabolic conditions are more common in the socioeconomically disadvantaged, but the majority of bariatric procedures are performed in the private sector, generating inequity and discriminating against individuals who are most likely to benefit [71]. National health services providing for all citizens are struggling to currently provide bariatric metabolic services to those of higher BMI, where the proven benefits of reduced mortality, improved quality of life, and favorable health economic profile are established [14, 153]. Those who may be considered prioritized for bariatric metabolic surgery, for example, individuals with a BMI > 50 kg/m^2 or type 2 diabetes with a BMI > 40 kg/m^2, are not provided access to surgery [35, 71]. Surgery is less likely to be cost-effective in individuals with class I obesity [156].

Comorbidity

Metabolic, mechanical, and psychological comorbidity of obesity often cluster and are associated with increased risk of morbidity and mortality that is poorly related to BMI [100, 101]. Staging systems may provide a useful way of identifying individuals of greatest risk and allow appropriately targeted extension of bariatric metabolic surgery into the BMI<35 kg/m^2 range; for example, the International Diabetes Federation has recommended for some circumstances for individuals with type 2 diabetes [71]. Caution needs to be considered when evaluating each individual's comorbidities and their likely response to bariatric–metabolic surgery in relation to how established therapies treat their conditions. Hypertension and raised LDL cholesterol levels respond well to pharmacological agents and variably to surgery [20], but in combination with other comorbidity, such as type 2 diabetes, nonalcoholic steato-hepatitis (NASH), knee osteoarthritis, or obstructive sleep apnea, the pendulum may swing to bariatric surgery being added to, and possibly replacing, conventional therapies. In many circumstances, we need higher-quality evidence for the effect of bariatric–metabolic surgery on comorbidity changes in patients with class I obesity. In those with severe obesity, the imperative for substantial weight loss with bariatric surgery has been the major focus, and the range of accompanying benefits substantial and welcome. But for those with class

I obesity, the changes in comorbidity and hard health outcomes will take center stage, and bariatric–metabolic surgery will have to compete with established therapies for each comorbidity rather than ride of the coat tails of major weight loss.

Low BMI as a Consequence of Previous Medical or Surgical Therapy

As previously specified in the inter-disciplinary European guidelines [68], BMI criterion for election to bariatric metabolic surgery should be the current BMI or a documented previous BMI of this severity. This means that weight loss as a result of intensified treatment before surgery (patients who reach a body weight below the required BMI for surgery) is not a contraindication for the planned bariatric surgery and that surgery is indicated in patients who exhibited a substantial weight loss in a conservative treatment program but started to gain weight again [68]. Similar considerations should be applied to bariatric patents having reached a low BMI after a first intervention, but requiring redo surgery for complications or side effects.

Research Gaps and Priorities

Introduction

The currently accepted thresholds for performing bariatric surgery were established in 1991 by the U.S. National Institutes of Health (NIH) [67]. The NIH assembled an "expert panel" that reviewed the prevailing literature to make their recommendations. The data they assessed were predominately published in the 1980s. At the time the only operative procedures performed were the gastric bypass and the vertical banded gastroplasty and the only method to perform these procedures was through a long midline incision (open technique). The NIH Consensus Development Statement concluded that bariatric surgery should only be considered for patients with a BMI of 40 kg/m^2 (35 kg/m^2 if the patient suffered from comorbid conditions such as type 2 diabetes or hypertension) [67]. This proclamation was adopted by private health insurance providers and society at large and become the rules of conduct for performing bariatric surgery. Unfortunately, it prevented patients whose BMI was 30–35 kg/m^2 from qualifying for surgery even if they suffered from comorbid conditions. As a consequence, there was little interest at that time in pursuing surgery for those patients.

However, in the present, the issue of whether it is appropriate to offer patients with BMI less than 35 kg/m^2 has developed considerable interest. It is now well understood that patients whose BMI is 30–35 kg/m^2 are likely to suffer from the same comorbid conditions as patients with higher BMIs and also are at risk for premature death [157]. Additionally, the introduction of less invasive techniques (laparoscopic access to the abdominal organs), less complex procedures (adjustable gastric banding and sleeve gastrectomy), and a growing body of literature that demonstrates bariatric surgery results in the improvement of several comorbid conditions in patients with BMI greater than 35 kg/m^2 has fueled this interest [158, 159]. There is a slowly growing body of literature demonstrating similar benefits for lower BMI patients [115, 129–132]. Additionally, there is an expanding experience with nonconventional procedures in this population to target diseases such as diabetes [65, 160].

Before the widespread of acceptance of conventional and nonconventional operative procedures occurs, ethical due diligence must occur. Unfortunately, that was not always the case. Patients have been subject to surgery outside of the accepted norm often without Institutional Review Board (IRB) approval, comprehensive informed consent, and proper investigational behavior. More concerning, novel procedures were performed on human subjects without adequate preclinical investigation. Published studies are often the result of small observational investigations with adequately small study populations, no control or sham groups, and short follow-up. Due to a multitude of limitations, randomized, prospective, trials are few. The observational trials are often prone to weak methodologies, subject to investigator bias, or conflicts of interest [161]. Risk adjustment to allow more meaningful outcome analysis has rarely been performed.

Long-Term Outcomes

One of the biggest deficiencies of the prevailing literature concerning both conventional and nonconventional surgical procedures for BMI < 35 kg/m^2 is the lack of long-term outcome data. Most of the published results reported are 12 months or less. This limited follow-up does not prove that the benefits of these surgical procedures are durable and does not account for consequences of these procedures, such as nutritional deficiencies, that may occur years after the surgery was performed. It is also highly conceivable that, in some cases, the weight loss and other benefits may decline with time. Reis et al. [129] did an extensive literature search for published articles that evaluated the effects of bariatric surgery on patients whose BMI < 35 kg/m^2 and had type 2 diabetes. There were 29 articles selected. Follow-up was as short as 1 month and as long as 60 months. 41 % of the studies had 12 months or less follow-up. Of these, 42 % had 6 months or less of follow-up. Additionally, only 24 % of the studies had any patient follow up beyond 36 months. This phenomenon is even more significant in the device and novel procedure literature, where few published papers report follow-up beyond a few months and rarely past 12 months [65, 160, 162, 163].

While there is no defined standard for adequate follow-up, in bariatric surgery, it should be longer than 12 months. Recent studies have suggested that the relapse of type 2 diabetes after

remission after gastric usually occurs within 5 years of surgery [164]. Similarly, reactive hypoglycemia also occurs 3 years after gastric bypass. Ritz and Hanaire [165] reviewed the 89 published cases of severe postoperative hypoglycemia. The time to symptoms varied from 6 to 264 months with a mean of 28.6 months. Nutritional deficiencies and conditions, such as osteoporosis, may even take longer. Given these examples, it would be reasonable to suggest that adequate postoperative follow-up for the sake of investigational data collection and procedure evaluation should be no less than 3 years and preferably 5 years.

How to Assess New Procedures, Devices, and Techniques

All new procedures, devices, and techniques mandate honest, thorough, and rigorous assessment before being offered to patients. Patient safety must be the first priority and risks minimized [166]. This includes not only early postoperative complications but also long-term sequelae. All new surgical interventions must first and foremost demonstrate a favorable risk/benefit profile. Therefore, for any given degree of risk, the potential for benefit must be on balance, superior. While the interpretation of a "favorable risk-to-benefit ratio" is variable, it should be defined reasonably and free of bias. Any nonconventional procedure must be subjected to the appropriate scientific analysis and prove to be safe and effective. This analysis should include a sufficient number of test subjects, a sound scientific method, correct use of statistics, adequate patient follow-up, and appropriate primary and secondary endpoints. To minimize harm, new procedures should undergo extensive preclinical investigation. This would mostly likely require evaluation in a representative animal model.

After the demonstration of efficacy and safety, the procedure should be rigorously evaluated in clinical human trials. For all of these trials, the study design must be carefully conceived to result in the maximal amount of information while minimizing patient risk. All study protocols should be submitted to the local Institutional Review Board (IRB), and all patients should agree to participate by signing an IRB approved informed consent [99]. A small open-label feasibility trial in a limited number of test subjects should be performed first. If successful, larger-scale investigations, possibly multisite, with adequate numbers of subjects and sufficient follow-up should be undertaken. Whether a randomized sham-controlled trial is feasible will depend, in part, on the procedure being evaluated.

It is neither appropriate nor scientifically sound to judge all new procedures by one set of universal standards such as weight loss or comorbidity improvements. Each procedure or device will have different safety profiles, degree of complexities, and outcome results. Therefore, each should be judged by its own set of criteria. For example, procedures that are less radical, less complex, and/or less risky for the patient, can be acceptable even if they result in significantly less benefit than more complex procedures that have higher complication profiles. Since dramatic improvements in health and well-being can be realized with as little as a mere 10 % body weight loss, new procedures can be deemed successful at significantly less weight loss than the current mainstream operations. Additionally, those criteria should be flexible and able to change as new information is obtained. Lerner et al. [166] has suggested that if the safety profile exceeds beyond expected, the efficacy endpoints could be lowered. Conversely, if over time, there is an emergence of additional health consequences, then the acceptable minimum efficacy threshold should be raised accordingly.

Traditionally in bariatric surgery, the amount of weight lost was the sole measure of a procedures success. For decades, criteria, such as that developed by Rheinhold (that a successful procedure must result in a 50 % or greater excess weight loss), was used as the litmus test for a procedure's success [167]. However, there are several deficiencies when an outcome measure is primarily focused on weight loss. Firstly, the 50 % excess weight loss milestone is an arbitrary one at best. There was no scientific analysis performed. There may be no metabolic difference between one patient who loses 52 % of excess weight and another who loses 48 %. Yet, in this one-dimensional system, the patient with a 48 % excess weight loss who has improvements in health, ambulatory ability, and quality of life would be classified as a failure. Secondly, a weight loss onlybased system would favor patients at lower baseline body weight as they would lose a greater percentage of their body weight than their much heavier counterparts. Lastly, a weight loss onlybased system would discriminate against less radical procedures. Operations, such as the gastric bypass, can achieve 50 % or greater excess weight loss because of their extreme restriction to food intake. However, some of the novel procedures under development do not rely on radical dietary restriction to achieve results. Some only induce early satiety as the mechanism of weight loss. As eating and calorie intake is only partly related to actual appetite and is greatly influenced by other factors such as mood, actively, culture, and the environment, it would be highly unlikely that such a procedure will universally achieve such weight loss. However, procedures that result in modest weight loss and improvements in comorbid conditions with a favorable risk/benefit profile can also be viewed as successful.

Reporting Weight Loss Outcomes

Throughout the early history of weight loss surgery, there was no consensus as to how to report postoperative weight loss. Published papers early on reported weight loss as total pounds or kilograms lost, or excess pounds or kilograms lost. However, these outcome measures are meaningless without taking the preoperative baseline weight into account. For example, a 50 kg weight loss might be quite significant in a patient whose preoperative weight was 150 kg but not so impressive if the starting weight was 250 kg. Similarly, reporting weight loss as

excess kilograms lost maybe equally as meaningless. There is no standard for how to determine "excess weight." It has traditionally been calculated from an insurance actuarial table that defines ideal body weight for men and women of all heights [168]. However, the determination of "ideal weights" was derived from actuarial data, not physiologic investigation. It also does not account for heterogeneity of body composition. Therefore, its value for assessing procedure outcome is generally considered dubious.

A very popular style for reporting weight loss was as a percentage of the excess weight lost [169]. Unfortunately, it too requires the use of an "ideal body weight" determination to calculate percent excess weight loss and does not take into account body composition [170]. Although clinically inaccurate, it is usually more meaningful than total weight lost in that it standardizes the outcome across all different degrees of obesity. However, percent excess weight loss is not always meaningful. It also is biased to patients of lesser obesity. For example, a 250 kg patient may lose 80 kg of weight but only 40 % of excess, while a 150 kg patient may lose 50 kg which calculates to 60 % of excess weight. The patient with the lower baseline weight would appear to have had the better result, but this may not clinically be the case. More recently, it has been suggested that weight loss outcomes be reported as %BMI units lost [171]. It was even chosen as the official language for reporting weight loss outcomes in surgical journals. While it does not rely on insurance actuarial tables for its calculations, it does utilize a BMI of 25 kg/m^2 as "normal weight" and it does not take body composition into account. Like using percent excess weight loss, it may be good for generalizations across patient populations, but has not been scientifically validated for individual patients. Finally, percent weight loss with standardization of preoperative baseline weights was advocated [146]. Belle et al. [172] demonstrated that this method was likely to be more accurate, taking into account that baseline weights are not only diverse but also will affect outcome results. Further scientific validation should occur before this technique is uniformly adopted.

Unfortunately, there is still no scientifically validated or even universally accepted method for measuring and recording weight loss outcomes. Professional medical societies and medical journals still differ on the preferred method. As the attention turns away from weight loss to other outcome measures such as improvements in disease states, reporting of weight loss may become less important.

Measuring and Reporting Comorbidity Outcomes

Like the reporting of weight loss, universal standard definitions for comorbidity outcomes need to also be instituted across different patient populations, operative procedures, clinical practice, and research protocols. First and foremost, there needs to be uniform acceptance of the definition of each disease state. For example, it is assumed that all morbidly obese patients with adult onset diabetes are therefore "type 2." However, that may not necessarily be the case. Some of these patients may very well have uncommon variants of type 1 diabetes mellitus such as latent autoimmune diabetes [113, 145, 146]. Since type 1 and type 2 patients will respond differently to surgical and medical intervention, it is of utmost importance for valid clinical research to ensure that all patients in a surgical trial evaluating the effects on type 2 diabetes be truly type 2 diabetics. Furthermore, there needs to be uniformity in the chemical markers used to label a patient with suffering from a particular disease or not. In the Stampede Trial, the definition of diabetes was a glycated hemoglobin >7.0 % and remission was defined as a glycated hemoglobin of 6 % or less [113]. Cohen et al. [119] defined type 2 diabetes as having 2 fasting serum glucose results greater than or equal to 120 mg/dl. Other studies do not state how the diagnosis of diabetes was made [65, 111].

Terminology also needs to be clarified for determining the severity of the disease. Currently, hyperglycemic conditions have been referred to as "prediabetes," "glucose intolerance," "diet-controlled diabetes," or "poorly controlled diabetes." Hypertension is defined as "mild," "severe," or "poorly controlled." Study subjects with well-controlled conditions are often included in study groups alongside patients who are poorly controlled despite multiple medications. However, those subjects may actually represent different diseases and their responses to surgical intervention would likely be different. For example, insulin-dependent type 2 diabetics are different than diet controlled or those patients well managed on oral agents. Therefore, the creation of universal definitions for the disease and its severity, and the effort to group "like" patients together, should result in richer outcomes data.

Criteria also need to be established for the various outcomes after surgery. Preferably, these criteria should be scientifically based. The difference between "improvement," "remission," or "cure" should be uniform across all clinical investigations. This is particularly important for the lower BMI patients where surgical intervention will be more focused on disease than weight. As the likelihood of relapse of the disease state exists [164], proclamation that a comorbid disease has resolved (cured) might require that the patient be observed for an extended period of time.

Another area of concern is the variability in the medical treatment offered to the control subjects. There is currently a generous use of the terms "best" or "intensive" medical therapy, yet no consensus as to what that truly means. In some studies, the diabetes management for all patients was controlled by an endocrinologist involved with the trial and by protocol [111, 113, 114]. In other trials, the subjects were managed by their health care providers independent of the study. Both suffer from limitations and biases that can adversely affect the study results. In the former where the study

manages the medical intervention by protocol, there is uniformity to the intervention, but it may not represent the best available treatment for every patient. In the latter, the management is diverse and inconsistent.

Lastly, patient compliance with their medical regimen must also be considered when designing outcome trials and interpreting the results of such trials. Patient compliance to interventions is extremely variable and may also be influenced by the degree of participation the patient has in their own care. While, compliance cannot be mandated, researcher can attempt to select patients more likely to be compliant and monitor the compliance of each subject as the study progresses. Additionally, study compliance needs to be recorded in the publication and its potential influence on the validity of the data acknowledged. Currently, few, if any, published outcome studies record and document patient compliance.

All of the above factors demonstrate the limitations of performing outcomes research in human subjects. These factors may explain the longstanding observations that several seemingly similar studies have resulted in different outcomes. Therefore, when designing new research studies, these factors should be recognized and every attempt made to minimize them. Similarly, when reviewing the results of completed investigations, these factors should be considered when analyzing the results.

Is There a Need for a Large RCT Looking at Hard Outcomes?

In the realm of clinical research, the most highly regarded investigation is the randomized control trial (RCT). Randomizing patients to different study groups dramatically reduces differences, inequalities, and biases between study and control subjects. However, while RCTs are relatively common in pharmaceutical trials, RCTs are difficult to conduct in the field or bariatric surgery and large long-term RCTs present formidable challenges. Only a handful can be found in the literature. Patients rarely will agree to be randomized to a perceived inferior intervention. Patients in a bariatric surgery program recruited to a RCT comparing conventional bariatric surgery to an endoluminal procedure or medications had generally entered the program seeking surgery and therefore would not likely be interested in anything else. Additionally, those who do agree to participate in such a trial may opt out of the trial before its completion if they become frustrated with inferior results. One must also consider that there may be patient biases for those patients who do enter such trials that could influence the outcomes.

The ethics of such RCTs needs also to be mentioned. Since there is currently substantial evidence that anastomotic procedures are significantly beneficial for treating type 2 diabetes, is it ethical to randomize patients with type 2 diabetes to less effective treatments such as purely restrictive procedures or novel technologies?

Ethics of Surgery for BMI < 35 kg/m^2

The ethical behavior for studying or treating patients whose BMI < 35 kg/m^2 by surgical interventions should be no less rigorous (maybe even more rigorous) than that for any other patient group. Although the criteria that excluded patients whose BMI < 35 kg/m^2 from consideration of having bariatric surgery is over 20 years old (US National Institutes of Health 1991) and likely outdated [67], it remains the generally accepted criteria [34, 35]. The body of evidence supporting surgery for BMI < 35 kg/m^2 is growing [115, 129] and even becoming increasingly supported by national medical societies [99]. Therefore, there is growing debate as to whether it should still be considered investigational and require an Institutional Review Board approval of the research protocol and a comprehensive informed consent [173]. While there is an overwhelming body of evidence that concludes that bariatric surgery is safe and effective for patients whose BMI ≥ 35 kg/m^2, it cannot be assumed that the results would be the same for patients with BMIs < 35 kg/m^2. These patients may be physiologically different, and therefore, their response to surgical intervention is currently not well known. Scopinaro et al. [125] reported that the improvements in type 2 diabetes for patients with lower BMIs undergoing the biliopancreatic bypass procedure was not as robust as for patients at higher weights. Additionally, there is currently no long-term data in lower BMI patients to validate that the observed efficacy will be lasting.

However, there is little debate over the status of novel metabolic operative procedures and devices. They are still investigational and must be treated as such. These new therapies are currently undergoing study. However, the majority of the published results are from small open-label trials or limited duration. The few RCTs have thus far yielded modest results [65, 174, 175]. The majority of the research was also conducted in patients BMI > 35 kg/m^2 not less than 35 kg/m^2. While there is insufficient data in the higher BMI patients, there is even less for the lower BMI subjects.

There are often tremendous pressures to advance a novel procedure or device to practice. These pressures include the potential financial gains of the developer or company producing the device or the academic pressures of the investigators. These pressures create action agendas that can knowingly or unknowingly result in unethical behavior. It is therefore critical that the standard rules of ethical research apply to these patients:

(1) Appropriate and sufficient preclinical testing was performed;
(2) The trial be well designed and the risks to the patient be minimized;
(3) The trial design and the informed consent receive IRB approval;
(4) Proper and comprehensive informed consent be given to the subject;

(5) Study participants should be selected without pressure or coercion;
(6) The subject should have all of his/her questions answered;
(7) Subjects are allowed to withdraw from the trial any time without consequence;
(8) Subjects understand the anatomic and physiologic changes resulting from the operative procedure and extent in which it can be reversed if the subject chooses to withdraw from the trial;
(9) The subject is informed of any knowledge of long-term effects of the surgical procedure; and
(10) The publication of the results of these trials, favorable or unfavorable, should be made public.

Conclusion

Performing bariatric operative procedures on class I obese patients with significant comorbid conditions is becoming increasingly popular. The publish data thus far is supportive both for low risk and for clinical benefits. However, the published literature on the subject is small and hampered by many factors related to poor study design, short follow-up, and diversity of clinical definitions. Better designed research is still indicated before wide acceptance particularly with regard to novel procedures and new devices. All research endeavors must be conducted with the highest levels of ethical behavior.

Final Recommendations

On the basis of the data and considerations on the use of bariatric surgery in patients with class I obesity (BMI 30–35 kg/m^2 down to BMI 27.5 kg/m^2 for at risk ethnicities) exposed in this document, the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) issues and endorses the following statements and clinical recommendations.

(1) The impact on health of class I obesity varies greatly between subjects. However, the physical, psychological, and social health burden imposed by class I obesity may be great at an individual level.
(2) Nonsurgical therapies may achieve a clinically meaningful weight loss in a significant number of patients with class I obesity, but this weight loss is maintained in the long term only in a smaller proportion of them.
(3) Bariatric surgery is a highly effective weight loss strategy in patients with class I obesity at least in the short term. Adverse event's rate in class I obese patients appears to be the same than in morbid obesity, with some studies reporting serious adverse events.
(4) Access to bariatric surgery should not be denied to a patient with class I obesity associated to significant obesity-related co-morbidity simply on the basis of the BMI level, which is an inaccurate index of adiposity and a poor health risk predictor. Patients with class I obesity who are not able to achieve adequate weight loss after a reasonable period of nonsurgical therapy should be considered for bariatric surgery.
(5) Bariatric surgery should be considered in patients with class I obesity on an individual basis and after a comprehensive clinical evaluation of the patient's global health and a prediction of its future disease risk. The use of bariatric surgery in patients with class I obesity should be considered only after failure of proper nonsurgical therapy.
(6) Indication to bariatric surgery in class I obesity should be based more on the comorbidity burden than on BMI levels. Comorbidities should be evaluated considering their likely response to surgery and in relation to how they can be treated by established medical therapies.
(7) The use of bariatric surgery should be avoided in patients with class I obesity and advanced obesity-related or obesity-unrelated comorbidities (frailty patients), in which intentional weight loss may not have any beneficial effect on prognosis or may be harmful.
(8) The use of bariatric surgery cannot be currently recommended in children/adolescents or in elderly obese patients with class I obesity.
(9) National and regional health providers need to consider the current evidences favoring the application of bariatric surgery in class I obesity in the context of local health resources and deliver services that are locally appropriate.
(10) Published literature on bariatric surgery in class I obesity is small and hampered by many factors related to poor study design, short follow-up, and diversity of clinical definitions. Accrual of controlled long-term data is strongly advised. The introduction in clinical practice of novel procedures and new devices should be guided by the results of appropriately designed research protocols conducted with the highest levels of ethical behavior.

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