



The Benefit of Sleeve Gastrectomy in Obese Adolescents on Nonalcoholic Steatohepatitis and Hepatic Fibrosis

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Objective To determine whether bariatric surgery is effective for the treatment of nonalcoholic steatohepatitis (NASH) in adolescence, we compared the efficacy of laparoscopic sleeve gastrectomy (LSG) with that of lifestyle intervention (nonsurgical weight loss [NSWL]) for NASH reversal in obese adolescents.

Study design Obese (body mass index ≥ 35 kg/m²) adolescents (13-17 years of age) with biopsy-proven NAFLD underwent LSG, lifestyle intervention plus intragastric weight loss devices (IGWLD), or only NSWL. At baseline and 1 year after treatment, patients underwent clinical and psychosocial evaluation, blood tests, liver biopsy, polysomnography, and 24-hour ambulatory blood pressure estimation.

Results Twenty patients (21%) underwent LSG, 20 (21%) underwent IGWLD, and 53 (58%) received lifestyle intervention alone (NSWL). One year after treatment, patients who underwent LSG lost 21.5% of their baseline body weight, whereas patients who underwent IGWLD lost 3.4%, and patients who underwent NSWL increase 1.7%. In patients who underwent LSG, NASH reverted completely in all patients and hepatic fibrosis stage 2 disappeared in 18 patients (90%). After IGWLD, NASH reverted in 6 patients (24%) and fibrosis in 7 (37%). Patients who received the NSWL intervention did not improve significantly. Hypertension resolved in all patients who underwent LSG with preoperative hypertension (12/12) versus 50% (4/8) of the patients who underwent IGWLD ($P = .02$). The cohort-specific changes in impaired glucose metabolism were similar: 100% (9/9) of affected patients who underwent LSG versus 50% (1/2) of patients who underwent IGWLD ($P = .02$). LSG was also more effective in resolving dyslipidemia (55% [7/12] vs 26% [10/19]; $P = .05$) and sleep apnea (78% [2/9] vs 30% [11/20]; $P = .001$).

Conclusion LSG was more effective than lifestyle intervention, even when combined with intragastric devices, for reducing NASH and liver fibrosis in obese adolescents after 1 year of treatment. (*J Pediatr* 2017;180:31-7).

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Morbid obesity affects about 5% of all adolescents in Westernized countries. Obesity poses an increased risk to young individuals of becoming morbidly obese adults and developing chronic diseases, such as type 2 diabetes, obstructive sleep apnea syndrome (OSAS), hypertension, and nonalcoholic fatty liver disease (NAFLD).¹ In adolescents and adults, NAFLD is the leading cause of chronic liver disease. Its spectrum ranges from simple steatosis to nonalcoholic steatohepatitis (NASH). NASH includes inflammation and hepatocellular injury, and can progress to fibrosis, even at a young age.²

Lifestyle intervention is the first-line treatment for obesity and its comorbidities, but its efficacy is short term.³ In adults, bariatric surgery produces long-lasting and stable weight loss leading to the partial or even complete reversal of chronic disease associated with obesity.⁴⁻⁶ Recent evidence also suggests the reversal of NASH by bariatric surgery.⁷

AHI	Apnea/hypopnea index
BIB	BioEnterics IntraGastric Balloon System
BMI	Body mass index
HOMA-IR	Homeostasis model assessment of insulin resistance
IGWLD	IntraGastric weight loss devices
LSG	Laparoscopic sleeve gastrectomy
NAS	Nonalcoholic fatty liver disease activity score
NASH	Nonalcoholic steatohepatitis
NAFLD	Nonalcoholic fatty liver disease
NSWL	Nonsurgical weight loss
OGB	Obalon Gastric Balloon
OSAS	Obstructive sleep apnea syndrome
QoL	Quality of life
T0	Baseline
T1	After 12 months
Teen-LABS	Teen-Longitudinal Assessment of Bariatric Surgery

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In 2015, the position statement of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition suggested bariatric surgery as a therapeutic option in morbidly obese adolescents with NAFLD.⁸ However, data on its efficacy for patients in this age group are lacking. The Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS), a multicenter study aimed at investigating the efficacy of bariatric surgery when performed in adolescence compared with adulthood, reported that NAFLD is highly prevalent in morbidly obese adolescents by the time of surgery.⁹ Midterm results of the Teen-LABS showed beneficial effects of this surgery on weight loss maintenance, quality of life (QoL), and reversal of major metabolic abnormalities. It did not provide data on liver histology at postoperative follow-up.¹⁰

We report the early effects of laparoscopic sleeve gastrectomy (LSG) on reversal of NASH of obese NAFLD patients. Outcomes (including data on QoL, metabolic abnormalities, and sleep apnea) of 2 contemporaneous cohorts of patients who refused surgery and opted for lifestyle intervention alone (nonsurgical weight loss [NSWL]) or in combination with intragastric weight loss devices (IGWLD) are compared with those after LSG.

Methods

Consecutive obese adolescents ($n = 164$; body mass index [BMI] ≥ 35 kg/m²) with biopsy-proven NAFLD and failure to lose $\geq 10\%$ of baseline body weight over the prior 6 months were offered enrollment in this prospective pilot intervention study to evaluate efficacy of LSG on liver histology; 93 patients entered the study (**Figure 1**; available at www.jpeds.com).

According to the European Society for Paediatric Gastroenterology, Hepatology and Nutrition guidelines,⁸ patients with BMI > 40 kg/m² were offered LSG as the first surgical option; lifestyle intervention plus IGWLD was offered as an alternative. Patients with BMI between 35 and 40 kg/m² or lower, but having associated metabolic comorbidities, were offered IGWLD as the first treatment option. IGWLD consisted of balloons placed in the stomach for 3 months (Obalon Gastric Balloon [OGB; Obalon Therapeutics Inc., Carlsbad, California] in patients aged ≤ 14 years and/or with a BMI between 35 and 38 kg/m²) or 6 months (BioEnterics intragastric balloon [BIB; Orbera, Apollo Endosurgery, Austin, Texas] in patients > 14 years old and/or with a BMI > 38 kg/m²). Those patients who refused LSG or IGWLD had access to a lifestyle intervention program (NSWL) consisting of a diet tailored to the individual's requirements and physical exercise.

Inclusion criteria included: age 13-17 years; BMI ≥ 35 kg/m²; biopsy-proven NAFLD; failure to achieve 10% weight loss using lifestyle intervention alone during the prior 6 months; willingness and motivation to adhere to treatment recommendations; clear understanding of risks and benefits deriving from medical treatment and surgery, including lifestyle commitment in case of LSG; and dedicated family relatives willing to serve as caregivers.

Exclusion criteria included: genetic obesity; any endocrine or systemic disease, except metabolic abnormalities related

to obesity; severe gastroesophageal reflux disease and/or esophagitis; large sliding hiatal hernia (> 5 cm) or paraesophageal hernia type III; psychiatric disorder; previous gastrointestinal surgery; and use of recreational drugs and/or alcohol abuse (> 140 g/wk).¹¹

At baseline (T0) and after 12 months (T1) patients were clinically assessed and underwent fasting biochemistry, oral glucose tolerance test, liver ultrasound examination and biopsy, polysomnography, 24-hour ambulatory blood pressure monitoring, and psychosocial evaluation according to protocols established at the Bambino Gesù Children's Hospital.^{3,12,13}

In accordance with the recommendations of the Ethics Committee at the Bambino Gesù Children's Hospital that approved the study protocol (NCT 02564679), it was designed as a prospective pilot investigation; patients were not assigned randomly to treatment groups. Written informed consent was obtained from parents/legal guardians and patients.

Glucose metabolism was assessed by calculating the homeostasis model assessment of insulin resistance (HOMA-IR) as fasting insulin (μ U/L) \times fasting glucose (nmol/L)/22.5 and the ratio between the incremental areas under the curve of glucose and insulin during the oral glucose tolerance test.

The polysomnography montage (Siesta; Compumedics, Abbotsford, Australia) was equipped as described elsewhere with simultaneous monitoring of end-tidal carbon dioxide pressures (Capnostream; Oridion, Needham, Massachusetts).¹² The apnea/hypopnea index (AHI) was defined as the number of apnea and hypopnea events per hour of total sleep time. OSAS was classified as mild (AHI ≥ 3 events/h), moderate (AHI 5-10 events/h), and severe (AHI ≥ 10 events/h).¹²

All patients underwent 24-hour ambulatory blood pressure monitoring (Spacelab 90207; Spacelab Inc, Redmond, Washington) equipped with an adequate cuff-size. Measurements were recorded as elsewhere described and hypertension defined on the basis of reference standards adjusted for sex and height.¹³

Liver biopsy was performed at T0 and T1 using an automatic core biopsy device (Biopince, Amedic, Sweden) with an 18-G needle under deep sedation and ultrasound guidance (Acuson Sequoia C512 scanner equipped with a 15L8 transducer; Davis Medical Electronics, Inc, Vista, California).¹⁴ A single pathologist, blind to the treatment arm, reviewed and scored liver histology. Steatosis (0-3), lobular inflammation (0-3), and hepatocyte ballooning (0-2) were scored using the NAFLD activity score (NAS), which ranged from 0 to 8 based on the criteria of the NAFLD Clinical Research Network. The stage of fibrosis was scored using a 5-point scale (stage 0-4). NASH was defined as NAS ≥ 5 .¹⁵

Intervention

Patients underwent nutritional counseling with registered dietitians at T0, T1, and throughout the follow-up period. Total calories, micronutrient and macronutrient intake, and alcohol consumption were estimated by 7-day dietary diary recall for all patients. A balanced diet (40 kcal/kg/d, carbohydrates 55%, proteins 15%, and lipids 30%)³ and aerobic physical activity (30 min/d) were prescribed.

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