



# 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  $\geq 35$  kg/m<sup>2</sup>) 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).<sup>1</sup> 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.<sup>2</sup>

Lifestyle intervention is the first-line treatment for obesity and its comorbidities, but its efficacy is short term.<sup>3</sup> 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.<sup>4-6</sup> Recent evidence also suggests the reversal of NASH by bariatric surgery.<sup>7</sup>

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.<sup>8</sup> 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.<sup>9</sup> 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.<sup>10</sup>

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]  $\geq 35$  kg/m<sup>2</sup>) 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](http://www.jpeds.com)).

According to the European Society for Paediatric Gastroenterology, Hepatology and Nutrition guidelines,<sup>8</sup> patients with BMI  $> 40$  kg/m<sup>2</sup> 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/m<sup>2</sup> 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  $\leq 14$  years and/or with a BMI between 35 and 38 kg/m<sup>2</sup>) or 6 months (BioEnterics intragastric balloon [BIB; Orbera, Apollo Endosurgery, Austin, Texas] in patients  $> 14$  years old and/or with a BMI  $> 38$  kg/m<sup>2</sup>). 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  $\geq 35$  kg/m<sup>2</sup>; 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).<sup>11</sup>

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.<sup>3,12,13</sup>

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 ( $\mu$ 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).<sup>12</sup> 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  $\geq 3$  events/h), moderate (AHI 5-10 events/h), and severe (AHI  $\geq 10$  events/h).<sup>12</sup>

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.<sup>13</sup>

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).<sup>14</sup> 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  $\geq 5$ .<sup>15</sup>

## 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%)<sup>3</sup> and aerobic physical activity (30 min/d) were prescribed.

OGB and BIB were offered on the basis of the patients' age and BMI.<sup>16</sup> Because the OGB was smaller than the BIB device (250 mL vs 600 mL), was more easily swallowed, and did not require sedation, the OGB was placed in 7 younger patients with BMIs of <38 kg/m<sup>2</sup>. The BIB was placed in either older patients or younger patients with BMIs of ≥38 kg/m<sup>2</sup>.

The OGB was usually swallowed and removed after 3 months without tracheal intubation; an outpatient procedure was used for both positioning and removal. A second OGB was added after 1 month if the patient complained of persistent hunger and/or to enhance weight loss. The risk of rupture and deflation was rare. The BIB was positioned using endoscopy under deep sedation during a hospital stay of ≤3 days and was removed after 6 months using tracheal intubation during an outpatient procedure. In the first 2 weeks after the BIB positioning, a semiliquid diet was prescribed. Risk of rupture and deflation was extremely rare.

LSG was performed with a 5-trocar approach under general anesthesia with endotracheal intubation. To greatly reduce surgical risk, an optical trocar was used for the first access, avoiding a blind access with a Veress needle. Complete dissection of the greater curvature, 6 cm from the pylorus up to the gastroesophageal junction, was obtained using a radiofrequency device (Ligasure; Medtronic, Minneapolis, Minnesota). The gastric sleeve was calibrated with a 40F bougie using 60 mm sequential firing (TristapleEndoGia; Medtronic). An intraoperative blue methylene test was performed to evaluate suture line integrity and gastric pouch volume. A semiliquid diet was prescribed for the first month after surgery, then a solid diet was reintroduced at the end of month 1 after performing a barium meal to evaluate both the gastric outlet and residual gastric volume.<sup>17</sup>

### Follow-Up

The multidisciplinary team evaluated the patients at baseline and 1, 3, 6, and 12 months. Body weight, nutritional habits, and physical activity were recorded during monthly meetings with dietitians and nurses. Clinical examinations, psychosocial questionnaires, blood tests, liver ultrasound and liver biopsy, ambulatory blood pressure monitoring, and polysomnography were performed at T0 and T1.

### Statistical Analyses

Data were expressed as mean values ± SD or counts and percentages. Data distribution was evaluated by the Kolmogorov-Smirnov test. Variables that were not normally distributed were log transformed (eg, AHI) but reported as "not log transformed" in the text for clarity. Because some patients in the lifestyle intervention group dropped out of the study at months 6 (n = 14) or 12 (n = 17), the analysis was performed using the last observation carried forward approach. Comparisons were performed using the Student *t* test, ANOVA, the Fisher exact test, and McNemar tests as appropriate.

Predictors of changes in OSAS and NASH after the intervention were identified using the Pearson correlation and the multiple linear regressions (stepwise method) with changes of BMI z-score, weight, waist circumference, and insulin

resistance (by HOMA-IR) over time as independent variables. Data were analyzed using STATISTICA (version 2010; Statistica, Chicago, Illinois). *P* ≤ .05 was considered significant.

## Results

Of 164 patients, 93 (56.7%) met the inclusion criteria and were enrolled in the study; 71 (43.3%) were excluded (Figure 1). Enrolled and excluded patients did not differ in anthropometrics, clinical characteristics, socioeconomic status, or cognitive performance as estimated by IQ (data not shown). Baseline anthropometrics, clinical, and metabolic characteristics of the 93 enrolled patients (46.2% males) are described in Table I (available at [www.jpeds.com](http://www.jpeds.com)). Twenty patients (21%) underwent LSG; 20 (21%) received intragastric devices plus lifestyle intervention (7 OGB and 13 BIB, respectively). Fifty-three patients (58%) opted for the lifestyle intervention with no device (NSWL).

### Perioperative (30 Days) and Follow-Up Surgery Complications

Of the 7 patients, 3 (42.8%) required placement of a second balloon 35 ± 6 days after the first procedure. In 2 cases, positioning required endoscopy. No major perioperative complications (gastric leak, perforation or erosion, bleeding, or persistent vomiting) were recorded. The OGB was removed endoscopically in all the patients under deep sedation after 13.5 ± 1 weeks by puncturing the balloon with a sclerotherapy needle and grasping it with foreign body forceps. One patient presented with asymptomatic deflation of 1 of the 2 balloons and that was evacuated spontaneously as confirmed by abdominal radiography.

One patient developed persistent vomiting that resolved after 5 days of treatment with ondansetron (0.15 mg/kg IV up to a maximum of 4 mg/d). All the gastric devices remained in place for the planned period and there were no complications or adverse events that required emergency removal. Balloons were removed endoscopically under general anesthesia with endotracheal intubation after 27.2 ± 4 weeks using accessories designed specifically to deflate and remove the device.<sup>17</sup>

The mean postoperative hospital stay was 4.5 ± 1.5 days. No major perioperative complication was recorded. One patient developed dysphagia that resolved completely after 15 days. Only 1 girl required hospital readmission; she presented with bronchopneumonia and pleural effusion 2 weeks after LSG and was treated with IV antibiotics (amoxicillin-clavulanate 50 mg/kg/d maximum 3 g/d and clarithromycin 8 mg/kg/d maximum 1 g/d).

### LSG versus Lifestyle Intervention with and without Intragastric Balloon: Follow-Up Data

All LSG and IGLWD patients regularly attended the follow-up clinical appointments and underwent liver biopsy at T1. In the NSWL group, 14 patients (26%) dropped out of the study at 6 and 17 months at T1; 22 patients (41.5%) completed the 12-month follow-up and underwent liver biopsy (Figure 1).

**Table II.** Liver histology in LSG versus nonsurgical group

	Surgical patients			Nonsurgical patients					
	LSG		<i>P</i>	IGWLD		<i>P</i>	NSWL		<i>P</i>
	T0	T1		T0	T1		T0	T1	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)			
20 (100)	20 (100)	20 (100)	20 (100)	53 (100)	22 (41.5)				
Steatosis									
0	0 (-)	15 (75)	.001	2 (10)	13 (65)	.02	3 (5.7)	14 (63.6)	.01
1	7 (35)	3 (15)	0.10	11 (55)	5 (25)	.06	41 (77.3)	3 (13.7)	.01
2	11 (55)	2 (10)	.05	4 (20)	2 (10)	0.11	6 (11.3)	5 (22.7)	0.10
3	2 (10)	0 (-)	.01	3 (15)	0 (-)	.01	3 (5.7)	0 (-)	.02
Inflammation									
0	3 (15)	9 (45)	.04	5 (25)	11 (55)	.09	18 (33.9)	8 (36.8)	0.86
1	17 (85)	11 (55)	.001	13 (65)	9 (45)	0.12	35 (66.1)	14 (63.6)	0.89
2	0 (-)	0 (-)	—	2 (10)	0 (-)	—	0 (-)	0 (-)	—
Portal inflammation									
0	0 (-)	6 (30)	.04	9 (45)	11 (55)	0.88	22 (41.5)	5 (22.7)	0.36
1	20 (100)	14 (70)	0.21	9 (45)	9 (45)	0.65	27 (51)	13 (59.1)	0.45
2	0 (-)	0 (-)	—	2 (10)	0 (-)	—	4 (7.5)	4 (18.2)	0.13
Ballooning									
0	0 (-)	16 (80)	.01	5 (25)	13 (65)	.03	27 (51)	14 (63.6)	0.39
1	12 (60)	4 (20)	.001	12 (60)	6 (30)	.04	20 (37.7)	3 (13.7)	0.21
2	8 (40)	0 (-)	—	3 (15)	1 (10)	0.13	6 (11.3)	5 (22.7)	0.16
Fibrosis									
0	0 (-)	0 (-)	—	0 (-)	0 (-)	—	0 (-)	0 (-)	—
1	0 (-)	18 (90)	.001	7 (35)	15 (75)	.02	37 (69.8)	12 (54.5)	0.67
2	20 (100)	2 (10)	.001	13 (65)	5 (25)	.04	16 (30.2)	10 (45.5)	0.52
NAS									
1	0 (-)	13 (66.5)	.001	0 (-)	5 (25)	—	0 (-)	3 (13.7)	.01
2	0 (-)	4 (20)	.04	1 (5)	6 (30)	.05	16 (30.2)	3 (13.7)	0.14
3	3 (15)	1(5)	0.14	9 (45)	9 (45)	0.46	21 (39.6)	11 (50)	0.34
4	11 (55)	2 (10)	.05	4 (20)	0 (-)	—	10 (18.9)	0 (-)	—
5	6 (30)	0 (-)	—	6 (30)	0 (-)	—	6 (11.3)	5 (22.6)	0.15
6	0 (-)	0 (-)	—	0 (-)	0 (-)	—	0 (-)	0 (-)	—
7	0 (-)	0 (-)	—	0 (-)	0 (-)	—	0 (-)	0 (-)	—

### Liver Histology

In the LSG cohort the fibrosis score improved significantly after surgery (Table II): all patients who underwent LSG (100%) had stage 2 fibrosis at T0, but 10% had stage 2 fibrosis at T1 ( $P = .001$ ). Frequencies of patients affected by steatosis and ballooning decreased from 55% to 10% for grade 2 steatosis and from 40% to 0% for grade 2 ballooning ( $P = .001$ ). NASH was diagnosed in 30% of patients at T0 and disappeared in all at T1.

In the nonsurgical cohorts ( $n = 73$ ; IGWLD and NSWL cohorts combined), 29 patients (40%) had stage 2 fibrosis at baseline. Forty-two (57.5%) underwent follow-up biopsy. Of the 29 patients with fibrosis at the baseline, 16 cases underwent follow-up biopsy and fibrosis persisted in all as did inflammation and ballooning (Figure 2).

In the entire study population, the reduction of NAS score was correlated with the changes over time in body weight ( $R^2 = 0.36$ ;  $\beta = 0.35$ ;  $P < .001$ ), BMI z-score ( $R^2 = 0.54$ ;  $\beta = 0.16$ ;  $P < .001$ ), waist circumference ( $R^2 = 0.55$ ;  $\beta = 0.10$ ;  $P < .001$ ), and HOMA-IR ( $R^2 = 0.53$ ;  $\beta = 0.38$ ;  $P < .001$ ).

### Weight Loss, Metabolic Abnormalities, and QoL

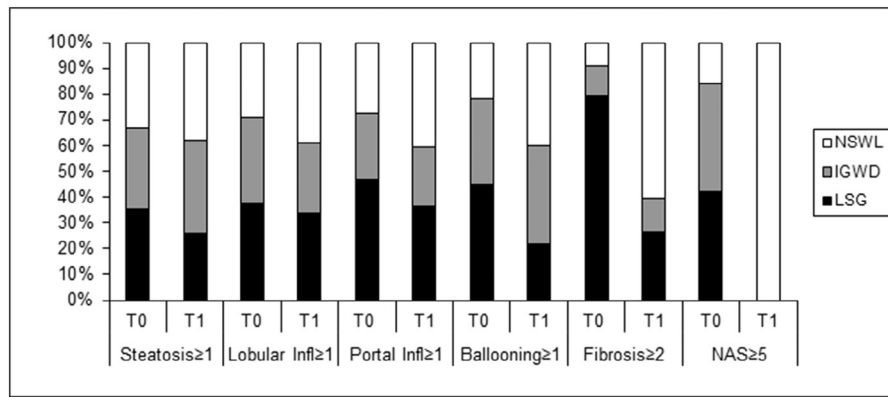
Weight and BMI decreased significantly at T1 only after LSG (by 21.5% and 20.6%, respectively). In the IGWLD cohort, they

decreased by 3.4% and 3.2%, but these changes were not significant. In the NSWL cohort, the weight increased by 1.7%, but the BMI decrease by 1.9%; in all cohorts there were no significant differences at T1 in the heights (Figure 3; available at www.jpeds.com). Table III shows follow-up metabolic data of 3 cohorts, patients who underwent LSG versus other cohorts (IGWLD and NSWL); at T2, the fasting insulin ( $P = .05$ ), 2-hour insulin ( $P = .03$ ), 2-hour glucose ( $P = .05$ ), and HOMA-IR ( $P = .04$ ) levels were significantly lower in the patients who underwent LSG than in the other cohorts.

LSG was followed by a significant improvement or even reversal of hypertension, dyslipidemia, impaired glucose metabolism, and OSAS (Table IV). Indeed, at T0, mild, moderate, and severe OSAS were diagnosed, in 3 (15%), 4 (20%), and 2 (10%), respectively, patients with LSG. In contrast, at T1 it persisted only in 2 patients (10%), one with mild and the other with moderate OSAS (5%). AHI ameliorated in parallel with the decrease of BMI z-score ( $R^2 = 0.44$ ;  $\beta = 0.26$ ;  $P < .001$ ), body weight ( $R^2 = 0.27$ ;  $\beta = 0.14$ ;  $P < .01$ ) and waist circumference ( $R^2 = 0.39$ ;  $\beta = 1.19$ ;  $P = .01$ ). OSAS did not ameliorate in the nonsurgical groups.

Patients who underwent LSG experienced a significant improvement in their overall QoL score (mean values decreased from  $74.14 \pm 12.66$  to  $86.18 \pm 11.74$ ;  $P = .05$ ) and in the social





**Figure 2.** The trends of liver histology at T0 and T1 in 3 groups. The trends of histological modifications is expressed as percentage (%).

(mean values decreased from  $60.23 \pm 19.91$  to  $72.46 \pm 13.44$ ,  $P = .02$ ), emotional (mean values decreased from  $62.47 \pm 22.18$  to  $81.77 \pm 16.22$ ;  $P = .04$ ), and physical functioning areas (mean values decreased from  $62.77 \pm 23.56$  to  $84.12 \pm 11.91$ ;  $P = .01$ ). Lifestyle intervention did not affect the patients' QoL.

### Discussion

LSG was followed by improved NASH and reverted hepatic fibrosis in 90% of cases. In the cohorts treated by lifestyle

intervention alone or combined with intragastric balloons to favor weight loss, NASH persisted in one-half the patients and fibrosis in one-third of patients after 1 year of treatment. Histology ameliorated primarily in the IGWLD group. In addition, LSG was followed by better results than NSWL interventions in terms of improvement of QoL and metabolic abnormalities. The ability to produce long-term weight loss remains a key issue in morbid obese adolescents. In the nonsurgical groups, weight loss at 1 year was minimal or null. In the NSWL cohort, compliance was poor and >50% were lost to follow-up.

**Table III.** Anthropometric, clinical, and laboratory variables in 3 groups at T1 and T0\*

	T0			P	T1			P
	LSG (20)	IGWLD (20)	NSWL (53)		LSG (20)	IGWLD (20)	NSWL (22)	
Age (y)	16.71 (1.44)	14.13 (2.12)	14.67 (1.89)	.06	17.63 (1.40)	15.32 (2.09)	15.05 (1.37)	.04
Sex (M/F)	7/13 (35/65%)	8/12 (40/60%)	28/25 (52.83/47.17%)	.10	7/13 (35/65%)	8/12 (40/60%)	8/14 (36.36/63.64)	.24
Weight, kg	137.12 (14.89)	107.78 (16.23)	103.94 (7.44)	.02	107.67 (11.08)	104.15 (14.65)	105.70 (6.92)	.24
Height, cm	167.71 (1.59)	163.45 (1.67)	160.06 (1.8)	.22	167.73 (1.14)	163.5 (1.66)	163.59 (1.24)	.69
BMI, kg/m <sup>2</sup>	48.56 (4.15)	40.24 (5.02)	40.40 (3.55)	.05	38.54 (3.51)	38.93 (4.67)	39.61 (3.71)	.67
WC, cm	119.52 (11.93)	104.35 (7.32)	105.29 (7.65)	.07	104.46 (13.44)	98.96 (7.22)	99.86 (11.57)	.09
BMI z-score	2.99 (0.37)	2.77 (0.69)	2.89 (0.64)	.10	2.12 (0.82)	2.21 (0.53)	2.41 (0.68)	.10
SBP, mm Hg	123 (8)	112 (14)	117 (12)	.21	116 (8)	113 (16.88)	114 (6.38)	.44
DBP, mm Hg	68 (10)	69 (10)	65 (7)	.11	71 (9)	66 (14.44)	64 (1.44)	.56
AST, UI/L	30 (10)	38 (19)	34 (16)	.10	22 (6)	25 (11.06)	32 (25.13)	.06
ALT, UI/L	38 (15)	31 (11)	47 (10)	.06	24 (10)	24 (16.68)	37 (14.43)	.05
Uric acid, mg/dL	8 (1)	7 (1)	6 (2)	.55	6 (1)	6 (1)	6 (1)	.64
Total cholesterol, mg/dL	162 (29)	166 (21)	162 (25)	.75	145 (20)	154 (19)	141 (26)	.12
LDL cholesterol, mg/dL	103 (18)	120 (35)	100 (25)	.11	92 (21)	96 (16)	94 (30)	.35
HDL cholesterol, mg/dL	42 (10)	40 (10)	43 (7)	.82	40 (10)	41 (9)	40 (14)	.47
Triglycerides, mg/dL	123 (51)	100 (36)	115 (23)	.33	95 (31)	93 (23)	105 (51)	.16
Fasting glucose, mg/dL	85 (16)	85 (10)	82 (8)	.79	78 (8)	86 (10)	84 (11)	.78
Glucose-120', mg/dL	123 (20)	106 (19)	113 (21)	.14	85 (17)	102 (18)	111 (21)	.05
HbA1c, mmol/mol	39.41 (6.08)	34.80 (2.43)	32.90 (1.95)	.56	34.16 (2.93)	34.41 (2.17)	32.54 (0.77)	.84
Insulin, mU/L	32 (13)	28 (9)	25 (13)	.41	16 (7)	20 (6)	24 (8)	.05
Insulin -120', mU/L	187 (96)	120 (64)	151 (96)	.04	74 (70)	99 (57)	103 (67)	.03
C-peptide, ng/mL	3.48 (0.92)	2.12 (0.34)	2.26 (1.17)	.24	2.18 (0.48)	2.24 (0.32)	2.09 (0.22)	.46
HOMA-IR	6.75 (2.56)	5.93 (1.98)	5.84 (2.05)	.06	3.14 (1.44)	4.80 (2.47)	5.46 (1.55)	.04
AUC <sub>Insulin(0-120)'/AUC<sub>Glucose(0-120)'</sub></sub>	1.23 (0.46)	0.91 (0.32)	0.85 (0.44)	.09	0.99 (0.21)	0.87 (0.15)	0.77 (0.28)	.65

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; C-peptide, connecting peptide; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; Tot-C, total cholesterol; WC, waist circumference. Data are presented as mean values ± SD.

\*Were considered statistically significant at  $P \leq .05$  at ANOVA test.

**Table IV.** The trend of comorbidities at T0 and T1 in 3 groups

	Hypertension (%)				OSAS (%)				Dyslipidemia (%)				IGT (%)			
	T0	T1	IC 95%	P	T0	T1	IC 95%	P	T0	T1	IC 95%	P	T0	T1	IC 95%	P
LSG	60	0	28.24 to 60	.005	45	15	2.44 to 30	.03	60	5	23.66 to 55	.001	25	0	-1.09 to 25	.05
IGWLD	45	40	-4.75 to 5	.97	30	20	-6.84 to 10	0.5	40	25	-6.23 to 15	.45	20	10	-6.84 to 10	.5
NSWL	39.62	22.72	5.66 to 16.9	.25	22.64	27.27	-5.01 to -4.63	.98	41.5	36.3	-6.22 to 5.2	.5	15.09	13.63	-4.3 to 2.27	.98

Bold values indicate statistically significant values and were considered statistically significant at  $P \leq .05$ .

We investigated the effect of bariatric surgery on liver histology in young patients. Biopsy-proven fatty liver was detected in 59% of the 242 obese adolescents undergoing bariatric surgery in the Teen-LABS.<sup>9</sup> The study has not yet reported the effect of surgery on abnormal liver histology. Studies of adult patients showed resolution of NAFLD after LSG in 84 patients<sup>18</sup> and amelioration of steatohepatitis and fibrosis in 109 morbidly obese individuals with biopsy-proven NASH who lost weight after either gastric banding or Roux-and-Y gastric bypass.<sup>7</sup> In the latter case series, 94% of patients with mild NASH and 70% of those with severe NASH experienced NASH remission. The NAS score decreased from 5 to 1, and fibrosis was reduced in 33.8% of patients. Interestingly, 1 year after surgery NASH persisted in patients who lost less weight.<sup>7</sup>

In our series, the best results in terms of NASH and fibrosis reversal were seen in the LSG cohort; these patients lost a significant amount of excess weight and the changes in NAS score paralleled their weight loss.

Several mechanisms might have produced the restitution of liver histology after LSG. Reduction of visceral fat depots after weight loss protects against the overflow of fatty acids to the liver. Increased availability of fatty acids, in turn, is pivotal to the pathogenesis of fatty liver causing mitochondrial dysfunction and lipotoxicity.<sup>19</sup> LSG leads to a reduction of the triglyceride-rich lipoprotein–apoB-100 production rate and an increase in the apoB-100 fractional catabolic rate.<sup>20</sup> Gastric surgery caused changes in the paracrine concentrations of glucagon-like peptide-1 and serum bile acids. In patients who underwent LSG, circulating insulin and glucagon-like peptide-1 concentrations increased soon after the meal. Glucagon-like peptide-1 directly affects hepatocytes by activating genes involved in fatty acid  $\beta$ -oxidation and insulin sensitivity.<sup>21,22</sup> In rats, bile acids increased after sleeve gastrectomy. Some bile acids downregulate hepatic lipogenic and bile acid synthetic genes that are responsible for the hepatic steatosis.<sup>23</sup> Consistent with the published literature,<sup>24</sup> we recently described altered gut microbiota in young patients with NAFLD,<sup>25</sup> and LSG might restore the physiological microflora as observed in experimental murine models. All these factors probably contributed to the amelioration of hepatic insulin resistance. Indeed, the HOMA-IR, a rough estimate of the hepatic insulin resistance, decreased significantly after surgery.

Surgery was also followed by beneficial remission of hypertension, the amelioration of dyslipidemia and OSAS. These results, as well as the significant amelioration of the QoL score, confirmed previous results.<sup>8,10,26</sup>

In the nonsurgical cohorts, the reversal of NASH and fibrosis was modest and occurred only in patients who lost

weight. There was no beneficial effect of lifestyle intervention on QoL despite the constant psychological support that was provided by the multidisciplinary therapeutic approach.

In this pilot study, we did not observe any major perioperative complication in patients undergoing LSG or in those who received intragastric balloons, probably owing to the long experience of our surgeons. Effectiveness of intragastric devices in terms of weight loss may be questionable because the procedure did not induce long-term benefits. However, fibrosis stage 2 was reduced and NAS score decreased in 50% of the patients in the IGWLD cohort (Table II). Furthermore, a recent meta-analysis of 5 studies in adolescents with 6-24 months of follow-up demonstrated that LSG induces weight loss similar to Roux-en-Y gastric bypass, with very few surgery-related complications and no mortality.<sup>27</sup>

A number of medical, surgical, and public health organizations endorse bariatric surgery in obese adolescents with metabolic comorbidities (BMI  $\geq 35$  kg/m<sup>2</sup> and  $\geq 1$  major comorbidity or BMI  $\geq 40$  kg/m<sup>2</sup> and at least a mild comorbidity) as an effective treatment in patients who fail to lose weight after lifestyle intervention.<sup>28</sup> Nevertheless, most young patients have still limited access to bariatric surgery because of ethical, efficacy, and safety concerns.

Results of the present investigation are promising, but the study was affected by limitations. It was a small pilot study of consecutive patients treated by surgery or lifestyle intervention; treatment was not assigned randomly. It is impossible to design a randomized clinical trial comparing surgery versus lifestyle because of the net superiority of the former, in terms of weight loss, and the low retention to treatment of the latter. Patients who opted for surgery were more complicated than patients who refused; they probably felt their severe and life-threatening obesity was an important condition. Patients in the IGWLD group experienced weight loss in the first 1-6 months of the follow-up with some benefits to their liver histology. Any further beneficial effect might have been masked or abolished, however, by the weight regain after the intragastric device removal.

LSG reverted steatohepatitis and reduced hepatic fibrosis in morbidly obese adolescents with NAFLD 1 year after surgery. It was also beneficial for resolving hypertension and ameliorating dyslipidemia and OSAS. In contrast, lifestyle intervention, alone or in combination with IGWLD, was not able to induce a sustained weight loss and therefore was less effective in reverting liver histology and metabolic abnormalities.

Longitudinal and larger cohort studies are needed to compare the effectiveness of bariatric surgery with that of lifestyle intervention for preventing the progression of NAFLD,

early in its natural history, toward more severe forms of liver derangement. ■

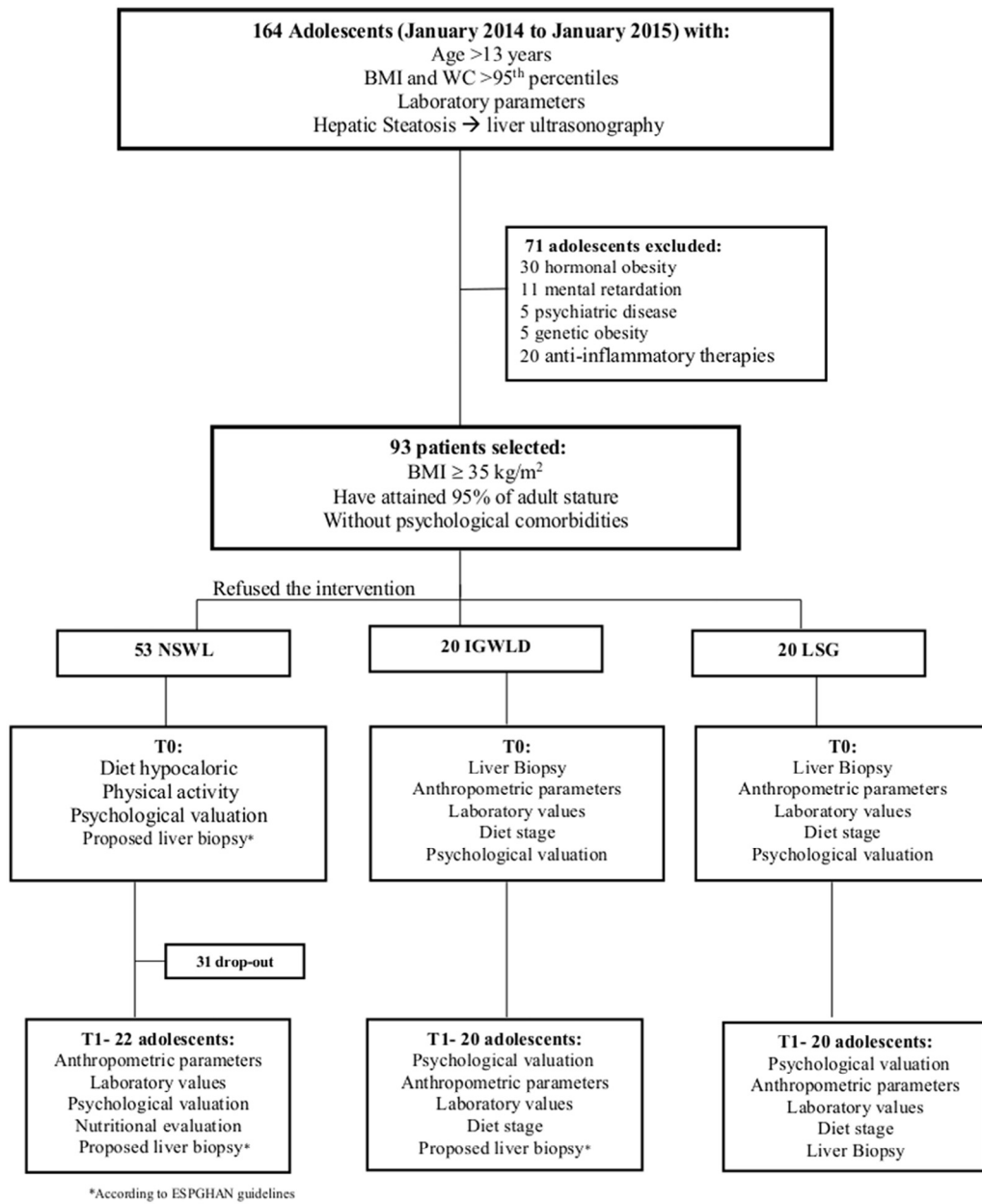
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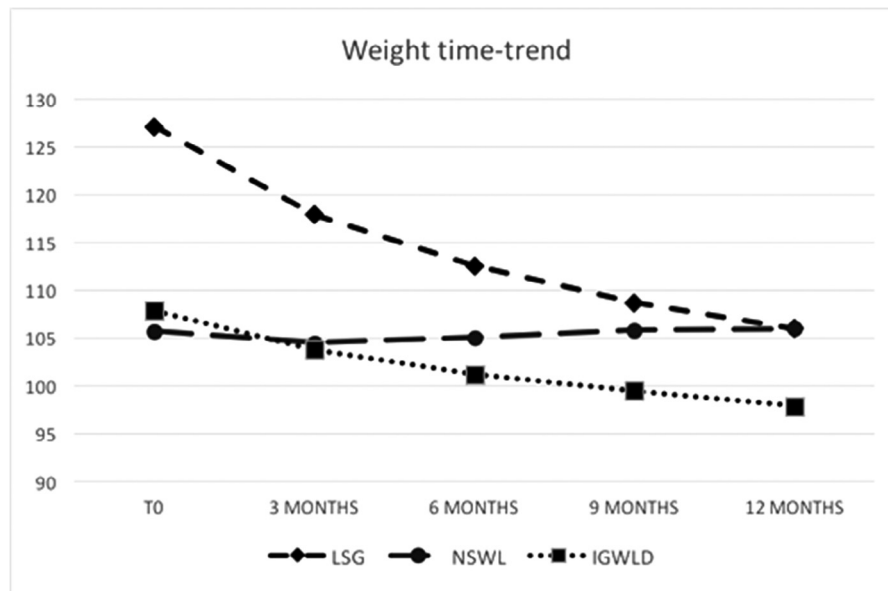
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**Figure 1.** Study flow diagram. Diagram displays enrollment and the follow-up procedures for each treatment group.





**Figure 3.** The weight trends during follow-up in the 3 treatment groups. Mean weight value with SD were plotted for 3 groups.

**Table I.** Anthropometrics, clinical, and metabolic variables of the entire population

Baseline n = 93	
Sex (M/F)	43/50 (46.23%/53.77%)
Age (y)	15.21 (1.88)
Weight, kg	118.31 (21.75)
BMI, kg/m <sup>2</sup>	43.16 (4.21)
WC, cm	110.96 (9.87)
BMI z-score	2.91 (0.65)
SBP, mm Hg	118 (11)
DBP, mm Hg	67 (9)
Hypertension, n (%)	20 (21.5%)
AST, U/L	34 (13)
ALT, U/L	40 (16)
Uric acid, mg/dL	6 (1)
Total cholesterol, mg/dL	164 (25)
LDL cholesterol, mg/dL	107 (23)
HDL cholesterol, mg/dL	42 (8)
Triglycerides, mg/dL	115 (37)
Dyslipidemia, n (%)	30 (32.3%)
Fasting plasma glucose, mg/dL	86 (12)
Plasma glucose 120', mg/dL	118 (29)
IGT, n (%)	11 (11.8%)
HbA1c, mmol/mol	36.47 (4.21)
Insulin, mU/L	29 (11)
Insulin -120', mU/L	152 (89)
C-peptide, ng/mL	2.88 (0.86)
HOMA-IR	6.16 (3.77)
AUC <sub>Insulin(0-120)'/AUC<sub>Glucose(0-120)</sub></sub>	0.87 (0.39)
OSAS, n (%)	27 (29.03%)
AHI	
3.5	14 (51.85%)
5-10	9 (33.33%)
>10	4 (14.81%)
NASH, n (%)	31 (90.32%)
Fibrosis ≥ 2 (n;%)	39 (67.34%)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; C-peptide, connecting peptide; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; SBP, systolic blood pressure; WC, waist circumference. Data are presented as mean values ± SD.