Bariatric Surgery in Adolescents with Obesity: Long-Term Perspectives and Potential Alternatives

Rana Halloun^a Ram Weiss^{a, b}

^aDepartment of Pediatrics, Ruth Children's Hospital, Rambam Medical Center, Haifa, Israel; ^bBruce Rappaport School of Medicine, Technion Institute of Technology, Haifa, Israel

Keywords

Bariatric surgery · Adolescent · Long-term follow-up · Metabolic complications of obesity · Nutritional deficiency

Abstract

Background: Severe obesity among adolescent shows a worrisome trend in regard to its increasing prevalence and poses a great challenge for treatment. Conservative measures have modest effects on weight loss, usually fail in achieving a sustainable weight loss and resolution of comorbidities. This has led to greater utilization of bariatric surgery (BS) that offers a fast reduction in body mass index with little perioperative complications. Despite the increasing utilization of BS, data are still insufficient, regarding their long-term outcome in adolescents. We review short- and long-term effects of BS and their implications on bone health and nutritional deficiencies in adolescents. In addition, we discuss possible pharmaceutical alternatives. **Summary:** BS results in a substantial weight loss of roughly 37% in the first-year post-operation and is superior to conservative measures in resolution of metabolic comorbidities. BS significantly improves health-related quality of life. Longer follow-up (F/U) shows weight regain in 50% of patients. Furthermore, reduced bone mass and nutritional deficiencies were reported

in up to 90% of patients. Most recently, alternative to BS became more relevant with approval of GLP-1 analogues use in adolescents. GLP-1 analogues are potent enough to induce moderate clinically meaningful weight loss and improvement of metabolic component. **Key Messages:** We conclude that obese adolescents without major obesity-related complications may benefit from pharmacological interventions with lifestyle modification. We advise considering BS as treatment approach in adolescents with severe obesity and major obesity-related complications with proper preoperative preparation and postoperative F/U in excellence centers.

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Introduction

The chronic disease of childhood obesity is a global epidemic and a major concern for public health that affects all ethnic groups and nationalities. Childhood obesity beholds greater risk for noncommunicable diseases, psychiatric morbidity, and higher mortality rate in adulthood [1–4]. Furthermore, the economic burden it poses on the health care system is substantial [5].

Table 1. Indications for BS in adolescents [27]

Weight criteria	Comorbidities
BMI >35 kg/m ² or >120% of the 95th percentile and a comorbidity	Obstructive sleep apnea (AHI 45), T2DM, idiopathic intracranial pressure, NASH, Blount's disease, SCFE, GERD, or hypertension
BMI >40 kg/m ² or >140% of the 95th percentile	Not required

AHI, Apnea-Hypopnea Index; the number of apnea/hypopnea events per hour of sleep. The apnea must last for at least 10 s and be associated with a decrease in oxygen saturation. The AHI is calculated by dividing the number of apnea events by the number of hours of sleep and a value >15 per hour represents moderate or severe obstructive sleep apnea [27]. GERD, gastroesophageal reflux disease; NASH, nonalcoholic steatohepatitis; SCFE, slipped capital femoral epiphysis; BS, bariatric surgery; BMI, body mass index; T2DM, type 2 diabetes mellitus.

The prevalence of obesity has increased from 4% in the mid-seventies to a peak of 18% in 2016, with 124 million children worldwide defined as obese [6]. Despite reports showing a stabilization of this trend in some countries, the prevalence of severe obesity continues to increase and poses a greater challenge for treatment [7, 8]. The definition of severe obesity includes class II and III obesity. Class II obesity is defined as body mass index (BMI) $\geq 120\%$ of the 95th percentile for age and sex corresponding to a BMI ≥ 35 kg/m² in adults. Class III obesity is defined as BMI $\geq 140\%$ of the 95th percentile for age and sex corresponding to a BMI ≥ 40 kg/m² in adults [9]. Weight loss in childhood reverses the CVD risk in adulthood [4] and greatly improves quality of life (QoL) and reduces mortality [10, 11]. A weight loss of 5–10% is sufficient in preventing long-term comorbidities, specifically cardiovascular disease [12]. Treating severe obesity with first-line therapy – modification of dietary habits, physical activity, and behavioral changes has a modest effect and renders with failure in most cases [13–15]. The sustainable weight loss is not preserved after the intervention program is over [16]. Pharmacotherapy as adjuvant to lifestyle modification may achieve better results [17]. In severely obese adolescents, the additive effect of orlistat and phentermine (both FDA approved for use in adolescents) in weight loss and reversal of comorbidities such as insulin resistance, hypertension, and hyperlipidemia are still minimal [18]. Furthermore, their side effects, especially gastrointestinal symptoms when using orlistat negatively affect the adherence to therapy [19]. Data are lack-

ing regarding their sustainable effect on weight loss. The off-label use of metformin may have a similar minimal effect of 1.16 kg/m² [20]. The limited success of conservative measures in treating severely obese adolescents has increased the utilization of bariatric surgery (BS). The use of BS has increased 2.7-fold in the past decade [21]. BS achieves fast reduction of BMI; resolution of most metabolic comorbidities alongside with few/rare perioperative complications and a strong safety profile have gained these procedures, great popularity among adolescents. Eligibility for BS differs depending on the applied guidelines [22–25]. The revised guidelines published in 2018 by the American Society for Metabolic and Bariatric Surgery Pediatric Committee recommend referring to BS, adolescents with a BMI >35 kg/m² or >120% of the 95th percentile and any comorbidity or a BMI >40 kg/m² or >140% of the 95th percentile [26] (see Table 1). Guidelines of Endocrine society differentiate between major and mild comorbidities and suggest BS in adolescents with BMI >35 kg/m² but <40 kg/m² only if accompanied with major comorbidity, such as type 2 diabetes mellitus (T2DM), moderate to extreme sleep apnea, pseudotumor cerebri, debilitating orthopedic problems, and nonalcoholic steatohepatitis (NASH) with advanced fibrosis or a BMI >40 kg/m². In addition, it emphasizes the importance of adolescents attaining at least Tanner stage 4 and near final height before referring to BS [25]. The criteria of The Interdisciplinary European Guidelines on Metabolic and Bariatric Surgery are more stringent and suggest considering BS only in adolescent with BMI >40 kg/m² and at least one comorbidity [24]. A shared requirement by the different guidelines is the necessity to evaluate the patient's ability to adhere to the postoperative dietary regimen, including micronutrient administration. Most commonly used bariatric procedures in adolescents are Roux en Y Gastric Bypass (RYGB) and sleeve gastrectomy (SG). SG is a restrictive procedure that includes resection of 85% of the stomach, along its greater curvature. RYGB is a combination of malabsorptive and restrictive procedure that includes the creation of a small stomach pouch anastomosed with the mid-jejunum (The Roux limb). The remainder, bypassed portion, of the stomach is connected to the jejunum allowing passage of bile acids and pancreatic secretions to the proximal jejunum, where they mix with ingested nutrients (The common limb). Both procedures show similar reduction in BMI and reverse of comorbidities [28, 29]. SG has gained more acceptances in the past decade and is currently the most common procedure performed in adolescents. The reason for this preference is lower perioperative complica-

Table 2. Short-term implications of bariatric procedures performed in adolescence [31, 33–40]

Participants number	Type of surgery	Age (mean age), years	F/U, years	BMI reduction, kg/m ²	Significant perioperative complications	Metabolic complications – resolution rate, %				Nutritional deficiencies			Bone health
						T2DM	HTN	IGT	DYSLIP	LFT	ferritin	B12	vit. D
Kaufers et al. [33]	61 (Teen-LABSRYGB cohort)	13.7–23.5 (17.3)		49.2 kg									BMC –7.4%, BMD z score –1.4*
Messiah et al. [34]	890	RYGB, AGB 11–19 (18.5)	1	RYGB –17.1 AGB –6.9	RYGB 21.6%, LAGB 49% 1 death	RYGB –60.7 AGB –54.3	RYGB 78.6 AGB 59.1		RYGB 58.8 AGB 23.3	RYGB 55.6 AGB 33.3	RYGB –24% ^{&} AGB 2% ^{&}		
Inge et al. [31]	242	RYGB, AGB, SG 13–19			19 (8%) (RYGB 9.3%, SG 4.5%) deaths –0								
Olbers et al. [35]	81	RYGB 16.5	5	–13.1 (–36.8 kg)	20 (25%) re-surgery	100	100	85	82.7	92	66%	16%	63%
Elhag et al. [36]	79	SG 13–17 (15.9)	2	–17 (–51.8 kg)		80	–	100	HDL 21.1 LDL 100 TG 83.3	ALT 75.9 AST 85.7	89.3% 38% had low albumin	15.3%	33.3%
Inge et al. [37]	161	RYGB 16.8–17.2 (17)	5	–26% (–37.7 kg)	1.9% deaths	86	68		HDL 78 TG 81		48.3%	3.7%	37.8%
Carbajo et al. [38]	39	OAGB 13–19 (17.8)	5	–22.3	None	100	100		100		Anemia – 1 patient		
Xanthakos et al. [39]	226 (teen labs cohort)	RYGB, SG 16.5	5	RYGB –13.9 SG –11							RYGB 71.3% SG 45.2%	NS	NS
Misra et al. [40]	22	SG 14–22	1	–12.8									BMD z-score femoral neck –0.947, lumbar spine –0.416

F/U, follow-up; AGB, adjustable gastric band; IB, intragastric balloon; SG, sleeve gastrectomy; MT, malabsorptive techniques; OAGB, One-Anastomosis Gastric Bypass; T2DM, type 2 diabetes mellitus; HTN, hypertension; DYSLIP, dyslipidemia; LFT, liver function tests; IGT, impaired glucose tolerance; BMC, bone mineral content; BMD, bone mineral density; NS, statistically not significant; RYGB, Roux en Y Gastric Bypass. *BMD z score after 2-year F/U did not fall below the expected value for gender and age. [&]Vitamins A, B12, D, folate, iron, magnesium, zinc, electrolytes.

tions including less dumping syndrome, less iron malabsorption, and less re-operations [30, 31]. Adjustable gastric banding (AGB) is not FDA approved for adolescents and shows higher failure rate and re-operation [32]. Despite the increasing use of bariatric procedures, data are still insufficient, regarding their long-term outcome in adolescents, weight regain, and their implication on bone health and nutritional deficiencies. In this review, we conducted a literature review of short- and long-term outcome and complications of BS.

Short-Term Implications of Bariatric Procedures Performed in Adolescence

Short-Term Safety

The short-term safety of bariatric procedures performed in adolescents is similar if not superior to that of adult patients (Table 2). In patients aged 18–21 years, the 30-day reoperation and readmission rates are 1.5% and 4.1%, respectively [41]. Of note, rates of acute and short-term (<12 months) complications are highly dependent of the procedure performed and the surgical center. For example, in Teen Labs, major complications that were defined as life-threatening and potentially capable of causing permanent harm or resulting in reoperation, occurred in 19 (8%) of all participants (RYGB 9.3%, SG 4.5%) [31]. In contrast – in the prospective Bariatric Outcomes Longitudinal Database (BOLD) collected from 423 surgeons at 360 hospitals across the USA evaluating short-term (≤1 year after surgery) complications of adolescents who underwent RYGB or LAGB – 21.6% of patients (98 of 454) who underwent RYGB and 49% (22 of 436) who underwent LAGB within this time frame had a significant complication. The authors reported 1 case of death due to cardiac failure occurring 5 months post-op. Twenty-nine of the RYGB patients (6.4%) and 8 of the LAGB patients (1.8%) were readmitted for re-operations [34]. Overall, bariatric procedures performed in excellence centers with a large patient volume can be considered as relatively safe [22].

Short-Term Efficacy

The impact of bariatric procedures on weight loss and obesity-related comorbidity is by far superior to forms of conservative obesity management. In the AMOS study, BMI was significantly lower in adolescent undergoing RYGB than age-matched controls who were treated conservatively. RYGB in these patients led to improvements in obesity-related cardiovascular risk factors (compo-

nents of the “metabolic syndrome”) such as altered glucose metabolism, plasma lipids, and systolic and diastolic blood pressure [42]. Similar metabolic outcomes were reported for by the Pediatric Bariatric Study Group showing a major weight loss in the first year post-op (37% reduction in BMI) along with resolution of most metabolic comorbidities [43]. Similar important improvement in the short postoperative period was also reported for QOL measures and for some but not all psychological outcomes [44]. Thus, one can safely argue that the short-term outcome data for weight loss, metabolic comorbidity resolution, and psychological outcomes in adolescents undergoing bariatric procedures in experienced centers is favorable and highly positive.

Long-Term Implications of Bariatric Procedures Performed in Adolescence

Impact on Obesity Status and Weight Regain

The main purpose of performing bariatric procedures at any age is long-term sustainable weight loss and recovery from obesity-related comorbidity. It is important to acknowledge that BS-induced weight loss, regardless of the procedure performed, is not different from other sorts of weight loss and leads to a sustained metabolic adaptation that favors weight regain [45, 46]. Data from multiple groups indicate that the early effect of these procedures in general (with some delicate differences between them) is highly positive and that the first 12–18 months post-op are characterized by a substantial excess weight loss. The weight loss reaches a plateau at about 18 months, and Inge et al. [28] have elegantly shown in obese adolescents that following RYGB, the percent change in BMI is consistent regardless of baseline BMI and is roughly 37%. This introduces a major dilemma to the caregiver regarding the optimal timing for performing such procedure. Allowing a severely obese adolescent to continue to gain weight while waiting and preparing for the procedure might adversely affect the lowest degree of BMI reached [47]. On the other hand, performing the procedure before meeting the criteria or without optimal preparation may lower the chance of achieving an optimal result [48].

The issue of weight regains following bariatric procedures raises significant questions regarding their utilization, specifically in adolescents. Studies from several groups have demonstrated in adults that 5 years or more following SG, the most commonly performed procedure in adolescents, there is a substantial weight regain and significant reduction in remission rates of obesity-related

metabolic complications [49, 50]. Moreover – on longer follow-up (F/U) of 7 years after SG – more than half of patients have regained weight substantially [51]. An important and significant predictor of weight regain following bariatric procedures is younger age of the patient [52], indicating that adolescents are probably closer to young adults in regards to their weight regain prognosis than to older obese patients. In adolescents, the presurgical weight loss of BS candidates is the best predictor of post-operative weight loss [53], suggesting that those who do adhere to compliance requirements and show up for visits yet fail to lose weight prior to surgery will probably gain less from the procedure in the long run. Surprisingly, despite high rates of severe obesity in caregivers of adolescents undergoing BS as well as family dysfunction, these factors are not related to the degree of weight loss success following the procedure [54].

It is important to mention in this context that weight regain, representing “weight cycling,” is a strong predictor of future morbidity. Significant weight cycling was shown among obese adults to relate to reduced muscle mass and strength [55]. Moreover, weight variation has been shown in adults to significantly increase the risk of cardiac mortality [56] (specifically when occurring in early adulthood in females [57]), development of T2DM [58, 59] and hypertension [60]. Thus, patients undergoing bariatric procedures with initial weight loss success followed by weight regain may be at increased risk for morbidity and mortality later. This issue has been studied in large populations yet not in the context of BS, thus longer F/U of surgical patients is warranted in order to draw reliable conclusions.

Impact on Metabolic Complications of Obesity

One of the main obesity-driven morbidities developing early in life is type T2DM. Indeed, diabetes is one of the significant complications that allow performing BS at lower BMI thresholds in adults and in adolescents. TEEN-LABS and the AMOS study clearly demonstrated that both RYGB and SG have a major and impressive effect on diabetes remission in obese adolescents. Specifically, at 5-year follow-up, in the AMOS study, 4 participants with T2DM at baseline were all in clinical remission at 5 years and in TEEN-LABS – the prevalence of T2DM went down from 14% at baseline (22 patients) to 2.4% at 5 years. The effect of BS on remission and metabolic control of T2DM is by far superior to any lifestyle or pharmacological intervention tested in obese adolescents. When the data regarding adolescents with T2DM were compared between the TEEN-LABS and TODAY [61], BS

emerged as by far superior to conservative/pharmacological management in regard to metabolic control, weight loss, and remission of other comorbidities [62]. Upon modeling future cardiovascular risk using the Framingham CVD event score – surgery reduced such risk significantly compared to medical interventions over 1 and 5 years of F/U [63]. Similarly, presence of diabetes and obesity-related kidney disease, manifested as hyperfiltration and elevated urinary albumin excretion, improved significantly in obese adolescents with T2DM undergoing surgery compared to medical therapy [64]. In view of the rather pessimistic results of the TODAY study [61], designed to test medical interventions in obese adolescents, bariatric procedures seem to be the most efficient and sustainable intervention for obese adolescents with T2DM.

Importantly, it has clearly been shown that the effects of RYGB and of SG in regard to glucose metabolism are similar [29] and are driven strictly by the weight loss per se and not by additional hormonal mechanisms, as previously postulated. Specifically – when a comparable weight loss (~18%) is induced by surgery and by diet – hepatic and muscle insulin sensitivity as well as beta-cell function are equally improved [65]. Similarly, caloric restriction in itself achieves T2DM remission as well and as fast as bariatric procedures by reducing hepatic and pancreatic lipid deposition and restoring beta-cell function [66]. The fact that weight loss is the main driving force of T2DM remission regardless of the way it was achieved highlights the fact that BS can be spared if comparable weight loss can be achieved using more conservative measures.

Nonalcoholic fatty liver disease (NAFLD) is common among obese adolescents while NASH, the marker of a significant obesity-related complication in BS guidelines, is less frequently encountered. Recent meta-analyses have shown that clinically significant improvements in NAFLD can be detected even with modest weight loss (independent of how it was achieved) yet greater weight loss is associated with greater improvements [67, 68]. Specifically, there was a dose-response relationship of weight lost with liver inflammation, ballooning, and resolution of NAFLD or NASH but limited evidence of such relation with fibrosis or NAFLD activity score. In a study performed specifically in adult patients with NASH – BS lead to resolution of NASH in 84% of participants at 5 years of F/U showing evidence of progressive reduction of fibrosis [69]. To put this result into perspective, a clinical trial of Semaglutide for obese adults with NASH resulted in a 13% weight loss, using the higher dose, after 72 weeks, and with 59% NASH resolution while changes in fibrosis

stage were not different compared to placebo [70]. These observations emphasize again that the determinant of NAFLD/NASH resolution is weight loss in general and not an effect of specific bariatric procedures.

Hypertension is commonly found in severely obese adolescents. Both AMOS and TEEN-LABS show very impressive remission of hypertension at 2 and 5 years of F/U. Specifically, in AMOS, 100% of bariatric patients had complete resolution of systolic and/or diastolic hypertension while in TEEN-LABS a 68% remission rate was observed. Other studies of obese adolescents undergoing bariatric procedures have shown comparable excellent remission rates of hypertension [38, 71]. Similarly, improvements in the typical dyslipidemia of obese adolescents (elevated triglycerides and low HDL-cholesterol [72]) are markedly improved following bariatric procedures with typical normalization occurring early post operatively yet significant recurrence over time (95% at 5-year F/U) [73]. Of note, RYGB produces the better improvements in dyslipidemia and hypertension than other bariatric surgical procedures.

The amount of weight loss needed to improve elements of the metabolic syndrome in obese children and adolescents, such as hypertension, elevated triglycerides and low HDL-cholesterol concentrations, is 0.25–0.50 BMI SD score [74]. This BMI SDs change translates to a BMI reduction of 1.0–2.0 kg/m² in a 13 years old adolescent, and is associated with an improvement of all abnormal cardiovascular risk factors, except fasting blood glucose. Specifically, in obese adolescents, a 1 mg/dL increase in HDL is typically associated with a 0.74-kg weight loss, and a 1 mg/dL decrease in triglycerides is associated with a 0.1-kg weight loss [75]. Thus, the degree of BMI change needed to improve components of the metabolic syndrome (hypertension, hypertriglyceridemia, and insulin resistance), which are the main determinants of cardiovascular morbidity in obese subjects [76], is well below that induced by bariatric procedures.

Impact on Bone Health and Fracture Risk

Despite the very positive effects of bariatric procedures on multiple metabolic parameters, there is increasing evidence of adverse skeletal effects related to these procedures. The mechanisms underlying the adverse effects of bariatric procedures on bone health may be due to potential vitamin D deficiency, significant mechanical unloading due to weight loss and an acute reduction in leptin concentrations [77]. SG has been shown to reduce bone mass by reducing bone formation along with rapid demineralization, independent of the weight loss or vitamin

D and calcium deficiencies [78]. Specifically, in adults, SG has been shown to reduce hip bone mineral density (BMD) by 9.2% at 24 months F/U [79]. Importantly, despite the fact that the majority of the weight loss following SG occurs by 24–36 months, the markers of bone turnover remain elevated well beyond that period [80]. The clinical impact of such BMD reductions is a significant increase (hazard ratio [HR] 1.3–2.3) in fracture risk following bariatric procedures [81, 82] with some studies showing even greater risk (HR up to 5) at specific skeletal sites [83]. The long-term fracture risk following RYGB seems to be even greater than that of SG [84]. Based on the current literature, fracture risk appears to manifest >2 years following the surgical procedure and seems to increase in following years [85]. The typical vulnerable site for fractures is the hip and although the absolute risk of fractures is modest, the age of fracture occurrence is much younger than expected for age-related fractures.

In obese adolescents, RYGB worsens deficiencies of micronutrients related to bone metabolism and is associated with secondary hyperparathyroidism and low BMD values [86]. The effect of bariatric procedures in adolescents manifests as clinically significant reductions in whole-body bone mineral content as well as BMD z score [33]. Compared to obese adolescents without surgery – those who underwent SG-induced weight loss had a negative impact on areal BMD and some high-resolution peripheral quantitative computed tomography parameters [40]. Specifically, SG had a negative effect on BMD z scores of the narrow neck and intertrochanteric regions of the hip [87]. Despite these findings, bone strength parameters remained stable, possibly because of a decrease in cortical bone porosity and an increase in cortical volumetric BMD. It is unclear yet whether the dynamics in parameters of bone density and strength stabilizes over time or continues to decline.

Taking into consideration that peak bone mass is not attained until early adulthood, the adverse impact of bariatric procedures performed in adolescence may have an even more deleterious effect later in life. It may be somewhat reassuring that obese adolescents typically have higher BMD than their lean peers, thus their starting point prior to surgery is better. There is a significant knowledge gap regarding the long-term impact of BS on fracture risk in adulthood of those operated during adolescence.

Impact on Postoperative Nutritional Deficiencies

Adult BS candidates have been shown to have significant nutritional deficiencies prior to surgery necessitat-

ing a structured preoperative nutritional preparation [88, 89]. Moreover, presence of such deficiencies in adults prior to performance of BS is the best predictor for their presence 12 months following surgery, specifically in SG [90]. When the F/U of patients undergoing SG is longer (4 years) – the rate of nutritional deficiencies increases with specific worsening of low vitamin D levels (86%) and presence of elevated parathyroid hormone levels (60%) [91].

When adherence to nutritional requirements is defined as taking the vitamin supplements at least 3 times a week – data from the AMOS study suggested that the adherence rate is 44–61% at 5 years of F/U [92]. More than 60% had iron deficiency regardless of adherence and rates of vitamin D and vitamin B12 were, as expected, significantly lower among those not adhering to supplementation. Two years following SG performed in obese adolescents, 89% had vitamin D insufficiency and 38% had low albumin levels [36]. In TEEN-Labs, ferritin levels decreased significantly after both procedures. Low ferritin levels were detected in 71% at 5 years after RYGB and in 45% 5 years after SG (both significantly greater rates than those observed at baseline) [39]. The authors indicated that at least 2 nutritional deficiencies were detected by 5 years in 59% of RYGB and 27% of SG patients. These observations highlight the fact that nutritional deficiencies are common in obese adolescent prior to and following bariatric procedures. The presence of such deficiencies preoperatively and poor adherence to nutritional recommendations post operatively are strong predictors of clinically significant nutritional deficiencies on F/U.

Impact on QOL and Mental Problems

Obese children and adolescents in general and BS candidates in particular typically report reduced QOL compared to their lean and overweight peers [93]. It is generally accepted that in adults there is an inverse association between weight changes and QOL, thus weight loss is usually associated with positive health related but not necessarily mental QOL changes [94]. BS in adults has been shown to increase self-harm emergencies over time including suicidal ideation and suicide attempts [95, 96]. Some studies indicate an alarming adjusted HR of 2.85 (95% CI: 2.40–3.39) for attempted suicide following bariatric procedures [97]. Importantly, the vast majority of self-harm events occurred in adults who were diagnosed with a mental health disorders within the 5 years prior to surgery.

In TEEN-Labs, joint pains, impaired physical function, and impaired health-related QOL significantly im-

proved at 1 and 3 years of F/U [98, 99]. Similar observations have been demonstrated in the AMOS study at the 5-year F/U – yet along with major improvements in health-related QOL parameters, significant mental health problems persisted despite the substantial weight loss [100]. Specifically, obese adolescents who underwent BS had significantly greater utilization of specialized psychiatric treatment services (that increased over time) compared to the control group that was treated conservatively. Self-esteem of patients undergoing surgery was significantly improved at 5 years compared to baseline yet overall mood was not. As shown in adults, poor mental health at baseline, prior to surgery, is a strong predictor of poor mental health on F/U, and the decline in mental health status seems to manifest after the first year post-op [101]. Of note, the poor mental outcome was not related to the degree of weight loss in adolescents nor in adults.

Are There Valid Alternatives to BS in Obese Adolescents?

The vast majority of obese adolescents have very low motivation for participation in lifestyle intervention programs [102]. Upon testing the long-term (at least 2 years) efficacy of such programs in >20,000 obese European adolescents treated in specialty centers, only a very modest portion of participants (7%) achieve clinically significant weight loss (at least 0.25 BMI SD score) while the vast majority are lost to F/U [103]. Of note, not surprisingly, the highest success rate of conservative obesity management was demonstrated in highly motivated patients [104]. The less obese participants of such programs usually respond better than their more obese counterparts, at least in regard to BMI reduction [15]. Regardless, the positive clinically meaningful impact on BMI of conservative management in cases of severe adolescent obesity is very modest at best. As a mandatory component of any adolescent bariatric program is the 6-month preparation period, these observations emphasize the importance of defining and identifying the compliance and motivation of participants as this can serve as a predictor of the long-term success of the surgical intervention.

Until recently, the pharmacological treatment options for obesity management in adolescents were limited. The efficacy of Orlistat and Metformin is rather modest at best and the impact of classic lifestyle interventions is modest and usually unsustainable over time [105]. The introduction of GLP-1 analogues therapy in this age-group represents a first demonstration of an agent that is potent

enough to induce moderate clinically meaningful weight loss. The recently published trial for Liraglutide in obese adolescents showed a treatment effect after 1 year of 7.14% body weight loss and 0.37 SD score in BMI with 43% of the treatment group losing at least 5% in BMI and 26.1% losing >10% of BMI [106]. These results are very similar to those shown for Liraglutide in obese adults [107, 108]. Importantly, when Liraglutide was tested in obese adolescents with T2DM, a metabolic improvement was demonstrated yet one that is much smaller than that induced by bariatric procedures without evidence of clinical remission [109]. Exenatide administered once weekly in obese adolescents reduced SD score by 0.09 over 6 months of treatment without affecting liver fat [110]. Of note, the effect size of GLP-1 analogues on BMI, specifically of Liraglutide, is within the range that is sufficient to improve most cardiovascular risk biomarkers such as hypertension and dyslipidemia yet is still significantly inferior in comparison to surgery. Moreover, cessation of drug administration results in weight regain, as in other pharmacological anti-obesity treatments [111]. Altogether, the current experience with the use of GLP-1 analogues in obese adolescents shows promising results and one could argue that a significant proportion of adolescent BS candidates could potentially benefit from such agents in order to reverse and improve minor obesity-related complications as well as their degree of obesity in general.

In summary, pharmacological treatment of obesity most probably cannot substitute BS in cases where significant complications are present, such as T2DM or steatohepatitis (although this hypothesis remains to be tested in this age-group). On the other hand, in obese adolescents with uncomplicated obesity or milder obesity-related complications (such as hypertension, dyslipidemia, or gastro-esophageal reflux disease), pharmacological treatment is highly likely to lead to a significant improvement and even normalization of the comorbidity. The advantage of pharmacological treatment in this context is its reversibility (ability to withhold treatment). On the other hand, the amount of BMI change induced by such therapy is far from sufficient in cases of obese adolescents with BMIs in the 40 s and above.

Conclusions

Bariatric surgical procedures for obese adolescents can be considered safe and efficacious in the short term. Accumulating data of longer F/U periods raises some concerns regarding the sustainability of the weight loss

achieved and the resolution of some metabolic complications along with concerns regarding bone health. For obese adolescents with severe obesity-related complications, such as T2DM, steatohepatitis, or life-threatening OSA, BS, performed with proper preoperative preparation and in excellence centers, is probably an excellent choice. Similarly, obese adolescents with BMI levels above 45 kg/m² will probably remain obese even after surgical interventions yet may benefit in regard to their complications. Obese adolescents with lower BMIs and milder obesity-related complications (such as hypertension, dyslipidemia, reduced mobility, and QOL among others) may significantly benefit from pharmacological interventions along with a structured lifestyle modification program. Such intervention will, at best, lead to a moderate weight loss that is smaller than that achieved by surgery but will probably lead to resolution of metabolic complications and improvement of psychological measures. Obviously, a combination of a pharmacological intervention and lifestyle modification will be safer in the short and long term and allow later consideration of surgery in cases of failure. We thus suggest that obese adolescents without major obesity-related complications may deserve treatment with medications with proven efficacy that are already available prior to referral to BS.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

The followings are the authors' contributions: Rana Halloun: writing – original draft and writing – review and editing; Ram Weiss: conceptualization, writing – review and editing, and supervision.

References

- 1 Zametkin AJ, Zoon CK, Klein HW, Munson S. Psychiatric aspects of child and adolescent obesity: a review of the past 10 years. *J Am Acad Child Adolesc Psychiatry*. 2004 Feb; 43(2):134–50.
- 2 Baker JL, Olsen LW, Sørensen TI. [Childhood body mass index and the risk of coronary heart disease in adulthood]. *Ugeskr Laeger*. 2008 Aug 11;170(33):2434–7.

- 3 Franks PW, Hanson RL, Knowler WC, Sievers ML, Bennett PH, Looker HC. Childhood obesity, other cardiovascular risk factors, and premature death. *N Engl J Med*. 2010 Feb 11; 362(6):485–93.
- 4 Juonala M, Magnussen CG, Berenson GS, Venn A, Burns TL, Sabin MA, et al. Childhood adiposity, adult adiposity, and cardiovascular risk factors. *N Engl J Med*. 2011 Nov 17;365(20):1876–85.
- 5 Hammond RA, Levine R. The economic impact of obesity in the United States. *Diabetes Metab Syndr Obes*. 2010 Aug 30;3:285–95.
- 6 NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. *Lancet*. 2017 Dec 16;390(10113):2627–42.
- 7 Ogden CL, Carroll MD, Curtin LR, Lamb MM, Flegal KM. Prevalence of high body mass index in US children and adolescents, 2007–2008. *JAMA*. 2010 Jan 20;303(3):242–9.
- 8 Claire Wang Y, Gortmaker SL, Taveras EM. Trends and racial/ethnic disparities in severe obesity among US children and adolescents, 1976–2006. *Int J Pediatr Obes*. 2011 Feb;6(1):12–20.
- 9 Skinner AC, Skelton JA. Prevalence and trends in obesity and severe obesity among children in the United States, 1999–2012. *JAMA Pediatr*. 2014 Jun;168(6):561–6.
- 10 Patrick DL, Skalicky AM, Edwards TC, Kuniyuki A, Morales LS, Leng M, et al. Weight loss and changes in generic and weight-specific quality of life in obese adolescents. *Qual Life Res*. 2011 Aug;20(6):961–8.
- 11 Pearl RL, Wadden TA, Tronieri JS, Berkowitz RI, Chao AM, Alamuddin N, et al. Short- and long-term changes in health-related quality of life with weight loss: results from a randomized controlled trial. *Obesity*. 2018 Jun;26(6):985–91.
- 12 Ryan DH, Yockey SR. Weight loss and improvement in comorbidity: differences at 5%, 10%, 15%, and over. *Curr Obes Rep*. 2017 Jun; 6(2):187–94.
- 13 Levine MD, Ringham RM, Kalarchian MA, Wisniewski L, Marcus MD. Is family-based behavioral weight control appropriate for severe pediatric obesity? *Int J Eat Disord*. 2001 Nov;30(3):318–28.
- 14 Johnston CA, Tyler C, Palcic JL, Stansberry SA, Gallagher MR, Foreyt JP. Smaller weight changes in standardized body mass index in response to treatment as weight classification increases. *J Pediatr*. 2011 Apr;158(4):624–7.
- 15 Danielsson P, Kowalski J, Ekblom Ö, Marcus C. Response of severely obese children and adolescents to behavioral treatment. *Arch Pediatr Adolesc Med*. 2012 Dec;166(12):1103–8.
- 16 Kalarchian MA, Levine MD, Arslanian SA, Ewing LJ, Houck PR, Cheng Y, et al. Family-based treatment of severe pediatric obesity: randomized, controlled trial. *Pediatrics*. 2009 Oct;124(4):1060–8.
- 17 Berkowitz RI, Wadden TA, Tershakovec AM, Cronquist JL. Behavior therapy and sibutramine for the treatment of adolescent obesity: a randomized controlled trial. *JAMA*. 2003 Apr 9;289(14):1805–12.
- 18 Chanoine JP, Hampl S, Jensen C, Boldrin M, Hauptman J. Effect of orlistat on weight and body composition in obese adolescents: a randomized controlled trial. *JAMA*. 2005 Jun 15; 293(23):2873–83.
- 19 Sun AP, Kirby B, Black C, Helms PJ, Bennie M, McLay JS. Unplanned medication discontinuation as a potential pharmacovigilance signal: a nested young person cohort study. *BMC Pharmacol Toxicol*. 2014 Mar 4;15:11.
- 20 McDonagh MS, Selph S, Ozipinar A, Foley C. Systematic review of the benefits and risks of metformin in treating obesity in children aged 18 years and younger. *JAMA Pediatr*. 2014 Feb;168(2):178–84.
- 21 Humayon S, Altieri MS, Yang J, Nie L, Spaniolas K, Pryor AD. Recent trends of bariatric surgery in adolescent population in the state of New York. *Surg Obes Relat Dis*. 2019 Aug; 15(8):1388–93.
- 22 Pratt JS, Lenders CM, Dionne EA, Hoppin AG, Hsu GL, Inge TH, et al. Best practice updates for pediatric/adolescent weight loss surgery. *Obesity*. 2009 May;17(5):901–10.
- 23 Kelly AS, Barlow SE, Rao G, Inge TH, Hayman LL, Steinberger J, et al. Severe obesity in children and adolescents: identification, associated health risks, and treatment approaches: a scientific statement from the American Heart Association. *Circulation*. 2013 Oct 8; 128(15):1689–712.
- 24 Fried M, Yumuk V, Oppert JM, Scopinaro N, Torres A, Weiner R, et al. Interdisciplinary European guidelines on metabolic and bariatric surgery. *Obes Surg*. 2014 Jan;24(1):42–55.
- 25 Styne DM, Arslanian SA, Connor EL, Farooqi IS, Murad MH, Silverstein JH, et al. Pediatric obesity-assessment, treatment, and prevention: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2017 Mar 1;102(3):709–57.
- 26 Pratt JSA, Browne A, Browne NT, Bruzoni M, Cohen M, Desai A, et al. ASMBS pediatric metabolic and bariatric surgery guidelines, 2018. *Surg Obes Relat Dis*. 2018 Jul;14(7): 882–901.
- 27 Chan J, Edman JC, Koltai PJ. Obstructive sleep apnea in children. *Am Fam Physician*. 2004 Mar 1;69(5):1147–54.
- 28 Inge TH, Jenkins TM, Zeller M, Dolan L, Daniels SR, Garcia VF, et al. Baseline BMI is a strong predictor of nadir BMI after adolescent gastric bypass. *J Pediatr*. 2010 Jan;156(1):103–8.e1.
- 29 Keidar A, Hershkop KJ, Marko L, Schweiger C, Hecht L, Bartov N, et al. Roux-en-Y gastric bypass vs sleeve gastrectomy for obese patients with type 2 diabetes: a randomised trial. *Diabetologia*. 2013 Sep;56(9):1914–8.
- 30 Rosenthal RJ, International Sleeve Gastrectomy Expert P, Diaz AA, Arvidsson D, Baker RS, Basso N, et al. International sleeve gastrectomy expert panel consensus statement: best practice guidelines based on experience of >12,000 cases. *Surg Obes Relat Dis*. 2012 Jan–Feb;8(1):8–19.
- 31 Inge TH, Zeller MH, Jenkins TM, Helmrath M, Brandt ML, Michalsky MP, et al. Perioperative outcomes of adolescents undergoing bariatric surgery: the teen-longitudinal assessment of bariatric surgery (Teen-LABS) study. *JAMA Pediatr*. 2014 Jan;168(1):47–53.
- 32 Zitsman JL, DiGiorgi MF, Zhang AZ, Kopolinski JS, Sysko R, Devlin MJ, et al. Adolescent gastric banding: a 5-year longitudinal study. *Obes Surg*. 2020 Mar;30(3):828–36.
- 33 Kaulfers AM, Bean JA, Inge TH, Dolan LM, Kalkwarf HJ. Bone loss in adolescents after bariatric surgery. *Pediatrics*. 2011 Apr;127(4): e956–61.
- 34 Messiah SE, Lopez-Mitnik G, Winegar D, Sherif B, Arheart KL, Reichard KW, et al. Changes in weight and co-morbidities among adolescents undergoing bariatric surgery: 1-year results from the bariatric outcomes longitudinal database. *Surg Obes Relat Dis*. 2013 Jul–Aug;9(4):503–13.
- 35 Olbers T, Beamish AJ, Gronowitz E, Flodmark CE, Dahlgren J, Bruze G, et al. Laparoscopic Roux-en-Y gastric bypass in adolescents with severe obesity (AMOS): a prospective, 5-year, Swedish nationwide study. *Lancet Diabetes Endocrinol*. 2017 Mar;5(3):174–83.
- 36 Elhag W, El Ansari W, Abdulrazzaq S, Abdullah A, Elsherif M, Elgenaid I. Evolution of 29 anthropometric, nutritional, and cardiometabolic parameters among morbidly obese adolescents 2 years post sleeve gastrectomy. *Obes Surg*. 2018 Feb;28(2):474–82.
- 37 Inge TH, Courcoulas AP, Jenkins TM, Michalsky MP, Brandt ML, Xanthakos SA, et al. Five-year outcomes of gastric bypass in adolescents as compared with adults. *N Engl J Med*. 2019 Aug 29;380(9):2136.
- 38 Carbajo MA, Gonzalez-Ramirez G, Jimenez JM, Luque-de-Leon E, Ortiz-de-Solorzano J, Castro MJ, et al. A 5-year follow-up in children and adolescents undergoing one-anastomosis gastric bypass (OAGB) at a European IFSO Excellence Center (EAC-BS). *Obes Surg*. 2019 Sep;29(9):2739–44.
- 39 Xanthakos SA, Khoury JC, Inge TH, Jenkins TM, Modi AC, Michalsky MP, et al. Nutritional risks in adolescents after bariatric surgery. *Clin Gastroenterol Hepatol*. 2020 May; 18(5):1070–81.e5.
- 40 Misra M, Singhal V, Carmine B, Bose A, Kelsey MM, Stanford FC, et al. Bone outcomes following sleeve gastrectomy in adolescents and young adults with obesity versus non-surgical controls. *Bone*. 2020 May;134: 115290.
- 41 Arafat M, Norain A, Burjonrappa S. Characterizing bariatric surgery utilization and complication rates in the adolescent population. *J Pediatr Surg*. 2019 Feb;54(2):288–92.

- 42 Olbers T, Gronowitz E, Werling M, Mårild S, Flodmark CE, Peltonen M, et al. Two-year outcome of laparoscopic Roux-en-Y gastric bypass in adolescents with severe obesity: results from a Swedish nationwide study (AMOS). *Int J Obes*. 2012 Nov;36(11):1388–95.
- 43 Lawson ML, Kirk S, Mitchell T, Chen MK, Loux TJ, Daniels SR, et al. One-year outcomes of Roux-en-Y gastric bypass for morbidly obese adolescents: a multicenter study from the Pediatric Bariatric Study Group. *J Pediatr Surg*. 2006 Jan;41(1):137–43; discussion 37–43.
- 44 Järholm K, Olbers T, Marcus C, Mårild S, Gronowitz E, Friberg P, et al. Short-term psychological outcomes in severely obese adolescents after bariatric surgery. *Obesity*. 2012 Feb;20(2):318–23.
- 45 Chu L, Steinberg A, Mehta M, O’Kane C, Toulany A, Langer JC, et al. Resting energy expenditure and metabolic adaptation in adolescents at 12 months after bariatric surgery. *J Clin Endocrinol Metab*. 2019 Jul;104(7):2648–56.
- 46 Golzarand M, Toolabi K, Hedayat M, Azam K, Douraghi M, Djafarian K. Comparative study of resting metabolic rate and plasma amino acid profile in patients who underwent laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy: 6-month follow-up study. *Obes Surg*. 2019;29(10):3125–32.
- 47 Weiss R. Surgery: bariatric surgery in adolescents—the sooner the better? *Nat Rev Endocrinol*. 2010 Mar;6(3):125–6.
- 48 Adams TD. In teens with severe obesity, can bariatric surgery wait until adulthood? *N Engl J Med*. 2019 May;380(22):2175–7.
- 49 Golomb I, Ben David M, Glass A, Kolitz T, Keidar A. Long-term metabolic effects of laparoscopic sleeve gastrectomy. *JAMA Surg*. 2015 Nov;150(11):1051–7.
- 50 Baig SJ, Priya P, Mahawar KK, Shah S, Group IBSORI. Weight regain after bariatric surgery—a multicentre study of 9617 patients from Indian Bariatric Surgery Outcome Reporting Group. *Obes Surg*. 2019 May;29(5):1583–92.
- 51 Sepúlveda M, Alamo M, Saba J, Astorga C, Lynch R, Guzmán H. Long-term weight loss in laparoscopic sleeve gastrectomy. *Surg Obes Relat Dis*. 2017 Oct;13(10):1676–81.
- 52 Shantavasinkul PC, Omotosho P, Corsino L, Portenier D, Torquati A. Predictors of weight regain in patients who underwent Roux-en-Y gastric bypass surgery. *Surg Obes Relat Dis*. 2016 Nov;12(9):1640–5.
- 53 Fennig U, Snir A, Halifa-Kurzman I, Sela A, Hadas A, Fennig S. Pre-surgical weight loss predicts post-surgical weight loss trajectories in adolescents enrolled in a bariatric program. *Obes Surg*. 2019 Apr;29(4):1154–63.
- 54 Zeller MH, Hunsaker S, Mikhail C, Reiter-Purtill J, McCullough MB, Garland B, et al. Family factors that characterize adolescents with severe obesity and their role in weight loss surgery outcomes. *Obesity*. 2016 Dec;24(12):2562–9.
- 55 Rossi AP, Rubele S, Calugi S, Calziari C, Pedelini F, Soave F, et al. Weight cycling as a risk factor for low muscle mass and strength in a population of males and females with obesity. *Obesity*. 2019 Jul;27(7):1068–75.
- 56 Cologne J, Takahashi I, French B, Nanri A, Misumi M, Sadakane A, et al. Association of weight fluctuation with mortality in Japanese adults. *JAMA Netw Open*. 2019 Mar;2(3):e190731.
- 57 Taing KY, Ardern CI, Kuk JL. Effect of the timing of weight cycling during adulthood on mortality risk in overweight and obese postmenopausal women. *Obesity*. 2012 Feb;20(2):407–13.
- 58 Rhee EJ, Cho JH, Kwon H, Park SE, Park CY, Oh KW, et al. Increased risk of diabetes development in individuals with weight cycling over 4 years: the Kangbuk Samsung Health study. *Diabetes Res Clin Pract*. 2018 May;139:230–8.
- 59 Neamat-Allah J, Barndahl M, Hüsing A, Katzke VA, Bachlechner U, Steffen A, et al. Weight cycling and the risk of type 2 diabetes in the EPIC-Germany cohort. *Diabetologia*. 2015 Dec;58(12):2718–25.
- 60 Zou H, Yin P, Liu W, Zhang Z, Yang Y, et al. Body-weight fluctuation was associated with increased risk for cardiovascular disease, all-cause and cardiovascular mortality: a systematic review and meta-analysis. *Front Endocrinol*. 2019;10:728.
- 61 Zeitler P, Hirst K, Pyle L, Linder B, Copeland K, Arslanian S, et al. A clinical trial to maintain glycemic control in youth with type 2 diabetes. *N Engl J Med*. 2012 Jun;366(24):2247–56.
- 62 Inge TH, Laffel LM, Jenkins TM, Marcus MD, Leibel NI, Brandt ML, et al. Comparison of surgical and medical therapy for type 2 diabetes in severely obese adolescents. *JAMA Pediatr*. 2018 May;172(5):452–60.
- 63 Ryder JR, Xu P, Nadeau KJ, Kelsey MM, Xie C, Jenkins T, et al. Effect of surgical versus medical therapy on estimated cardiovascular event risk among adolescents with type 2 diabetes and severe obesity. *Surg Obes Relat Dis*. 2021;17(1):23–33.
- 64 Bjornstad P, Hughs K, Kelsey MM, Shah AS, Lynch J, Nehus E, et al. Effect of surgical versus medical therapy on diabetic kidney disease over 5 years in severely obese adolescents with type 2 diabetes. *Diabetes Care*. 2020 Jan;43(1):187–95.
- 65 Yoshino M, Kayser BD, Yoshino J, Stein RI, Reeds D, Eagon JC, et al. Effects of diet versus gastric bypass on metabolic function in diabetes. *N Engl J Med*. 2020 Aug;383(8):721–32.
- 66 Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia*. 2011 Oct;54(10):2506–14.
- 67 Koutoukidis DA, Astbury NM, Tudor KE, Morris E, Henry JA, Noreik M, et al. Association of weight loss interventions with changes in biomarkers of nonalcoholic fatty liver disease: a systematic review and meta-analysis. *JAMA Intern Med*. 2019 Sep;179(9):1262–71.
- 68 Koutoukidis DA, Koshiaris C, Henry JA, Noreik M, Morris E, Manoharan I, et al. The effect of the magnitude of weight loss on non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Metabolism*. 2020 Nov;115:154455.
- 69 Lassailly G, Caiazzo R, Ntandja-Wandji LC, Gnemmi V, Baud G, Verkindt H, et al. Bariatric surgery provides long-term resolution of nonalcoholic steatohepatitis and regression of fibrosis. *Gastroenterology*. 2020 Oct;159(4):1290–301.e5.
- 70 Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. *N Engl J Med*. 2021;384(12):1113–24.
- 71 Castellani RL, Toppino M, Favretti F, Camoglio FS, Zampieri N. National survey for bariatric procedures in adolescents: long time follow-up. *J Pediatr Surg*. 2017 Oct;52(10):1602–5.
- 72 Weiss R, Kaufman FR. Metabolic complications of childhood obesity: identifying and mitigating the risk. *Diabetes Care*. 2008 Feb;31 Suppl 2:S310–6.
- 73 Qi L, Guo Y, Liu CQ, Huang ZP, Sheng Y, Zou DJ. Effects of bariatric surgery on glycemic and lipid metabolism, surgical complication and quality of life in adolescents with obesity: a systematic review and meta-analysis. *Surg Obes Relat Dis*. 2017 Dec;13(12):2037–55.
- 74 Reinehr T, Lass N, Toschke C, Rothermel J, Lanzinger S, Holl RW. Which amount of BMI-SDS reduction is necessary to improve cardiovascular risk factors in overweight children? *J Clin Endocrinol Metab*. 2016 Aug;101(8):3171–9.
- 75 Rajjo T, Almasri J, Al Nofal A, Farah W, Al-sawas M, Ahmed AT, et al. The association of weight loss and cardiometabolic outcomes in obese children: systematic review and meta-regression. *J Clin Endocrinol Metab*. 2017 Mar;102(3):758–62.
- 76 Zimmet P, Alberti KG, Kaufman F, Tajima N, Silink M, Arslanian S, et al. The metabolic syndrome in children and adolescents – an IDF consensus report. *Pediatr Diabetes*. 2007 Oct;8(5):299–306.
- 77 Casimiro I, Sam S, Brady MJ. Endocrine implications of bariatric surgery: a review on the intersection between incretins, bone, and sex hormones. *Physiol Rep*. 2019 May;7(10):e14111.

- 78 Li Z, Hardij J, Evers SS, Hutch CR, Choi SM, Shao Y, et al. G-CSF partially mediates effects of sleeve gastrectomy on the bone marrow niche. *J Clin Invest*. 2019 May;129(6):2404–16.
- 79 Maghrabi AH, Wolski K, Abood B, Licata A, Pothier C, Bhatt DL, et al. Two-year outcomes on bone density and fracture incidence in patients with T2DM randomized to bariatric surgery versus intensive medical therapy. *Obesity*. 2015 Dec;23(12):2344–8.
- 80 Muschitz C, Kocijan R, Marterer C, Nia AR, Muschitz GK, Resch H, et al. Sclerostin levels and changes in bone metabolism after bariatric surgery. *J Clin Endocrinol Metab*. 2015 Mar;100(3):891–901.
- 81 Zhang Q, Chen Y, Li J, Chen D, Cheng Z, Xu S, et al. A meta-analysis of the effects of bariatric surgery on fracture risk. *Obes Rev*. 2018 May;19(5):728–36.
- 82 Ablett AD, Boyle BR, Avenell A. Fractures in adults after weight loss from bariatric surgery and weight management programs for obesity: systematic review and meta-analysis. *Obes Surg*. 2019 Apr;29(4):1327–42.
- 83 Javanainen M, Pekkarinen T, Mustonen H, Scheinin T, Leivonen M. Two-year nutrition data in terms of vitamin D, vitamin B12, and albumin after bariatric surgery and long-term fracture data compared with conservatively treated obese patients: a retrospective cohort study. *Obes Surg*. 2018 Sep;28(9):2968–75.
- 84 Blom-Høgestøl IK, Hewitt S, Chahal-Kummen M, Brunborg C, Gulseth HL, Kristinsson JA, et al. Bone metabolism, bone mineral density and low-energy fractures 10 years after Roux-en-Y gastric bypass. *Bone*. 2019 Oct;127:436–45.
- 85 Beavers KM, Greene KA, Yu EW. Management of endocrine disease: bone complications of bariatric surgery: updates on sleeve gastrectomy, fractures, and interventions. *Eur J Endocrinol*. 2020 Nov;183(5):R119–32.
- 86 Santos D, Lopes T, Jesus P, Cruz S, Cordeiro A, Pereira S, et al. Bone metabolism in adolescents and adults undergoing Roux-En-Y gastric bypass: a comparative study. *Obes Surg*. 2019 Jul;29(7):2144–50.
- 87 Misra M, Animashaun A, Bose A, Singhal V, Stanford FC, Carmine B, et al. Impact of sleeve gastrectomy on hip structural analysis in adolescents and young adults with obesity. *Surg Obes Relat Dis*. 2020 Dec;16(12):2022–30.
- 88 Schweiger C, Weiss R, Berry E, Keidar A. Nutritional deficiencies in bariatric surgery candidates. *Obes Surg*. 2010 Feb;20(2):193–7.
- 89 Ben-Porat T, Weiss R, Sherf-Dagan S, Nabulsi N, Maayani A, Khalaileh A, et al. Nutritional deficiencies in patients with severe obesity before bariatric surgery: what should be the focus during the preoperative assessment? *J Acad Nutr Diet*. 2020 May;120(5):874–84.
- 90 Ben-Porat T, Elazary R, Yuval JB, Wieder A, Khalaileh A, Weiss R. Nutritional deficiencies after sleeve gastrectomy: can they be predicted preoperatively? *Surg Obes Relat Dis*. 2015 Sep–Oct;11(5):1029–36.
- 91 Ben-Porat T, Elazary R, Goldenshluger A, Sherf Dagan S, Mintz Y, Weiss R. Nutritional deficiencies four years after laparoscopic sleeve gastrectomy—are supplements required for a lifetime? *Surg Obes Relat Dis*. 2017 Jul;13(7):1138–44.
- 92 Henfridsson P, Laurenius A, Wallengren O, Beamish AJ, Dahlgren J, Flodmark CE, et al. Micronutrient intake and biochemistry in adolescents adherent or nonadherent to supplements 5 years after Roux-en-Y gastric bypass surgery. *Surg Obes Relat Dis*. 2019 Sep;15(9):1494–502.
- 93 Zeller MH, Inge TH, Modi AC, Jenkins TM, Michalsky MP, Helmrath M, et al. Severe obesity and comorbid condition impact on the weight-related quality of life of the adolescent patient. *J Pediatr*. 2015 Mar;166(3):651–9.e4.
- 94 Hayes M, Baxter H, Müller-Nordhorn J, Hohls JK, Muckelbauer R. The longitudinal association between weight change and health-related quality of life in adults and children: a systematic review. *Obes Rev*. 2017 Dec;18(12):1398–411.
- 95 Bhatti JA, Nathens AB, Thiruchelvam D, Grantcharov T, Goldstein BI, Redelmeier DA. Self-harm emergencies after bariatric surgery: a population-based cohort study. *JAMA Surg*. 2016 Mar;151(3):226–32.
- 96 Lim RBC, Zhang MWB, Ho RCM. Prevalence of all-cause mortality and suicide among bariatric surgery cohorts: a meta-analysis. *Int J Environ Res Public Health*. 2018 Jul;15(7):1519.
- 97 Backman O, Stockeld D, Rasmussen F, Näslund E, Marsk R. Alcohol and substance abuse, depression and suicide attempts after Roux-en-Y gastric bypass surgery. *Br J Surg*. 2016 Sep;103(10):1336–42.
- 98 Bout-Tabaku S, Gupta R, Jenkins TM, Ryder JR, Baughcum AE, Jackson RD, et al. Musculoskeletal pain, physical function, and quality of life after bariatric surgery. *Pediatrics*. 2019 Dec;144(6):e20191399.
- 99 Inge TH, Courcoulas AP, Jenkins TM, Michalsky MP, Helmrath MA, Brandt ML, et al. Weight loss and health status 3 years after bariatric surgery in adolescents. *N Engl J Med*. 2016 Jan;374(2):113–23.
- 100 Järholm K, Bruze G, Peltonen M, Marcus C, Flodmark CE, Henfridsson P, et al. 5-Year mental health and eating pattern outcomes following bariatric surgery in adolescents: a prospective cohort study. *Lancet Child Adolesc Health*. 2020 Mar;4(3):210–9.
- 101 Järholm K, Karlsson J, Olbers T, Peltonen M, Marcus C, Dahlgren J, et al. Characteristics of adolescents with poor mental health after bariatric surgery. *Surg Obes Relat Dis*. 2016 May;12(4):882–90.
- 102 Finne E, Reinehr T, Schaefer A, Winkel K, Kolip P. Overweight children and adolescents – is there a subjective need for treatment? *Int J Public Health*. 2009;54(2):112–6.
- 103 Reinehr T, Widhalm K, l'Allemand D, Wiegand S, Wabitsch M, Holl RW, et al. Two-year follow-up in 21,784 overweight children and adolescents with lifestyle intervention. *Obesity*. 2009 Jun;17(6):1196–9.
- 104 Denzer C, Reithofer E, Wabitsch M, Widhalm K. The outcome of childhood obesity management depends highly upon patient compliance. *Eur J Pediatr*. 2004 Feb;163(2):99–104.
- 105 Oude Luttikhuis H, Baur L, Jansen H, Shrewsbury VA, O'Malley C, Stolk RP, et al. Interventions for treating obesity in children. *Cochrane Database Syst Rev*. 2009 Jan; (1):CD001872.
- 106 Kelly AS, Auerbach P, Barrientos-Perez M, Gies I, Hale PM, Marcus C, et al. A randomized, controlled trial of liraglutide for adolescents with obesity. *N Engl J Med*. 2020 May;382(22):2117–28.
- 107 Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med*. 2015 Jul;373(1):11–22.
- 108 Chadda KR, Cheng TS, Ong KK. GLP-1 agonists for obesity and type 2 diabetes in children: Systematic review and meta-analysis. *Obes Rev*. 2021;22(6):e13177.
- 109 Tamborlane WV, Barrientos-Perez M, Fainberg U, Frimer-Larsen H, Hafez M, Hale PM, et al. Liraglutide in children and adolescents with type 2 diabetes. *N Engl J Med*. 2019 Aug 15;381(7):637–46.
- 110 Weghuber D, Forslund A, Ahlström H, Alderborn A, Bergström K, Brunner S, et al. A 6-month randomized, double-blind, placebo-controlled trial of weekly exenatide in adolescents with obesity. *Pediatr Obes*. 2020 Jul;15(7):e12624.
- 111 Dong Z, Xu L, Liu H, Lv Y, Zheng Q, Li L. Comparative efficacy of five long-term weight loss drugs: quantitative information for medication guidelines. *Obes Rev*. 2017 Dec;18(12):1377–85.