Indications and Limitations of Bariatric Intervention in Severely Obese Children and Adolescents With and Without Nonalcoholic Steatohepatitis: ESPGHAN Hepatology Committee Position Statement

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ABSTRACT

Morbid obesity is strongly associated with nonalcoholic fatty liver disease (NAFLD), which is one of the most common causes of chronic liver disease worldwide. The present best treatment for NAFLD and nonalcoholic steatohepatitis (NASH) is weight reduction through lifestyle modification. Because of frustrating inefficiency of such a therapeutic approach, bariatric surgery is increasingly performed in adolescents as an alternative option for weight reduction. Standards of care and consensus for indications are, however, scarce. We explore the indications and limitations of bariatric surgery in children with severe obesity with and without NASH and aim to provide guidance for the exceptional indications for adolescents with extreme obesity with major comorbidity that may benefit from these controversial interventions. Present evidence suggests that bariatric surgery can decrease the grade of steatosis, hepatic inflammation, and fibrosis in NASH. Uncomplicated NAFLD is not an indication for bariatric surgery. Roux-en-Y gastric bypass is considered a safe and effective option for adolescents with extreme obesity, as long as an appropriate long-term follow-up is provided. Laparoscopic adjustable gastric banding has not been approved by the Food and Drug Administration for use in adolescents and therefore should be considered investigational. Finally, sleeve gastrectomy and other types of weight loss surgery that have grown increasingly common in adults, still need to be considered investigational. Temporary devices may be increasingly being used in pediatrics; however, future studies, including a long-term risk analysis of patients who undergo surgery, are much needed to clarify the exact indications for bariatric surgery in adolescents.

Key Words: bariatric surgery, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, obesity

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INTRODUCTION

The continuing global rise in the prevalence of overweight and obesity among people of all ages and all ethnic groups has grown into an epidemic that affects daily medical practices everywhere. This phenomenon goes hand in hand with a commensurate increase in the incidence in serious health complications starting in childhood and adolescence (1). Therefore, the concern is that pathophysiological adaptations and changes become irreversible and detrimental outcomes in adulthood are the programmed result.

Nonalcoholic fatty liver disease (NAFLD) as a feature of the metabolic syndrome has become the most common liver disease worldwide and will affect long-term physical and psychological development of a large proportion of young people despite many attempts to counteract the problem (2). In a long-term observation of 66 teenagers with features of metabolic syndrome, 2 of them underwent liver transplantation at the ages of 23 and 25 years, respectively (3).

Lifestyle intervention and diet are the mainstay of present medical management of obesity, but there are no precise evidence-based guidelines establishing optimal dietary interventions. Dietary interventions in conjunction with exercise are effective in reducing metabolic risks, particularly high-density lipoprotein-cholesterol and fasting insulin levels in overweight and obese children with NAFLD in the short term (4,5). Persistent lifestyle modifications, however, are difficult to achieve and long-term results of such

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interventions are often disappointing. Only an extremely low percentage of individuals are able to exercise regularly and steadily lose weight (6). For children with successful weight loss Nobili et al (7) showed that a repeated biopsy at 24 months displayed significant improvement of liver histology with reduction of the grade of steatosis, hepatic lobular inflammation, hepatocyte ballooning, and NAFLD activity score.

It has been demonstrated that an early intervention in obesity in children and adolescents, inducing weight loss by performing bariatric surgery in carefully selected patients (1), can dramatically reduce the risk of adulthood obesity and obesity-related diseases including NAFLD (8). Moreover, bariatric surgery appears to be cost-effective when evaluating the quality-of-life years gained (9). In fact, from 1997 to 2003, the number of adolescent bariatric surgical procedures performed in the United States was estimated to increase 5-fold, from 51 to 282 (10). It, however, becomes increasingly evident that bariatric interventions are not the ''quick fix'' for this systemic disease. It alleviates symptoms and may aid recovery of comorbidities but needs careful and intense postoperative multidisciplinary follow-up.

It should be highlighted that while the criteria for undergoing bariatric surgery in adults are well established (11), the exact indications and the role of bariatric surgery in the pediatric patient are still controversial. This is owing to the paucity of long-term outcome information and to related ethical considerations (12). But a new quantity of data has been published, allowing for the satisfactory formulation of a criterion for bariatric surgery in adolescents (Tables 1 and 2, (13–16)). In fact, in 2009, the International Pediatric Endosurgery Group published guidelines for pediatric bariatric surgery (13) on the basis of numerous publications regarding the clinical impact of surgery on the most common early-onset obesity-related diseases. Also, a multidisciplinary panel from the Nutrition Committee for the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition and the National Association of Children's Hospitals and Related Institutions, with experience in nutrition and adolescent weight loss surgery, has already reviewed the medical literature for evidence-based practice for patients undergoing bariatric surgery (14).

The aim of this position paper is to outline present indications and limitations in this controversial field of therapy and to define a standardized approach for extremely affected adolescents with complications such as NAFLD (Fig. 1, (15,16)). Despite only limited evidence for bariatric interventions, the authors aim to provide guidance for clinical scenarios of complicated obesity in the presence of advanced NAFLD when all of the established therapy has failed. This article presents an overview of existing views and evidence on bariatric surgery in adolescents as well as some treatment results achieved. This European position statement aims to support the individual clinician faced with advanced liver disease in morbid obesity in the difficult decision-making process when established therapy has failed and whom to refer for bariatric intervention.

TABLE 1. Additional criteria for surgery in adolescents

BMI $>$ 40 kg/m^2 with severe comorbidities
Type 2 diabetes mellitus
Moderate-to-severe sleep apnea
Pseudotumor cerebri
NASH with advanced fibrosis (ISHAK score $>$ 1)
BMI $>$ 50 kg/m^2 with mild comorbidities
Hypertension
Dyslipidemia
Mild obstructive sleep apnea
Chronic venous insuffiency
Panniculitis
Urinary incontinence
Impairment in activities of daily living
NASH
Gastroesophageal reflux disease
Severe psychological distress
Arthropathies related to weight

Modified from (13). BMI = body mass index; NASH = nonalcoholic steatohepatitis.

CLINICAL INDICATIONS

It is well documented that the prevalence of NAFLD and nonalcoholic steatohepatitis (NASH) in adolescents with obesity is increasing constantly, along with the risk of progression of this to cirrhosis (17). Therefore, NASH should be considered a strong indication for early bariatric surgery in the adolescent patient once conventional treatment has failed.

There is a lack of randomized controlled trials examining the effects of bariatric surgery on NAFLD or NASH (18–20). There are, however, a small number of retrospective and prospective cohort studies that compare liver histology in individuals with severe obesity before and after bariatric surgery.

Mathurin et al (18) prospectively correlated metabolic and clinical data with liver histology before, then 1 and 5 years after, the bariatric surgery in 381 adult patients with severe obesity. There was a significant decline in the prevalence and severity of steatosis and ballooning, and resolution of probable or definite NASH at 1 and 5 years following bariatric surgery. No differences in liver histology between 1 and 5 years following bariatric surgery were seen (18).

Mummadi et al (20), in a meta-analysis of 15 studies with 766 paired liver biopsies, showed that the overall proportion of patients with improvement or resolution in steatosis was 91.6%, steatohepatitis 81.3%, fibrosis 65.5%, and for complete resolution of NASH 69.5% after bariatric surgery–induced weight loss (20).

In a Cochrane review, Chavez-Tapia et al (21) concluded that the lack of randomized clinical trials or quasirandomized clinical studies prevents definitive assessment of benefits and harms of bariatric surgery as a therapeutic approach for patients with NASH. In fact, there are a small number of retrospective and prospective cohort studies that compare liver histology in severely obese individuals before and after bariatric surgery.

Bariatric surgery procedures have made an impact on diabetes that has been largely evaluated in adults (14–16,22). In addition, studies performed in children clearly suggest that diabetes can go into complete remission in adolescents who undergo Roux-en-Y gastric bypass (RYGB) procedures (23). Thus, it is now established that type 2 diabetes mellitus is a strong indication for bariatric surgery in adolescents with morbid obesity.

The prevalence of obstructive sleep apnea (24) is extremely high among adolescents who present for bariatric surgery, and data have demonstrated substantial improvements and/or resolution after

TABLE 2. Additional criteria for surgery in adolescents

Have attained 95% of adult stature
Have failed to attain a healthy weight with previously organized behavioral/medical treatments
Demonstrate commitment to psychological evaluation perioperatively
Avoid pregnancy for 1 year after surgery
Will adhere to nutritional guidelines after surgery
Have decisional capacity and will provide informed assent/consent, as age appropriate

Modified from (13).

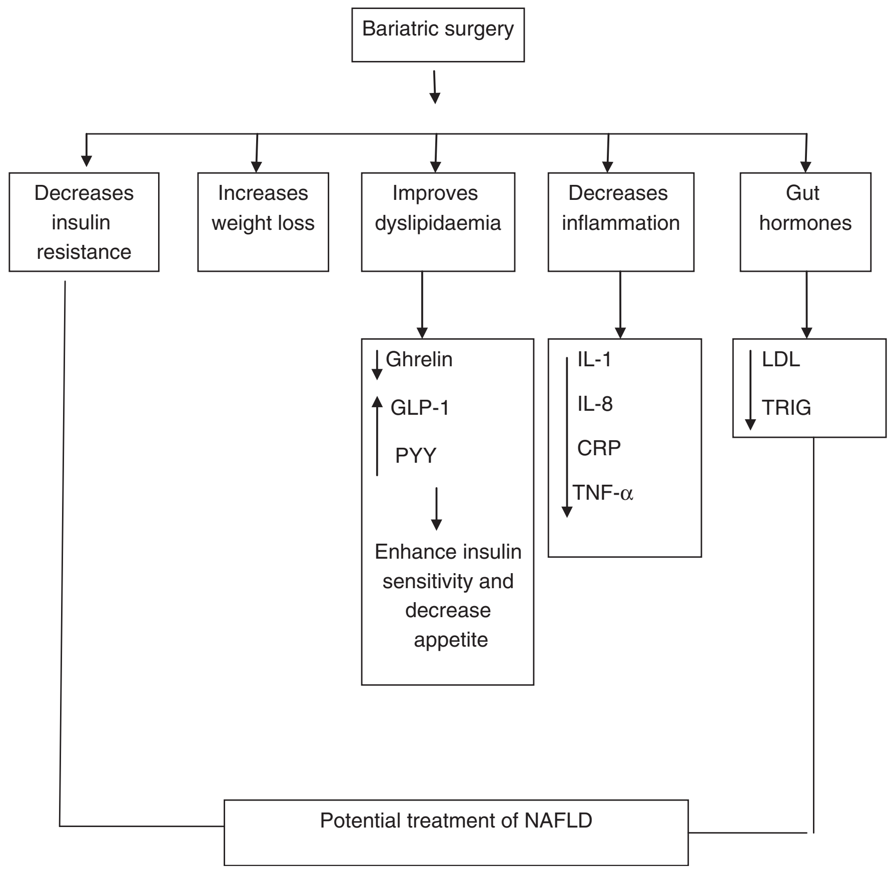

FIGURE 1. Potential mechanism of action of bariatric surgery in the treatment for NAFLD. GLP-1 = glucagon-like peptide-1; IL = interleukin; LDL = low-density lipoprotein; NAFLD = nonalcoholic fatty liver disease; PYY = peptide YY; TNF = tumor necrosis factor; TRIG = triglycerides. Adapted from (15).

bariatric surgery in those patients; this is consistent with outcomes in adults. Thus, moderate or severe obstructive sleep apnea (eg, apnea-hypopnea index >15) is a strong indication for early bariatric surgery in adolescents.

In addition to weight loss, bariatric surgery normalizes insulin resistance and decreases dyslipidemia and inflammation reported in various studies (25–27). Pories et al (25) showed that in 608 obese people with type 2 diabetes mellitus, 83% maintained normal levels of plasma glucose, glycosylated hemoglobin, and insulin, before weight loss but within days of RYGB. Gastric bypass also corrected or alleviated a number of other comorbidities of obesity, including sleep apnea and hypertension (25,26).

Bariatric surgery is not only associated with being able to stop antihypertensive medication but also in stopping lipid-lowering medication (27). Several studies show that bariatric surgery is associated with marked decrease in low-density lipoprotein-cholesterol, triglycerides, and lipoprotein markers (27).

In addition to ameliorating insulin resistance (25), bariatric surgery has been shown to improve the adiponectin level, as well as decrease interleukin-18, C-reactive protein, and tumor necrosis factor-α (26). Therefore, it is possible to suggest that bariatric surgery to treat obesity has a potential benefit of decreasing the associated low-grade inflammatory state.

For all of these reasons even adolescents are increasingly undergoing surgical treatment for obesity, although the guidelines for eligibility are not standardized (28,29). To date, whether NAFLD or NASH should be a major or minor criterion has not been determined. Furthermore, whether NASH-related cirrhosis should preclude surgery, or conversely, accelerate the decision to perform surgery, has not been established.

We suggest bariatric intervention be considered for adolescents with severe obesity with NASH and significant fibrosis (ISHAK score ≥1) when other treatment modalities have failed (expert opinion). Generally, as reported in some studies (30–32), children with a clinical diagnosis of having NAFLD tend to be younger and less obese than adolescents undergoing bariatric surgery. Although in several studies bariatric surgery in adults has been shown to improve histology, outcomes data in adolescents are lacking.

One study has evaluated the symptoms of pseudotumor cerebri in adolescents with obesity and showed that these symptoms improved after bariatric surgery (33). Thus, pseudotumor cerebri is a strong indication for surgery in adolescents with severe obesity.

Present data have also demonstrated an increased incidence of left ventricular hypertrophy in young adults (ages 20–38 years); this is a consequence of early-onset obesity (26). Although weight loss after bariatric surgery has been shown to improve cardiovascular disease risk factors in adults (26), more robust data on the longitudinal effects in the adolescent population undergoing weight loss surgery are required. Thus, cardiovascular disease risk factors are less strong indicators for early bariatric intervention.

The diagnosis of metabolic syndrome in this age group is still not defined and not well standardized (34). Therefore, a diagnosis of metabolic syndrome in adolescents with obesity is a relative and less important indication for bariatric surgery.

In fact, several recent studies have shown a significant improvement in the postoperative quality of life after RYGB and laparoscopic adjustable gastric banding (LAGB) in adolescents, similar to improvements seen in adult cohorts (35).

Black et al (36), in a meta-analysis (1955–2013) performed with 23 studies (637 patients) to examine different procedures of bariatric surgery among children and adolescents with obesity, showed a change in BMI, a comorbidity resolution, and improvements in health-related quality of life 1 year after surgery.

Short-term data demonstrate that depression improves markedly in adolescents after bariatric surgery (37), but long-term data not been well studied. Thus, depression is not an exclusion criterion for bariatric surgery (37,38). Furthermore, although not specifically studied in adolescents, the presence of eating disturbances is not an exclusion criterion. If an eating disorder is identified, treatment should be initiated, and the patient should be considered stable before bariatric surgery.

In fact, even if bariatric surgery proves to be effective for morbid obesity and its complications, patients have to be carefully selected and be medically prepared for this novel treatment modality. Psychological evaluation of the candidates should be regarded as part of the procedure (38). On the contrary, patients undergoing bariatric surgery usually improve in psychological health (ie, self-esteem) (39). It is important to note that patients who have undergone bariatric surgery show higher suicide rates than the general population (40). Patients after bariatric surgery require medical, dietary, and psychological advice and counseling. Postoperative multidisciplinary behavioral management by staff credentialed as specialized in surgical care, behavioral and psychological care, and nutritional care has the potential to facilitate optimal weight loss following the surgery but also to reduce the risk of psychological consequences indicated by a systematic review (41). Insufficient weight loss and weight regain following bariatric surgery could result from physiological factors (such as slippage of the gastric band because of pouch dilatation, gastrogastric fistulas, etc) but also may be affected by psychosocial status following surgery, as some patients' initial improvement in psychosocial status diminishes over time (41). Poor weight loss and weight regain more likely, however, result from a return to preoperative eating and/or a lifetime history of depression and eating disorders (41,42). To ensure compliance with such changes and to identify patients in need for treatment for relevant psychopathology including eating disorders, the guidelines of the American Society for Metabolic and Bariatric Surgery (43) and European Bariatric Surgery Guidelines (44) advise careful management by mental health care professionals to ensure long-term weight loss success.

CRITERIA FOR ADOLESCENT BARIATRIC SURGERY: PATIENT SELECTION

A study by Freedman et al (45) showed that that increasing metabolic risks is associated with higher BMI for age, especially $\geq$99th BMI percentile. Because all adolescent boys, and most girls of age <18 years with a BMI of 35, are above the 99th BMI percentile (45), the selection criteria for BMI thresholds used for adults appears to be appropriate for adolescents. They recommend more aggressive weight control strategies for this group.

To summarize what has been described above, the selection criteria for adolescents to consider for a bariatric procedure should include a BMI >97th percentile (or >40 kg/m^2) with major comorbidities (ie, type 2 diabetes mellitus, moderate-to-severe sleep apnea [apnea-hypopnea index >15), pseudotumor cerebri, or NASH with significant fibrosis (ISHAK score $\geq$1, as an index of rapidly progressing liver disease); alternatively, a BMI >97th percentile (or >50 kg/m^2) with other mild comorbidities (eg, hypertension, insulin resistance, glucose intolerance, a substantially impaired quality of life, or activities of daily living, such as dyslipidemia, or sleep apnea with an apnea-hypopnea index >5). Additional criteria for surgery in adolescents include a documented attempt to lose weight by diet and lifestyle intervention, a Tanner stage of 4 or greater, 95% skeletal maturity determined by dual-energy x-ray absorptiometry scan, a demonstrated commitment to complimentary lifestyle change and a stable psychosocial environment (Tables 1 and 2) (13).

Considerations other than comorbidities and BMI must remain an important part of medical decision making for adolescents. These include, and are not limited to, physical and psychological maturity, treatment and stability of psychological comorbidities, the desire of the patient to have surgery, adequacy of prior weight loss attempts, and firm evidence of ability to comply with follow-up medical care.

For individuals with mental retardation, we suggest inclusion of an ethicist in the multidisciplinary evaluation team. They vary in their capacity to demonstrate motivation, knowledge, and compliance; they should, therefore, be evaluated for bariatric surgery on a case-by-case basis.

Patients with endocrine disorders, that is, oncological patients following hypothalamic surgery who can develop rapidly progressive liver disease (46), and those in whom obesity cannot be controlled through medical interventions, should be considered for bariatric surgery.

Contraindications to adolescent bariatric surgery include a documented substance abuse problem, a medically correctable cause of obesity, and a disability that would impair adherence to post-operative treatment, present pregnancy, or breast-feeding (11–13). The associated risk-to-benefit analysis should obviously also include the consideration of the potential long-term health risks of untreated or inadequately treated obesity for each patient individually.

PREOPERATIVE PATIENT EVALUATION

A full blood count, liver function tests, a lipid profile, thyroid function tests, fasting glucose and insulin measurements, hemoglobin A1c levels, urinalysis, vitamin D levels, parathyroid hormone levels, and *Helicobacter pylori* testing should be performed in all of the patients preoperatively. Polysomnography is indicated if there is any symptom suggestive of sleep apnea. Abdominal ultrasonography is required if biliary colic symptoms are present, and it may be helpful to screen for asymptomatic gallstones in all of the patients with NAFLD. A dual-energy x-ray absorptiometry scan for bone mineral density may be necessary for appropriate patients. Deep venous thrombosis and pulmonary embolism are known complications of bariatric surgery. All of the patients undergoing bariatric procedures, including adolescents, should receive prophylaxis for deep venous thrombosis with both pharmacological therapy and mechanical compression stockings. A psychological evaluation needs to be performed in all of the patients by a mental health specialist (psychologist, psychiatrist, or other qualified mental health specialist with specialty training in pediatric, adolescent, and family treatment).

INFORMED CONSENT

Written informed consent is obtained from the parents or legal guardian of all of the patients, depending on the age. Informed assent by the adolescent should be obtained separately from the parents to avoid misunderstandings. The patient's knowledge of the risks and benefits of the procedure and the importance of postoperative follow-up should be formally evaluated to ensure the true informed assent. The parental permission process should include discussion of the risks of adult obesity, available medical treatments, surgical alternatives, and the specific risks and outcomes of the proposed bariatric surgery.

Surgical Procedures

The selection of the correct procedure for each adolescent is based on an evaluation of the patient's medical, psychological, and social issues, as well as a thorough discussion of the risks and benefits of the surgery with the patient and family.

The bariatric surgical procedures performed on pediatric patients can be divided into 2 categories: ''restrictive'' and ''malabsorptive.'' LAGB, laparoscopic sleeve gastrectomy (LSG), and intragastric balloon (IB) are purely ''restrictive'' procedures. The biliopancreatic diversion is a mostly ''malabsorptive'' procedure, and the RYGB is a ''combination of restrictive'' and ''malabsorptive'' surgical procedures.

Restrictive Procedures

Laparoscopic Adjustable Gastric Banding

The LAGB is a laparoscopic surgical procedure used to promote weight loss. This restrictive procedure involves the placement of a band around that part of the stomach located just below the junction of the esophagus, resulting in a small gastric pouch. The extent of restriction by the inserted band can be adjusted as needed after surgery by injecting a saline solution via a port surgically implanted on the abdominal wall beneath the skin to find the optimal diameter for the band.

The advantages of this procedure include its potential reversibility and that it does not interfere with the absorption of micronutrients (47). In fact, it has an excellent safety profile with a lower risk of postoperative vitamin deficiencies when compared with biliopancreatic diversion and RYGB. The Food and Drug Administration) has not yet approved the use of LAGB in children <18 years old, but its use has increased dramatically. A substantial number of reports supporting the use of LAGB in adolescents have been published during the past several years (48–50).

Treadwell et al (51), in a meta-analysis of 8 studies (Table 3) on adolescent bariatric surgery, reported data on 352 patients (mean BMI of 45.8 kg/m^2, age range 9–21, median 15). Here, a significant and sustained BMI reduction after LAGB was shown to be effective during a 3-year follow-up period (51). Complications were similar to those reported in adult patients with LAGB. The most frequently reported complications were micronutrient deficiency and band slippage; only sporadic cases of hiatal hernia, band erosion, wound infection, port/tube dysfunction, and pouch dilatation were reported. LAGB has also been shown to effectively reduce medical comorbidities such as hypertension and type 2 diabetes mellitus in adolescent patients (51).

In another study on LAGB including 221 adolescents (BMI of 43–48 kg/m^2, age range 9–19, median 14), Pratt et al (52) demonstrated a substantial loss of excess body weight (37%–63%) during a 6-month to 7-year follow-up period. The complication rates were 6% to 10%. No deaths were observed. The reoperation rates, including band removal, were 8% to 10%.

Holterman et al (53) also demonstrated a 41% weight loss and a resolution of the metabolic syndrome in 82% of patients in a group of 20 adolescent patients, ages 14 to 17 years, who underwent LAGB during an 18-month follow-up period postsurgery (53). Complications requiring reoperation, however, developed in more than one-quarter of the adolescents undergoing LAGB. Generally, the most frequent complications with this procedure include band slippage, erosion of the band into the stomach, band migration, and micronutrient deficiency (53,54). Sporadic cases of band erosion, port/tube dysfunction, hiatal hernia, wound infection, and pouch dilation were also reported.

To date, no study has indicated long-term data on whether LAGB had consequent nutritional deficiencies, growth impact, or development impact.

Long-term weight loss outcomes also are still lacking. In 1 study, at least 80% of adolescents had sustained weight loss 5 years after LAGB but the total number of treated patients was small and the number lost to follow-up was not provided (55). Precise descriptions of changes in comorbidities after LAGB in adolescents are still lacking, although initial reports appear to be encouraging (53,54). LAGB is more effective than behavioral interventions alone, and results in significant weight loss when used as part of a comprehensive weight loss program for adolescents. It is considered investigational if done in an institutional review board–approved study.

Sleeve Gastrectomy

LSG is a new, alternative, and effective weight loss surgical procedure used with increasing frequency (56). This surgical procedure was originally performed as the first step in a staged weight loss procedure for severely obese adults (57). It was initially introduced in 1990 as an alternative to distal gastrectomy with the duodenal switch procedure to reduce the rate of complications (58,59). Sleeve gastrectomy was first performed laparoscopically by Ren et al (60). In this restrictive procedure, the stomach is reduced to approximately 20% of its original size by the surgical removal of a large portion. The open edges are then stapled together to form a sleeve or narrow banana-shaped tube. As a result, the size of the stomach is permanently reduced and cannot be reversed (61). Although LSG functions as a restrictive procedure, it may also cause early satiety by removing the ghrelin-producing portion of the stomach (57). Early postoperative complications, following LSG surgery, that need to be identified urgently, include bleeding (intra- or extraluminal), staple line leak, and any development of an abscess. Delayed complications include strictures, nutritional deficiencies, and gastroesophageal reflux disease (57,62). Short-term data suggest that LSG may be a safe alternative, with fewer nutritional risks than other laparoscopic surgical procedures such as RYGB, but its irreversibility and the present lack of longitudinal data on outcome are drawbacks to this procedure (63). The benefits of this procedure include the lack of a foreign body, no need for frequent adjustments necessary with LAGB, fewer nutritional deficiencies than those seen in malabsorptive procedures, and a decreased risk of dumping syndrome because the vagus nerve is preserved (63).

The majority of studies on outcomes after sleeve gastrectomy involve adult patients. A small case study (n = 4, girls) of adolescent patients (mean age 14.5 years, mean BMI 48.4 kg/m^2) demonstrated weight loss after a mean follow-up of 12 months (mean BMI 37.2 kg/m^2). No patients had operative complications, and no patients had postoperative malnutrition or vitamin deficiency (Table 3, (64)).

Another small study (n = 7) of pediatric patients (mean age 16.2 years) demonstrated a weight loss in 85.7% of patients (n = 6). No operative complication was described and comorbid conditions improved (Table 3, (65)).

Hutter et al (66), in a large recent multicenter trial on adults, comparing LSG with LAGB and RYGB, showed a significant decrease in BMI (11.87 with LSG vs 7.05 with LAGB and vs 15.34 with RYGB). The LSG had a higher risk–adjusted morbidity, readmission, and reoperation/intervention rates when compared with LAGB, but a lower reoperation/intervention rate when compared with RYGB.

Angrisani et al (67), in a study of 121 adult patients (66% women, mean operative time 105 minutes) found a 6-person (5%)

TABLE 3. Studies and outcomes of adolescent patients who underwent LAGB*, LSG,** and RYGB***

Study	N	Age, y; sex	Initial mean BMI, kg/m^2	Results	Complications (no. cases)	Treatment for complications	Follow-up
LAGB (51)*							
Dillard et al 2007, United States	24	14–20 y, 18 F	49	22%–42% EWL	Pouch enlargement (6), port leak (1)	2/6 pouch enlargements required reoperation (band repositioning); port leak was repaired under local anesthesia. No. reoperations: 2	5 y
Angrisani et al 2005, Italy	58	15–19 y, 47 F	46.1	39.7%–55.6% EWL 20% had <25% EWL	Band slippage (1), gastric pouch dilatation (2), intragastric migration (3), psychological intolerance of band (2)	Band reposition for band slippage and gastric pouch dilations, band removal for intragastric migration and psychological intolerance. No. reoperations: 11	7 yrs
Nadler et al 2007, United States	53	13–17 y, 41 F	47.6	37%–63% EWL	Band slippage (2), hiatal hernia (2), wound infection (1), nephrolithiasis and cholelithiasis (1), gastroesophageal reflux (1), mild hair loss (5), iron deficiency (4)	Laparoscopic band reposition, laparoscopic hiatal hernia repair, medical therapy for GERD, and nutritional counseling and supplementations. No. reoperations: 4	6 mo– 2 y
Silberhumer et al 2006, Austria	50	9–19 y, 31 F	45.2	EWL 62%–67% resolution, comorbidities 64%	Dislocated port (1)	Not reported. No. reoperations: 0	3 y
Al Qahtani et al 2007, Arabia	51	9–19 y, 27 F	49.9	EWL 42%–60%	Port repositioning under fluoroscopic guidance (1), readmission and rehydration because of an overly tight adjustment (1), repeated attacks of vomiting (9)	No. reoperations: 1	2 y
Yitzhak et al 2006, Israel	60	9–18 y, 42 F	43	BMI decreased to 30	Band slippage (8)	Band reposition (6) and band removal (2). No. reoperations: 9	>3 y
Fielding at al 2005, Australia	52	12–19 y, 30 F	42.4 ± 8.2		Band slippage (1), tubing track (1)	Laparoscopic band reposition for band slippage and exploratory procedure to repair the tubing crack. No. reoperations: 2	<3 y
Abu-Abeid et al 2003, Israel	11	11–17 y, 8 F	46.4	BMI decreased to 32.1	Iron deficiencies (4)	Iron supplementation. No. reoperations: 0	2 y
LSG (64,65)**							
Till et al 2008, Germany	47	8–17 y, 4 F	48.4	BMI decreased to 37.2	No complications	No. reoperations: 0	1 y
Landau et al 2011, Israel		13.8–18 y, 7 F	44.4	BMI decreased to 32.55	No complications	No. reoperations: 0	1 y–15 mo
RYGB (51)***							
Collins et al 2007, United States	11	15–18 y; 7 F	50.5	BMI decreased	Immediate postoperative bleeding (1), marginal ulcer (2)	Laparoscopic re-exploration for postoperative bleeding and use of proton pump inhibitor for marginal ulcers	0.96 y

(Continued overleaf)

TABLE 3. (*Continued*)

Study	N	Age, y; sex	Initial mean BMI, kg/m^2	Results	Complications (no. cases)	Treatment for complications	Follow-up
Lawson et al 2006, United States	38	13–21 y; 23 F	56.5	BMI decreased to 35.8	There were no perioperative deaths nor severe surgical complications. Two patients had at least 1 of the following: death and severe beriberi. Four patients had at least 1 of the following: persistent iron deficiency anemia, peripheral neuropathy secondary to vitamin deficiency, reoperation (for staple line leak, obstruction, or gastrostomy revision), shock, and internal hernia. Nine patients had at least 1 of the following: endoscopy (for melena, suspected obstruction, or stricture), food obstruction, wound infection, anastomotic stricture/gastrojejunostomy stricture, nausea, dumping syndrome secondary to overeating, diarrhea, dehydration, mild beriberi, hypokalemia, deep vein thrombosis.	Not reported	1 y
Barnet et al 2005, United States	14	13–17 y; 8 F	58.5 ± 13.7	BMI decreased to 32.1 ± 9.7	The following were linked to the 5 RYGB cases: Dumping syndrome (2); hypoglycemia (1)	Both dumping syndrome cases were resolved within 1 y without further surgical intervention. The hypoglycemia case was treated medically without difficulty	6 y
Sugerman et al 2003, United States	33	12.4–17.9 y; 19 F	52	BMI decreased	Early complications: pulmonary embolism (1), major wound infection (1), minor wound infection (4), stomal stenosis (3), marginal ulcer (4), late complications: small bowel obstruction (1), incisional hernia (6), conversion from DGBP to standard gastric bypass because of severe protein calorie malnutrition (1)	Endoscopic dilation for stomalstenoses, medical treatments for marginal ulcers, adhesiolysis for small bowel obstruction, and herniorrhaphy with polypropylene for incisional hernias	0–14 y
Strauss et al 2001, New Jersey	10	15–17 y; 7 F	53.6	EWL 62%	No early complications Late complications: incisional hernia (1), symptomatic cholelithiasis (2), protein calorie malnutrition and micronutrient deficiency (1), small bowel obstruction caused by adhesion and internal hernia (1), minor nutritional complications include iron deficiency anemia (5), transient folic acid deficiency (3)	Laparoscopic cholecystectomy for symptomatic cholelithiasis, TPN and Abx for protein calorie malnutrition, operative correction for small bowel obstruction, operative repair of incisional hernia, vitamin and mineral supplementation for iron and folic acid deficiencies	6.3 y
Rand et al 1994, Florida	32	11–19 y; 27 F	47	BMI decreased to 32	There were no major postoperative complications	Revisional surgery to reduce size of the pouch for better weight loss results (3 performed, 2 scheduled), cholecystectomy (4), and abdominal panniculectomy (1)	6 y

BMI = body mass index; DGBP = distal gastric bypass; GERD = gastroesophgal reflex disease; TPN = total parenteral nutrition.
* LAGB = laparoscopic adjustable gastric banding; EWL = excess weight loss. From the (51).
** LSG = laparoscopic sleeve gastrectomy (64,65).
*** RYGB = Roux-en-Y gastric bypass. From the (51).

complication rate, including wound infection (n = 2/6), stricture (n = 1/6), and intraoperative leak (n = 1/6). Two patients showed a trocar-site bleed and renal failure, respectively (67).

Stroh et al (68) reported an overall complication rate of 14.1% and a surgical complication rate of 9.4% in a group of 144 patients (mean BMI 54.5 kg/m^2) when undergoing LSG. The single most common postoperative complication was a leak from the suture line (7%), followed by stenosis. Long-term complications of LSG, including nutritional deficiencies and failure-to-sustain weight loss, are not well described because this is a relatively new procedure. The postoperative mortality rate is approximately 1.4% (68).

LSG in the pediatric age group is of a similar safety and effectiveness when compared with adults. Pediatric patients had fewer major complications and were more compliant with follow-up than adults; however, its applicability in the adolescent age group remains controversial (69). Nevertheless, long-term results are required to further clarify the safety and effectiveness of LSG in pediatric patients.

Intragastric Balloon

IB is an endoscopic device for the temporary nonpharmaceutical and nonsurgical treatment for morbid obesity (70,71). In past years, devices such as those of Ballobes and Garren had no significant effects on weight reduction, offered a large number of complications (gastric erosion 26%, gastric ulcer 14%, Mallory-Weiss tears 11%) and a small volume of the balloon (220 mL for Garren-Edwards and 400 mL for Ballobes) (71–73). The BioEnterics intragastric balloon (BIB) (74) has a spherical shape, a high volume capacity (500–700 mL) and is designed to remain in the gastric cavity for a period of 6 months (74,75). The insertion of a BIB is usually easy and safe. Its use is totally reversible and repeatable. Although an endoscopic treatment for morbid obesity with an IB has been tested in adults with simple obesity (76), there are limited data in the literature about the use of BIB in adolescents with morbid obesity. In a large multicenter study, Genco et al (76) showed that the use of BIB induced a significant reduction of BMI and an improvement of comorbidities. Indications for BIB usage in lower degrees of obesity have been increasingly accepted (74,77), and the improvement in metabolic profile after the BIB placement has been reported in several studies (75,78–83).

The long-term effect of BIB, combined with pharmacotherapy, was superior to the combination with lifestyle modification only (84,85). Some patients were reported to continue losing weight for up to 22 months of follow-up after balloon extraction (86). Long-term maintenance of weight loss is controversial. Some studies confirm it (87), whereas others report that weight regain after BIB was universal and that almost all of the patients needed surgery after balloon removal (88).

Complication rates (eg, stapling complications) are low as suggested by several studies (58,89). Therefore, the balloon can be a preoperative treatment for patients with morbid obesity, before undergoing elective surgeries (bariatric, etc) in selected cases. So although this reversible device appears to be attractive for use in children, to date there are no published data regarding the use of this technique in children and adolescents with obesity, and it is not yet fully established whether BIB is of long-term benefit in patients with morbid obesity.

Nobili et al (90) evaluated the efficacy of Obalon intragastric balloon (OGB) on weight loss and metabolic and cardiovascular parameters for the first time in children in a group of 10 pediatric patients (range 9–17 years) with severe obesity (BMI > 30 kg/m^2 associated with obesity-related diseases or BMI > 35 without comorbidities). This study is registered on ClinicalTrials.gov (NCT02137330) and is presently ongoing; a first manuscript is in press. OGB seems to be more manageable, placeable without sedation (swallowed spontaneously in 70% of patients) and characterized by few if any adverse effects. The efficacy in inducing significant weight loss in a sizable proportion of patients starts after only 3 months.

Malabsorptive Procedure

Reports describing the outcomes related to biliopancreatic diversion and duodenal switch exist, but presently the reports are not robust. Concerns regarding associated fat-soluble vitamin deficiencies and long-term protein malnutrition limit the ability to offer specific recommendations at present (91,92), especially in pediatrics.

Protein malnutrition is usually seen after malabsorptive procedures and occurs more often in patients who do not follow dietary recommendations. Vitamin B12 deficiency results from a decrease in intrinsic factors, decreased protein intake, and decreased uptake in an often defunctionalized ileum, and can lead to anemia, glossitis, and peripheral neuropathy if unrecognized (93). Fat-soluble vitamin deficiencies are commonly seen in these procedures, with up to a 60% prevalence (94). Calcium deficiency is of particular concern in adolescent patients, given the potential for additional bone mineralization (95). Kaulfers et al (96) found significant bone density loss in patients after bariatric surgery.

The multitude and complexity of nutritional deficiencies after these procedures underscore the need for consultation with an experienced dietician both before and after the surgery and largely limit the choice of this surgical technique in adolescents.

Biliopancreatic Diversion

The duodenal switch with biliopancreatic diversion is primarily a malabsorptive operation that involves a subtotal gastrectomy (sleeve gastrectomy) with the preservation of the pylorus and the transaction of the duodenum to 3 to 4 cm from the pylorus with anastomosis to a Roux limb. This leads to a bypass of the distal 250 cm of ileum. Malabsorption is achieved by this bypass, which results in only approximately 100 cm of bowel exposed to both digestive enzymes and food (97). Although the procedure has been determined to be highly effective for weight loss, it is the least common (5% of bariatric procedures) and has fallen out of favor owing to increased nutritional deficiencies and greater operative complexity.

In 1 series of 10 adolescent patients undergoing biliopancreatic diversion (98), all of the patients lost a significant amount of weight, and all of the patients had a resolution of their comorbidities. Two patients had operative complications, including an obstruction and a gastric ulcer, but the reported nutritional deficiencies were mild. In another series of adolescents (93), 68 patients were studied retrospectively for long-term outcomes (mean 11 years). Although immediate postoperative complications were rare, this series of patients had 19 reoperations in 14 patients (including 4 obstructions and 5 incisional hernias), 3 deaths (protein malnutrition, pulmonary edema, and pancreatitis), and 9 patients with documented protein malnutrition.

Combination of Restrictive and Malabsorptive Surgical Procedures

Roux-en-Y Gastric Bypass

RYGB is still one of the most commonly used bariatric procedures for adolescents (99). For the restrictive portion of the procedure, the proximal stomach is divided, creating a small 15 to

20 cm^3 gastric pouch. The mid-jejunum is transected approximately 40 cm from the ligament of the Treitz, and a Roux limb is brought up to the new gastric pouch. The biliopancreatic limb is attached to the distal jejunum, 100 to 125 cm from the gastric pouch (97). The benefits of an RYGB include a proven ability to induce long-term weight loss and to decrease comorbid disease (92,93). The procedure is, however, irreversible, causes significant change to the normal gut orientation, and carries a risk of malnutrition if proper attention is not paid to diet and the supplementation of essential nutrients (100).

The efficacy of an RYGB for weight loss is well documented in both adults and adolescents. In the meta-analysis of RYGB procedures among adolescents by Treadwell et al (Table 3, (51)) BMI decreased anywhere from 17.8 to 22.3. A resolution of hypertension occurred in more than half of the patients, and sleep apnea was resolved in all of the patients (51).

Perioperative complications from an RYGB include pneumonia; deep venous thrombosis; pulmonary embolus; gastrointestinal hemorrhage, anastomotic obstruction leading to a rupture of the gastric pouch, obstruction of the jejunojejunal anastomosis, leakage from the staple lines or anastomoses, incisional hernias; and wound infections. Long-term complications include stomal stenosis, gastric staple line breakdown with gastrogastric fistula formation, symptomatic cholelithiasis, and internal herniation (99). In a meta-analysis (Table 3, (51)) of 131 adolescents who underwent an RYGB, there were 4 reported postoperative deaths, with only 1 of those deaths potentially related to the procedure (*Clostridium difficile* colitis 9 months after surgery). The most commonly encountered complication was protein malnutrition. In 6 studies of adolescents undergoing RYGB, complication rates ranged from 0% (n = 34) to 39% (n = 36) (51,101–103). Despite the potential for significant complications from an RYGB, data have so far indicated that this procedure is effective with a good risk-to-benefit ratio in the adolescent population, making it the presently preferred surgical therapy for adolescents (103).

At present, to our knowledge there have been no trials directly comparing LAGB to RYGB in the adolescent population. With respect to the previously described LAGB, RYGB presents a combination of restrictive and malabsorptive surgical procedures. Although it is an irreversible procedure with a risk of malabsorption of essential nutrients, RYGB includes a proven ability to induce long-term weight loss and to decrease comorbid diseases reported in various studies (104–106).

The treatment for metabolic disease provides another important factor in considering this type of bariatric surgery in adolescents with obese. Lawson et al (104) found a 37% decrease in BMI of the surgical group compared with a 3% decrease in BMI of the behavioral therapy group at 1 year. In addition, RYGB was found to be associated with remission of type 2 diabetes mellitus while improving cardiovascular risk factors. Also, Lee et al (105) found that RYGB achieves superior weight loss in adolescents when compared with LAGB in a short-term 24-month follow-up. Randomized studies with longer-term follow-ups will be needed before definitive recommendations can be made on the appropriate operation for this age group (106).

LONG-TERM FOLLOW-UP

Any adolescent undergoing bariatric intervention needs post-interventional long-term multidisciplinary follow-up. Morbidly obese patients often have nutritional deficiencies, particularly in fat-soluble vitamins, folic acid, and zinc (107). After bariatric surgery, these deficiencies may increase and new ones appear, especially because of the limitation of food intake in gastric reduction surgery and of malabsorption in bypass procedures. The risk of nutritional deficiencies depends on the percentage of weight loss and the type of surgical procedure performed. Purely restrictive procedures, for example, can induce digestive symptoms, food intolerance or maladaptative eating behaviors because of pre- or postsurgical eating disorders. Iron deficiency is common with almost all types of bariatric surgery, especially in menstruating women. Anemia can be secondary to iron deficiency, folic acid deficiency, and even vitamin B12 deficiency (108).

Malabsorption of fat-soluble vitamins and other nutrients, especially if diagnosed after bypass surgery, rarely cause clinical symptoms. Some complications have, however, been reported such as bone demineralization because of vitamin D deficiency (109) or hair loss secondary to zinc deficiency (107). Long-term problems such as changes in bone metabolism or neurological complications need to be carefully monitored. In addition, routine nutritional screening, recommendations for appropriate supplements, and monitoring compliance are imperative, whatever the bariatric procedure. Key elements of lifelong multidisciplinary management are virtually routine mineral and multivitamin supplementation, avoidance of alcohol intake, reduction in sugar/sucrose and reduction in soft drinks rich in fructose and prevention of gallstone formation with the use of ursodeoxycholic acid during the first 6 months. Pre- and postoperative therapeutic patient education programs, involving a new multidisciplinary approach based on patient-centered education, may be useful for increasing patients' long-term compliance, which is often poor. The role of the general pediatrician also must be emphasized: clinical visits and follow-ups should be monitored and coordinated with the bariatric team, including the surgeon, the obesity specialist, the dietitian, and mental health professionals (110).

RISKS AND OUTCOMES

Patients with a greater BMI and more serious medical illness are at increased risk for complications after bariatric surgery. Earlier surgical intervention alters the natural course of many obesity-related comorbidities such as NASH that otherwise would put the patient at risk for long-term complications and early mortality. Providing access to bariatric surgery earlier in life when the disease burden and severity is lower may decrease the operative risk, morbidity, and mortality. Although present short-term data show improvement in quality of life after weight loss induced by bariatric surgery (111), the long-term results have not been well studied, particularly in adolescents (112). Present data suggest bariatric intervention induced weight reduction will also improve NASH. From a methodological point of view however, irrefutable scientific evidence that improvement in liver disease results in an actual reduction in risk of death and a real increase in the life expectancy of the patient with severe obesity presents significant technical and logistical problems. A prospective randomized controlled trial that compares the mortality rate in patients with severe obesity subjected to surgical therapy to comparable patients treated with the best available medical therapies would be the ideal tool to achieve a result of indisputable evidence. The study that comes closest to this theoretical model is the Swedish Obese Subjects Study (113), in which the mortality of a vast group of patients treated with various types of surgery was prospectively compared with the mortality of a group of patients of equal obesity and similar clinical characteristics who had chosen not to undergo the surgical procedure. Relative risk of mortality was significantly lower in the surgery group (0.76, 95% confidence interval from 0.59 to 0.99, $P = 0.04$), with a reduction of 24.6% of total mortality in 10 years being the effect of surgical treatment on body weight and comorbidities (113). In the specific case of adolescents one should take into consideration the long life expectancy after surgery (which could affect the type of action and the use of device, which may be suitably modified), the increase of possible reinterventions, as well as the methods and effects of alternative and integrative therapies.

CONCLUSIONS

Bariatric surgery in pediatric patients with morbid obesity results in sustained and clinically significant weight loss and improves NASH, but also has the potential for serious complications. RYGB and LAGB are the 2 main surgical procedures that have been used in pediatric obesity. RYGB is considered a safe and effective option for adolescents with extreme obesity, as long as appropriate long-term follow-up is provided. LAGB has not been approved by Food and Drug Administration for use in adolescents, and therefore should be considered investigational only. Sleeve gastrectomy, and other types of weight loss surgery, which have gained significant use in adults, should also be considered investigational. Limited experience exists on temporary weight loss devices but because of the major advantage of reversibility they may become the initial choice in pediatric populations after investigational device exemption and institutional review board approval.

Existing data are not sufficient to recommend widespread and general use of weight loss intervention in adolescents who have no other major comorbidities. The burden of obesity–associated comorbidity such as NASH in selected patients may impact intolerably on the child?s long-term prospects that allows us to agree with a list of exceptional indications suggested in Table 1. Future studies and a long-term risk analysis of patients with obesity associated liver disease are much needed to clarify the exact indications for bariatric surgery in adolescents, and the multitude and complexity of nutritional deficiencies after these procedures limit the choice of technique in children and adolescents. We propose the rigorous collection of experiences of any and all weight loss interventions in children until prospective and controlled trials are performed. The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition provides a focus point, and on behalf of the society, the first author of this article will collect and share (anonymized) patient data from any such intervention (*nobili66@yahoo.it*) for future reference.

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