ORIGINAL ARTICLE

Endoscopic sleeve gastroplasty plus liraglutide versus endoscopic sleeve gastroplasty alone for weight loss

Dilhana Badurdeen, MD,[1] Anna Carolina Hoff, MD,[2] Abdellah Hedjoudje, MD, MSc,[1] Atif Adam, PhD, MD,[1] Mohamad I. Itani, MD,[1] Jad Farha, MD,[1] Shahem Abbarh, MBBS,[1] Anthony N. Kalloo, MD,[1] Mouen A. Khashab, MD,[1] Vikesh K. Singh, MD, MSc,[1] Andrea Oberbach, MD, PhD, MPH,[1] Manoel Galvao Neto, MD,[3] Sergio Barrichello, MD,[4] Vivek Kumbhari, MD, PhD[1]

Baltimore, Maryland, USA; São José dos Campos, São Paulo, Brazil

Background and Aims: Endoscopic sleeve gastroplasty (ESG) has been shown to be effective for inducing weight loss. The efficacy of liraglutide, a glucagon-like peptide-1 agonist, to augment weight loss after ESG is unknown. This study aims to evaluate the efficacy of ESG and liraglutide (ESG-L) compared with ESG alone.

Methods: This was a retrospective study of prospectively collected data from patients undergoing ESG at 3 outpatient clinics in Brazil between November 2017 and July 2018. Liraglutide was offered to all patients 5 months after ESG. Patients who opted to take liraglutide (ESG-L) were matched 1:1 to patients who declined it (ESG). The primary outcome was percent total body weight loss (%TBWL), and percent excess weight loss (%EWL) 7 months after initiation of liraglutide (12 months after ESG). The secondary outcome was change in percent body fat 12 months after ESG. ESG technique and postprocedure follow-up were identical at all 3 sites.

Results: Propensity score matching yielded 26 matched pairs. Adjusted comparisons between the 2 groups showed that patients who opted to take liraglutide had a superior mean %TBWL 7 months after initiation of liraglutide (ESG-L) compared with those who declined it (ESG) (24.72% ± 2.12% vs 20.51% ± 1.68%, respectively; $P < .001$). ESG-L had a statistically greater reduction in percent body fat compared with ESG (7.85% ± 1.26% vs 10.54% ± 1.88%, respectively; $P < .001$) at 12 months.

Conclusions: Addition of liraglutide at 5 months results in superior weight loss and improved efficacy as demonstrated by decreased body fat 12 months after ESG. Further studies are imperative to determine optimal dose, timing, and duration of liraglutide. (Gastrointest Endosc 2020;■:1-9.)

Obesity is a major public health crisis, increasing the incidence of diabetes mellitus type 2, dyslipidemia, hypertension (HTN), cardiovascular and nonalcoholic fatty liver diseases, and all-cause mortality.[1] In the United States alone, there are 93.3 million adults (39.8%) with a body mass index (BMI) greater than 30 kg/m^2.[2] The annual

Abbreviations: BMI, body mass index; EBT, endoscopic bariatric therapy; ESG, endoscopic sleeve gastroplasty; ESG-L, endoscopic sleeve gastroplasty and liraglutide; HbA_{1c}, hemoglobin A_{1c}; HTN, hypertension; IGB, intragastric balloon; %EWL, percent excess weight loss; %TBWL, percent total body weight loss.

DISCLOSURE: *The following authors disclosed financial relationships: A. C. Hoff: Shareholder in Hoff Medical Group. A. N. Kalloo: Founding member of, equity holder in, and consultant for Apollo Endosurgery. M. A. Khashab: Medical advisory board for Boston scientific and Olympus America; consultant for Boston Scientific, Medtronic, and Olympus America. M. G. Neto: Consultant for Fractyl Labs, USGI, GI Dynamics, Apollo EndoSurgery, and Colubris Mx; proctor for Fractyl Labs, USGI, GI Dynamics, and Apollo EndoSurgery; scientific advisory board for GI Dynamics, and Keyron (UK); trainer for Apollo EndoSurgery, Ethicon EndoSurgery, Olympus America, and Medtronic. V. Kumbhari: Consultant for Medtronic, Pentax Medical, Boston Scientific, FujiFilm, Apollo Endosurgery, and Obalon; research support from ERBE USA and Apollo Endosurgery. All other authors disclosed no financial relationships.*

0016-5107/$36.00
https://doi.org/10.1016/j.gie.2020.10.016

Received May 4, 2020. Accepted October 11, 2020.

Current affiliations: Division of Gastroenterology and Hepatology, Johns Hopkins Medical Institutions, Baltimore, Maryland, USA (1), Angioskope Clinic, São José dos Campos, Brazil (2), Division of Gastrointestinal Endoscopy, ABC Medical School, São Paulo, Brazil (3), Healthme gerenciamento de perda de peso, Sao Paulo, Brazil (4).

Reprint requests: Vivek Kumbhari, MD, PhD, Division of Gastroenterology and Hepatology, Johns Hopkins Medical Institutions, 1800 Orleans St, Sheikh Zayed Tower, Ste 2058, Baltimore, MD 21287.

medical cost of obesity is gradually increasing, from $149 billion in 2008 to $209.7 billion in 2016.[3,4] Percent total body weight loss (%TBWL) of 5% improves triglycerides, blood pressure, and hemoglobin A_{1c} (HbA_{1c}); however, to improve cardiovascular outcomes and liver fibrosis, weight loss of at least 10% is imperative.[5-13]

The endoscopic sleeve gastroplasty (ESG) is a minimally invasive endoscopic bariatric therapy (EBT). Based on a recent meta-analysis %TBWL at 12 months is 16.5% with ESG, with less than 3% of serious adverse events.[14] Furthermore, improvements in HbA_{1c}, alanine aminotransferase, dyslipidemia, and diabetes mellitus type 2 and resolution of HTN have been noted in prospective observational studies.[15] Contrarily, %TBWL with liraglutide 3 mg is 6% to 8% at 56 weeks.[16]

Combination therapy using EBT and medications is a novel and intriguing idea that uses the physiology and mechanism of action of individual therapies to augment weight loss. The efficacy of pharmacotherapy (metformin, phentermine/topiramate, liraglutide, bupropion, topiramate, lorcaserin, and phentermine) has been investigated in patients with weight regain or inadequate weight loss after ESG, demonstrating that 75% of patients with inadequate weight loss who began weight loss medications lost ≥10% of their initial weight.[17] However, a combination of liraglutide, a glucagon-like peptide-1 agonist, to prevent weight regain after intragastric balloon (IGB) insertion demonstrated that combination therapy did not decrease the risk of weight regain 6 months after balloon removal.[18] To our knowledge, no study has investigated the effect of liraglutide 5 months after ESG to augment weight loss and improve metabolic outcomes. The aim of this study was to evaluate the efficacy of ESG and liraglutide (ESG-L) compared with ESG alone.

METHODS

Study design

This retrospective study was conducted at 3 outpatient obesity clinics in Brazil (Angioskope São Paulo, Angioskope São José dos Campos, and Endogastrorio Rio de Janeiro) with the approval of the institutional review board (IRB no. ANH002341). Patients who were over age 18 years with a BMI >27 kg/m^2 who were unable to achieve weight loss through intense diet and lifestyle modification attempts and subsequently underwent ESG between November 2017 and July 2018 were included. None of these patients was included in previous studies. Contraindications to undergoing ESG included previous gastric surgery, gastric ulceration, hiatal hernia >5 cm, use of anticoagulant medications, pregnancy, or lactation. Patients who had a contraindication to initiating liraglutide were excluded from the study. None of the patients had a history of previous IGB insertion for weight loss.

Demographic data including age, sex, comorbid illnesses, weight, and percent body fat were collected before ESG. Weight before initiation of liraglutide and at months 2, 4, and 7 after initiation of liraglutide and percent body fat at the end of the study was obtained in both patients who chose liraglutide and those who declined it. Figure 1 shows the timeline of study interventions. Participants were followed in the weight loss clinic by a medical weight loss specialist, dietician, and exercise physiologist for a total of 12 months. The pre- and postprocedure follow-up were identical at the 3 clinics.

Outcomes

Baseline weight was measured in kilograms with a calibrated scale, and height was measured in meters using a wall-mounted stadiometer. The baseline BMI, change in BMI, absolute weight loss, %TBWL, and percent excess weight loss (%EWL) were calculated at 2, 4, and 7 months after initiation of liraglutide in ESG only and ESG-L patients.

Body fat composition was measured using bioimpedance with the InBody270 (Ottoboni, Rio de Janeiro, Brazil) machine[19,20] before ESG and 7 months after initiation of liraglutide at the end of the study (12 months). Serious adverse events were defined as per the American Society for Gastrointestinal Endoscopy guidelines.[21]

Endoscopic sleeve gastroplasty

ESG is an incisionless, minimally invasive technique that involves remodeling of the greater curvature of the stomach by placement of full-thickness sutures. The technique has been described in previous publications.[22] All procedures were performed in an outpatient endoscopy suite with the patient under general anesthesia and carbon dioxide insufflation. Full-thickness sutures were applied with an endoscopic suturing system (OverStitch; Apollo Endosurgery, Austin, Tex, USA) along the greater curvature of the stomach to create a narrow sleeve-like structure and reduce the volume by approximately 70%. The tissue helix (Apollo Endosurgery) was used to ensure full-thickness bites.

In the 3 outpatient obesity clinics included in the study, all 3 bariatric endoscopists (A.C.H., and S.B.) performed the ESG using an identical technique. Two endoscopists (A.C.H. and E.J.J.) were trained by the same mentor (M.G.N.), whereas the third (S.A.B.) was trained by another mentor (A.C.H.). A "U" shaped pattern was used with an average of 9 to 13 bites per suture. Six sutures were used per ESG, except in 3 patients with a smaller gastric volume where 5 sutures were used (2 in the ESG-L group and 1 in the ESG alone group). Supplementary Table 1 (available online at www.giejournal.org) reviews between-clinic patient characteristics. Patients received cefazolin 1 mg, ondansetron 4 mg, and tramadol 100 mg intravenously intraoperatively. Dexlansoprazole 40 mg was initiated 2 weeks before the procedure and continued for 8 weeks after ESG with sucralfate every 8 hours for 14 days after ESG.

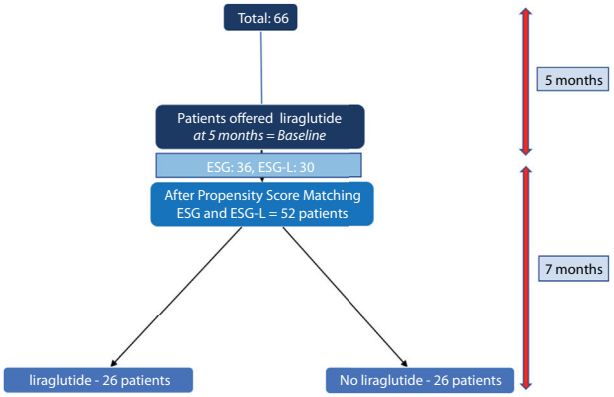

Figure 1. Timeline of study interventions. *ESG,* Endoscopic sleeve gastroplasty; *ESG-L,* endoscopic sleeve gastroplasty with liraglutide.

Patients were discharged home the same day with ondansetron 8 mg and dimenhydrinate 50 mg every 8 hours for 5 days as needed for nausea. Patients were given paracetamol 500 mg every 6 hours and codeine 30 mg daily for 3 days as needed for pain control.

Post-ESG follow-up

The first postprocedure visit was 1 week after ESG, and patients had follow-ups on a bimonthly basis for the first 2 months and monthly for 10 months thereafter. None of the patients was lost to follow-up.

After ESG, all patients were instructed to consume a clear liquid diet for 1 week followed by a full-liquid diet for 1 week based on 50% of their basal metabolic rate. The basal metabolic rate was calculated using the Inbody270 body composition analyzer (Ottoboni).[19,20] Weeks 3 and 4 consisted of a soft diet based on 66% of patients' basal metabolic rate. Whey protein supplementation was recommended from weeks 1 to 4, and subsequently patients were encouraged to eat animal-derived proteins such as eggs, fish, chicken, and red meat to prevent loss of lean muscle mass. Patients were finally transitioned to a regular diet consisting of a caloric intake of 80% of their basal metabolic rate.

High-intensity interval training was prescribed by a personal trainer based on individual patient abilities and included treadmill, stair climbing, jump rope, and jumping jacks/star jumping for 20 minutes a day for 5 days per week. Patients met with the trainer before their procedure at the clinic's private gym where they were given a personalized workout program. Additionally, they were provided with links to YouTube workout videos to follow at home.

All patients were added to a WhatsApp group that included a specialized weight loss coach, personal trainer, dietician, program coordinator, nurse, and 2 physicians. Patients were encouraged to follow-up in the clinic as frequently as once per week, and bioimpedance testing was offered at no cost at these visits to monitor progress.

Liraglutide

Liraglutide (Saxenda; Novo Nordisk, Bagsvaerd, Denmark) lowers HbA_{1c} at daily doses of 1.8 mg and 3 mg[23,24] and improves metabolic control and reduces body weight at a dose of 3 mg.[24] It was approved by the U.S. Food and Drug Administration in 2014 for weight loss[25] in adults with a BMI >30 kg/m^2 or a BMI >27 kg/m^2 with at least 1 weight-related comorbid condition such as HTN, dyslipidemia, insulin resistance, or diabetes mellitus type 2.[26] Fatigue, hypoglycemia, nausea, dyspepsia, and abdominal pain are rare side effects. Pancreatitis and thyroid cancer are serious but rare side effects and occur in .3% and >.1% of patients, respectively.[24,27]

Liraglutide was offered to patients in all 3 clinics at the 5-month visit regardless of their %TBWL to further augment weight loss. In patients who opted to take liraglutide, it was initiated per protocol at .6 mg/day and increased in increments of .6 mg/wk based on tolerance and side effects to the maximal tolerated dose. Side effects were mild, and none of the patients discontinued the medication because of side effects. Subjects were trained to self-administer the injection. Patients paid for the medication out of pocket, and no incentive was offered for taking it. If patients had financial difficulty, it was provided through the clinic without cost. Patients who discontinued the medication were excluded from the study. None of the patients included in the study was taking metformin or insulin and no other weight loss medications were initiated during the study period. Patients who did not opt to take liraglutide were included as ESG only control subjects.

Statistical analysis

Because liraglutide therapy was not randomly assigned, propensity score matching was used to minimize potential confounding and selection biases between the ESG only and ESG-L groups.[28] Propensity scores were estimated using multivariable logistic regression. The propensity score model included BMI at baseline, weight at baseline, prediabetes at baseline, HTN at baseline, obstructive sleep apnea status at baseline, %TBWL at 5 months after ESG (Time 0 in Fig. 1), and clinic location. We formed matched pairs between patients who underwent ESG only or ESG-L using a 1:1 nearest-neighbor matching with a caliper width of 1.8 without replacement. Only patients matched with propensity scores were included in the analyses.

After propensity score matching, qualitative variables were compared using the Fisher exact test, χ^2 test, or χ^2 trend test. Quantitative variables were tested for normal distribution by the Kolmogorov-Smirnov test. In accordance with the result of this test, the statistical significance of differences in qualitative variables was tested using the Student *t* test or Mann-Whitney U test. In case of nonparametric distribution, Wilcoxon rank-sum test for pairwise nonparametric and the Kruskal-Wallis test were used for

TABLE 1. Baseline characteristics before ESG before and after matching (without replacement)

	Before matching				After matching			
	Overall (n = 66)	ESG alone (n = 36)	ESG plus liraglutide (n = 30)	*P* value	Overall (n = 52)	ESG alone (n = 26)	ESG plus liraglutide (n = 26)	*P* value
Age, y, mean (SD)	42.08 (11.71)	43.53 (13.95)	40.33 (8.17)	.273	40.90 (9.62)	41.15 (10.64)	40.65 (8.69)	.854
Male	22 (33.3)	11 (30.6)	11 (36.7)	.793	19 (36.5)	10 (38.5)	9 (34.6)	1.000
Initial weight, kg, mean (SD)	101.21 (10.06)	100.62 (9.70)	101.90 (10.61)	.611	101.46 (10.58)	101.89 (10.71)	101.03 (10.64)	.771
Height, m, mean (SD)	1.68 (.09)	1.68 (.09)	1.68 (.08)	.761	1.69 (.09)	1.69 (.09)	1.68 (.08)	.595
Initial body mass index, kg/m^2, mean (SD)	35.80 (2.06)	35.73 (1.96)	35.87 (2.21)	.787	35.70 (2.02)	35.56 (1.68)	35.83 (2.33)	.638
Obstructive sleep apnea	32 (48.5)	19 (52.8)	13 (43.3)	.605	26 (50.0)	13 (50.0)	13 (50.0)	1.000
Arthropathy	18 (27.3)	10 (27.8)	8 (26.7)	1.000	12 (23.1)	5 (19.2)	7 (26.9)	.742
Dyslipidemia	32 (48.5)	20 (55.6)	12 (40.0)	.312	26 (50.0)	14 (53.8)	12 (46.2)	.782
Prediabetes	22 (33.3)	11 (30.6)	11 (36.7)	.793	16 (30.8)	8 (30.8)	8 (30.8)	1.000
Nonalcoholic fatty liver disease	24 (36.4)	14 (38.9)	10 (33.3)	.833	16 (30.8)	7 (26.9)	9 (34.6)	.764
Hypertension	35 (53.0)	22 (61.1)	13 (43.3)	.233	26 (50.0)	16 (61.5)	10 (38.5)	.166
Coronary artery disease	2 (3.0)	1 (2.8)	1 (3.3)	1.000	1 (1.9)	0 (.0)	1 (3.8)	1.000
Polycystic ovary syndrome	12 (18.2)	6 (16.7)	6 (20.0)	.977	9 (17.3)	3 (11.5	6 (23.1)	.463
Baseline body fat percentage, mean (SD)	18.83 (2.09)	18.83 (2.34)	18.83 (1.78)	1.000	18.77 (2.23)	18.81 (2.58)	18.73 (1.87)	.902
Weight before initiating liraglutide, kg, mean (SD)	87.38 (8.23)	87.59 (7.73)	87.13 (8.93)	.823	13.95 (1.65)	87.59 (7.73)	87.13 (8.93)	.823
Angioskope São José dos Campos	34 (51.5)	22 (61.1)	12 (40.0)	.144	25 (48.1)	14 (53.8)	11 (42.3)	.579
Angioskope SP	17 (.36)	8 (22.2)	9 (30.0)	.662	15 (28.8)	7 (26.9)	8 (30.8)	1.000
Health Me	15 (.23)	6 (16.7)	9 (30.0)	.321	12 (23.1)	5 (19.2)	7 (26.9)	.742

Values are n (%) unless otherwise defined.
ESG, Endoscopic sleeve gastroplasty; *SD*, standard deviation.

pairwise and multiple group comparisons, respectively. In case of continuous data, variables are presented as mean value ± standard deviation or median (interquartile range). Categorical variables are presented as frequency and percentages. All reported *P* values are 2-tailed. Associations were considered statistically significant at a 2-tailed value of .05.

Univariable and multivariable linear regression analyses were performed to determine predictors of weight loss at 7 months after initiation of liraglutide. Coefficient and corresponding *P* values were estimated. Variables found to be significantly associated with weight loss 7 months after initiation of liraglutide (12 months after ESG) through the univariate analysis and other relevant variables based on clinical intuition were used in our multivariable analysis models. We used backward-stepwise elimination methods to identify the most parsimonious model. Akaike information criterion was used to identify the "best fit" model.

We recognize that multiple testing of outcome data arise from individual patients. The univariable outcome analyses were exploratory, and their *P* values are to be seen as descriptive only; those *P* values are not corrected for multiple testing. The multivariable linear regression result is to be taken as the main, definitive finding with no correction for multiple testing needed. The propensity score matching and statistical analysis were performed with R software (http://www.R-project.org; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

Fifty-two patients were eligible for propensity score matching at a 1:1 ratio, resulting in 26 patients included in each group. Table 1 depicts the baseline characteristics of patients before and after matching. Demographic characteristics after matching were similar in both groups. A total of 36.5% of eligible patients were men with an average weight of 101.46 ± 10.58 kg and average BMI of 35.7 ± 2.02 kg/m^2. Initial weight before and after matching were similar in both cohorts before ESG and before initiating liraglutide. Body fat percentage before ESG was not significantly different before and after matching. Comorbidities observed in the study population

TABLE 2. Comparison of change in absolute weight loss, percent total body weight loss, body mass index loss, percent excess weight loss, visceral fat, and hemoglobin A_{1c} after ESG in patients using or not using liraglutide

Variable	Time (mo)	ESG alone (n = 26)	ESG and liraglutide (n = 26)	*P* value
Absolute weight loss, kg	2	16.93 (3.34)	18.63 (2.62)	.046
	4	19.23 (3.33	22.28 (3.26)	.002
	7	20.95 (3.21)	25.02 (3.80)	<.001
Absolute body mass index, kg/m^2	2	29.65 (1.20)	29.22 (1.88)	.334
	4	28.85 (1.10)	27.93 (1.76)	.028
	7	28.25 (1.06)	26.96 (1.60)	.001
Total body weight loss, %	2	16.57 (2.37)	18.43 (1.55)	.002
	4	18.82 (2.01)	22.02 (1.84)	<.001
	7	20.51 (1.68)	24.72 (2.12)	<.001
Body mass index loss, kg/m^2	2	5.92 (1.00)	6.61 (.77)	.007
	4	6.71 (.93)	7.90 (.95)	<.001
	7	7.31 (.86)	8.88 (1.14)	<.001
Excess weight loss, %	2	56.33 (7.58)	63.12 (12.51)	.022
	4	64.05 (6.43)	75.32 (14.19)	.001
	7	69.94 (6.30)	84.33 (14.57)	<.001
Visceral fat, %	7	10.54 (1.88)	7.85 (1.26)	<.001
Hemoglobin A_{1c}	7	5.40 (.45)	5.09 (.41)	.013

Values are mean (standard deviation).
ESG, Endoscopic sleeve gastroplasty.

before ESG were HTN (53%), obstructive sleep apnea (48.5%), dyslipidemia (48.5%), nonalcoholic fatty liver disease (36.4%), prediabetes (33.3%), arthropathy (27.3%), polycystic ovary syndrome (18.2%), and coronary artery disease (3%).

Weight loss and change in visceral fat

The absolute weight loss, BMI, %TBWL, BMI loss, and % EWL at 2, 4, and 7 months after initiation of liraglutide and change in visceral fat at 7 months after initiation of liraglutide is shown in Table 2. The absolute weight loss in ESG-L was superior to ESG at 4 and 7 months after initiation of liraglutide, 22.28 ± 3.26 kg versus 19.23 ± 3.33 kg (P = .002) and 25.02 ± 3.80 kg versus 20.95 ± 3.21 kg (P < .001), respectively. There was a statistically significant greater mean %TBWL at 2, 4, and 7 months after initiation of liraglutide in ESG-L compared with ESG (18.43% ± 1.55% vs 16.57% ± 2.37% [P = .002], 22.02% ± 1.84% vs 18.82% ± 2.01% [P < .001], and 24.72% ± 2.12% vs 20.51% ± 1.68% [P < .001], respectively) (Table 2, Fig. 2A and B). There was a superior mean %EWL in ESG-L at 2, 4, and 7 months compared with ESG; however, this was statistically significant only at 4 and 7 months (75.32% ± 14.19% vs 64.05% ± 6.43% [P = .001] and 84.33% ± 14.57% vs 69.94% ± 6.3% [P < .001], respectively). The percent visceral fat 12 months after ESG was significantly lower in ESG-L compared with ESG (7.85% ± 1.26% vs 10.54% ± 1.88% [P < .001], respectively) with a decrease in visceral fat of –10.92% ± 1.89% versus –7.96% ± 2.32% in the ESG-L cohort compared with ESG alone 12 months after ESG (Table 2).

Predictors of weight loss 7 months after initiation of liraglutide (12 months after ESG)

On univariable linear regression analysis, initial BMI and liraglutide were significant predictors of weight loss 7 months after initiation of liraglutide (12 months after ESG). After performing a backward-stepwise elimination method using age, initial BMI, HTN, coronary artery disease, and use of liraglutide to identify the most parsimonious (best fit) model, only the use of liraglutide remained a significant predictor of weight loss 12 months after ESG (Table 3).

We performed a subgroup analysis of %TBWL and percent visceral fat based on the dose of liraglutide (Fig. 3A and B). There was no significant difference in the %TBWL and percent visceral body fat at 12 months after ESG for the varying doses of liraglutide.

Adverse events

One patient had a CT for severe abdominal pain after ESG secondary to pneumoperitoneum that resolved with conservative management. No other serious adverse events were encountered after ESG. None of the patients experienced serious adverse events from liraglutide. Mild nausea, dyspepsia, and abdominal pain were observed, but liraglutide was not discontinued in any patient because of these mild side effects.

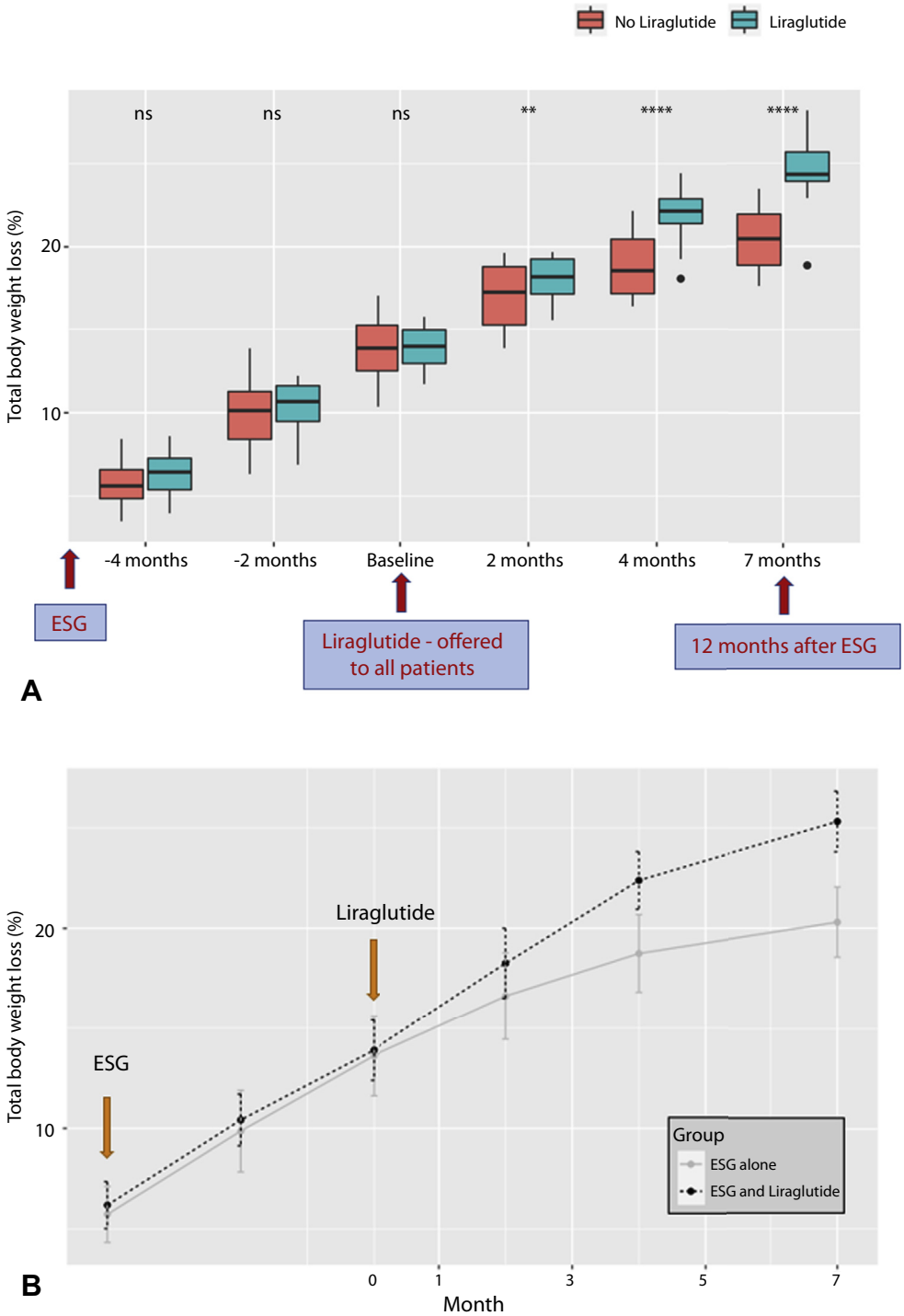

Figure 2. A, Percentage total body weight loss (%TBWL) in those patients who chose liraglutide versus those who declined it. **B,** %TBWL in the endoscopic sleeve gastroplasty plus liraglutide (ESG-L) group versus the ESG alone group.

DISCUSSION

Previous studies have demonstrated that EBT is more effective than high-intensity diet and lifestyle modification therapy.[29] However, the mechanism of weight loss after ESG is debatable. Proposed mechanisms include a delay in gastric emptying and increased satiation.[30] In a case-matched study comparing the efficacy of laparoscopic sleeve gastrectomy with ESG, %TBWL was equivalent in patients with a BMI between 30 and 40 kg/m^2 at 6 months.[31] However, as the BMI rises, bariatric surgery is likely more effective than ESG. Bariatric surgery remains the criterion standard because of substantially sustained weight loss and reversal of metabolic adverse events.[32,33] Yet despite

TABLE 3. Univariable and multivariable analyses of predictors for weight loss 7 months after initiation of liraglutide (12 months after endoscopic sleeve gastroplasty) with variance inflation factor

Variable	Coefficient (univariable)	Coefficient (multivariable)				Variance inflation factor
		Model 1	Model 2	Model 3	Model 4	
Age	–.07 (–.14 to .01, $P = .076$)	.01 (–.07 to .08, $P = .885$)	—	—	—	
Sex, male	–.21 (–1.90 to 1.49, $P = .809$)	—	—	—	—	
Weight	–.21 (–1.90 to 1.49, $P = .809$)	—	—	—	—	
Height	4.05 (–4.93 to 13.04, $P = .369$)	—	—	—	—	
Initial body mass index	.70 (.29-1.12, $P = .001$)	.35 (–.04 to .75, $P = .077$)	.35 (–.04 to .74, $P = .074$)	.31 (–.02 to .64, $P = .062$)	.31 (–.01 to .64, $P = .061$)	1.001153
Obstructive sleep apnea	–.32 (–2.04 to 1.40, $P = .711$)	—	—	—	—	
Arthropathy	–1.30 (–3.41 to .82, $P = .223$)	—	—	—	—	
Dyslipidemia	–.73 (–2.41 to .95, $P = .389$)	—	—	—	—	
Prediabetes	–.15 (–1.98 to 1.68, $P = .868$)	—	—	—	—	
Nonalcoholic fatty liver disease	.06 (–1.74 to 1.86, $P = .946$)	—	—	—	—	
Hypertension	–1.18 (–2.87 to .51, $P = .166$)	–.41 (–1.84 to 1.01, $P = .558$)	–.43 (–1.82 to .95, $P = .533$)	–.37 (–1.70 to .96, $P = .578$)	—	
Coronary artery disease	–4.95 (–10.95 to 1.04, $P = .103$)	.57 (–3.73 to 4.88, $P = .788$)	.72 (–3.03 to 4.47, $P = .700$)	—	—	
Polycystic ovary syndrome	.99 (–1.34 to 3.32, $P = .397$)	—	—	—	—	
Use of liraglutide	5.02 (4.11-5.93, $P < .001$)	3.17 (1.73-4.61, $P < .001$)	3.17 (1.74-4.59, $P < .001$)	3.22 (1.84-4.60, $P < .001$)	3.27 (1.92-4.63, $P < .001$)	1.001153
Akaike information criterion	—	74.69	72.71	70.88	69.23	

Values are coefficient (univariable/multivariable).

conventional wisdom, less than 2% of eligible patients undergo bariatric surgery because of the misleading negative perception of invasiveness, perceived risk of associated adverse events, lack of resources, and availability of care.[34] Thus, alternate modes of treatment are essential.

This study demonstrates that initiation of liraglutide 5 months after ESG can be effective for inducing weight loss (higher mean %TBWL and %EWL) 7 months after initiation of liraglutide (12 months after ESG). Unlike bariatric surgery, ESG has less hormonal alteration–induced added weight loss that accompanies the anatomic change, although it appears to decrease secretion of ghrelin without significant changes in glucagon-like peptide-1 or peptide YY levels.[30] Thus, combination therapy with ESG and liraglutide is a unique proposition because weight loss can be maximized by manipulating a similar mechanism of action at the central and peripheral levels. Liraglutide is a glucagon-like peptide-1 agonist that amplifies glucose-stimulated insulin secretion, delays gastric emptying, and increases satiety by central effects on the hypothalamus.[35-38] In randomized control trials, weight reduction was seen at doses of 1.2, 1.8, 2.4, or 3.0 mg in a dose-dependent fashion of 4.8 kg, 5.5 kg, 6.3 kg, and 7.2 kg, respectively, compared with 2.8 kg with placebo after 20 weeks.[35,36,39] Additionally, our study demonstrated that if liraglutide is initiated 5 months after ESG, a significant decline in percent body fat will occur at 12 months, indicating a possible synergistic added metabolic benefit.

A study that included 1000 patients who underwent ESG showed that most weight loss occurred in the first 3 months, where weight loss at 1, 3, 6, 9, and 12 months was 7.5 ± 2.9 kg, 9.0 ± 4.3 kg, 12.2 ± 6.2 kg, 14.1 ± 7.7 kg, and 13.8 ± 7.9 kg, respectively.[15] There is a deceleration in the speed of weight loss at around 4 to 6 months. In lieu of this decline, we offered liraglutide at 5 months after ESG to enhance weight loss; however, the ideal time to start pharmacotherapy is yet to be determined.

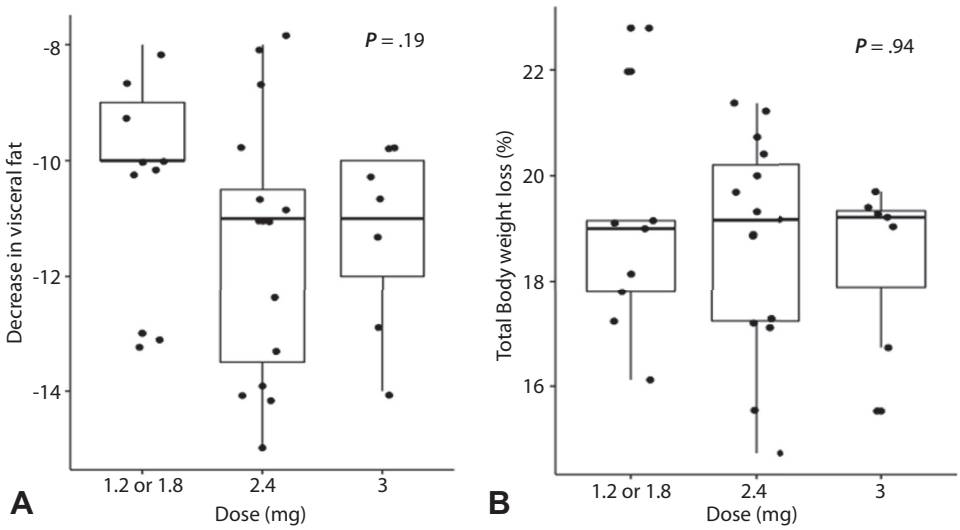

Figure 3. A, Effect of liraglutide dose on the decrease in body fat at 12 months (7 months after initiation of liraglutide). **B,** Effect of liraglutide dose on percent total body weight loss at 12 months (7 months after initiation of liraglutide).

Mosli and Elyas[18] studied the effect of initiating liraglutide 1 month after IGB insertion for a total of 6 months to augment weight loss and prevent weight regain and found that patients treated with IGB alone had a higher mean body weight loss at the time of IGB removal and 6 months later compared with those treated with combination therapy. Even though combination therapy using EBT and liraglutide has not demonstrated superior weight loss outcomes, liraglutide has shown promise in patients with weight regain, inadequate weight loss, and weight loss plateau after bariatric surgery. In a retrospective study, median percentage of weight loss was 9.7% 28 weeks after initiation of liraglutide, and patients with poor initial weight loss or weight regain had a superior response.[40] Pajecki et al[41] in their study of liraglutide for treatment of unsatisfactory weight loss or weight regain after bariatric surgery demonstrated a 7.5 ± 4.3 kg reduction in weight at a mean duration of 12.5 ± 4.7 weeks after initiation of liraglutide. Other studies evaluating the effect of weight loss medications after bariatric surgery for suboptimal weight loss or weight regain have demonstrated varying outcomes at 1 year, but more than one-third achieved >5% weight loss with the addition of weight loss medications.[42]

In our study, other than liraglutide use, baseline patient characteristics were not significantly predictive of higher weight loss on multivariable linear regression analysis. However, previous studies have demonstrated that weight at the time of initiation of liraglutide may impact the final weight loss outcome. Thus, it would be critical to determine if liraglutide should be initiated at the time of endoscopic bariatric intervention, even though this may increase overall side effects including abdominal pain and nausea immediately after ESG. In looking at dose stratification of liraglutide, no significant difference was seen in % TBWL or decline in visceral fat composition (Fig. 3A and B). It may be more important to titrate the dose to maximal tolerability versus maximum dose to optimize weight loss, because increasing the dose too fast may result in poor compliance and discontinuation of the medication. Further randomized control studies are needed to determine the optimal timing and dose of liraglutide after ESG.

We recognize limitations in this study including its retrospective nature and the limited number of patients included. However, to our knowledge, this is the first study using liraglutide alone 5 months after ESG to augment weight loss outcomes 12 months after ESG. The study is subject to selection bias, because the decision to take liraglutide was made by the patient in a nonrandomized fashion. Even though most patients lost more than 10% of their total body weight, we lack data on follow-up after 12 months. This includes weight maintenance, weight regain, and improvement in comorbidities such as HTN and dyslipidemia or resolution of nonalcoholic fatty liver disease. Despite these limitations, our study provides valuable information, because at this time the literature is lacking in studies that combine EBTs with weight loss medications.

In conclusion, this study demonstrates that liraglutide, when used in combination with ESG, will likely augment weight loss and promote reduction in visceral fat at 12 months. Further studies are needed to determine if liraglutide is the ideal medication to initiate in a patient after ESG or if other medications such as phentermine, topiramate, naltrexone, or bupropion alone or in combination would produce superior weight loss. It is also unclear whether liraglutide should be initiated at the time of ESG, when the patient reaches a weight loss plateau, or when the patient begins to regain lost weight. Additional randomized control studies are imperative to determine the ideal medication and EBT combination, timing, and dose of

medications and duration for which the medication would be continued not only to maximize weight loss but also to achieve improvement in metabolic parameters.

REFERENCES

1. Afshin A, Forouzanfar MH, Reitsma MB, et al. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med 2017;377:13-27.
2. Hales CM, Carroll MD, Fryar CD, et al. Prevalence of obesity among adults and youth: United States, 2015-2016. NCHS data brief. 2017;288:1-8.
3. Kim DD, Basu A. Estimating the medical care costs of obesity in the United States: systematic review, meta-analysis, and empirical analysis. Value Health 2016;19:602-13.
4. Kushner RF, Kahan S. Introduction: the state of obesity in 2017. Med Clin North Am 2018;102:1-11.
5. Wing RR, Bolin P, Brancati FL, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013;369:145-54.
6. Wing RR, Koeske R, Epstein LH, et al. Long-term effects of modest weight loss in type II diabetic patients. Arch Intern Med 1987;147:1749-53.
7. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation 2014;129:S102-38.
8. Vigneri P, Frasca F, Sciacca L, et al. Obesity and cancer. Nutr Metab Cardiovasc Dis 2006;16:1-7.
9. Adams KF, Schatzkin A, Harris TB, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. N Engl J Med 2006;355:763-78.
10. Wing RR, Lang W, Wadden TA, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes Care 2011;34:1481-6.
11. Magkos F, Fraterrigo G, Yoshino J, et al. Effects of moderate and subsequent progressive weight loss on metabolic function and adipose tissue biology in humans with obesity. Cell Metab 2016;23:591-601.
12. Gregg EW, Jakicic JM, Blackburn G, et al. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. Lancet Diabetes Endocrinol 2016;4:913-21.
13. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology 2015;149:367-78; quiz e14-5.
14. Hedjoudje A, Dayyeh BA, Cheskin LJ, et al. Efficacy and safety of endoscopic sleeve gastroplasty: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2020;18:1043-53.e4.
15. Alqahtani A, Al-Darwish A, Mahmoud AE, et al. Short-term outcomes of endoscopic sleeve gastroplasty in 1000 consecutive patients. Gastrointest Endosc 2019;89:1132-8.
16. Davies MJ, Bergenstal R, Bode B, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. JAMA 2015;314:687-99.
17. Hajifathalian K, Mehta A, Shah SL, et al. Efficacy of pharmacotherapy in the treatment of weight regain and inadequate weight loss following endoscopic sleeve gastroplasty. Gastroenterology 2019;156:S1168-9.
18. Mosli MM, Elyas M. Does combining liraglutide with intragastric balloon insertion improve sustained weight reduction? Saudi J Gastroenterol 2017;23:117-22.
19. Demura S, Sato S, Kitabayashi T. Percentage of total body fat as estimated by three automatic bioelectrical impedance analyzers. J Physiol Anthropol Appl Hum Sci 2004;23:93-9.
20. Ling CH, de Craen AJ, Slagboom PE, et al. Accuracy of direct segmental multi-frequency bioimpedance analysis in the assessment of total body and segmental body composition in middle-aged adult population. Clin Nutr 2011;30:610-5.
21. Cotton PB, Eisen GM, Aabakken L, et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. Gastrointest Endosc 2010;71:446-54.
22. Barrichello S, Hourneaux de Moura DT, Hourneaux de Moura EG, et al. Endoscopic sleeve gastroplasty in the management of overweight and obesity: an international multicenter study. Gastrointest Endosc 2019;90:770-80.
23. Garber A, Henry R, Ratner R, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet 2009;373:473-81.
24. Pi-Sunyer X, Astrup A, Fujioka K, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med 2015;373:11-22.
25. Saxenda (liraglutide), US Food and Drug Administration approval for weight management. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/206321Orig1s004.pdf.
26. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2015;100:342-62.
27. Saxenda liraglutide injection [package insert]Plainsboro, NJ: . Novo Nordisk; 2015.
28. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 1998;17:2265-81.
29. Cheskin LJ, Hill C, Adam A, et al. Endoscopic sleeve gastroplasty versus high-intensity diet and lifestyle therapy: a case-matched study. Gastrointest Endosc 2020;91:342-9.
30. Abu Dayyeh BK, Acosta A, Camilleri M, et al. Endoscopic sleeve gastroplasty alters gastric physiology and induces loss of body weight in obese individuals. Clin Gastroenterol Hepatol 2017;15:37-43.
31. Fayad L, Adam A, Schweitzer M, et al. Endoscopic sleeve gastroplasty versus laparoscopic sleeve gastrectomy: a case-matched study. Gastrointest Endosc 2019;89:782-8.
32. Rega-Kaun G, Kaun C, Jaegersberger G, et al. Roux-en-Y-bariatric surgery reduces markers of metabolic syndrome in morbidly obese patients. Obes Surg 2019.
33. Sjostrom L. Review of the key results from the Swedish Obese Subjects (SOS) trial—a prospective controlled intervention study of bariatric surgery. J Intern Med 2013;273:219-34.
34. Rega-Kaun G, Kaun C, Jaegersberger G, et al. Roux-en-Y-bariatric surgery reduces markers of metabolic syndrome in morbidly obese patients. Obes Surg 2020;30:391-400.
35. Nauck MA, Niedereichholz U, Ettler R, et al. Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. Am J Physiol 1997;273:E981-8.
36. Flint A, Raben A, Astrup A, et al. Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. J Clin Invest 1998;101:515-20.
37. Blonde L, Russell-Jones D. The safety and efficacy of liraglutide with or without oral antidiabetic drug therapy in type 2 diabetes: an overview of the LEAD 1-5 studies. Diabetes Obes Metabol 2009;11(Suppl 3):26-34.
38. Wadden TA, Hollander P, Klein S, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. Int J Obes 2013;37:1443-51.
39. Astrup A, Rossner S, Van Gaal L, et al. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. Lancet 2009;374:1606-16.
40. Rye P, Modi R, Cawsey S, et al. Efficacy of high-dose liraglutide as an adjunct for weight loss in patients with prior bariatric surgery. Obes Surg 2018;28:3553-8.
41. Pajecki D, Halpern A, Cercato C, et al. Short-term use of liraglutide in the management of patients with weight regain after bariatric surgery. Rev Col Brasil Cirurg 2013;40:191-5.
42. Nor Hanipah Z, Nasr EC, Bucak E, et al. Efficacy of adjuvant weight loss medication after bariatric surgery. Surg Obes Relat Dis 2018;14:93-8.

SUPPLEMENTARY TABLE 1. Baseline characteristics of subjects who underwent endoscopic sleeve gastroplasty across the 3 clinics

	Overall (n = 66)	Angioskope São José dos Campos (n = 34)	Angioskope São Paulo (n = 17)	Health Me gerenciamento de perda de peso, São Paulo (n = 15)	*P* value
Age, y, mean (SD)	42.08 (11.71)	42.56 (12.88)	42.82 (10.98)	40.13 (10.11)	.769
Male	22 (33.3)	13 (38.2)	3 (17.6)	6 (40.0)	.279
Initial weight kg, mean (SD)	101.21 (10.06)	102.92 (10.72)	95.58 (6.57)	103.70 (9.88)	.025
Height, m, mean (SD)	1.68 (.09)	1.69 (.09)	1.65 (.07)	1.70 (.08)	.197
Initial body mass index, kg/m^2, mean (SD)	35.80 (2.06)	36.14 (2.12)	35.11 (1.18)	35.79 (2.57)	.245
Obstructive sleep apnea	32 (48.5)	19 (55.9)	7 (41.2)	6 (40.0)	.463
Arthropathy	18 (27.3)	13 (38.2)	4 (23.5)	1 (6.7)	.067
Dyslipidemia	32 (48.5)	17 (50.0)	8 (47.1)	7 (46.7)	.968
Prediabetes	22 (33.3)	11 (32.4)	8 (47.1)	3 (20.0)	.265
Nonalcoholic fatty liver disease	24 (36.4)	12 (35.3)	8 (47.1)	4 (26.7)	.480
Hypertension	35 (53.0)	20 (58.8)	8 (47.1)	7 (46.7)	.623
Coronary artery disease	2 (3.0)	2 (5.9)	0 (.0)	0 (.0)	.379
Polycystic ovary syndrome	12 (18.2)	3 (8.8)	6 (35.3)	3 (20.0)	.068
Initial body fat percentage, mean (SD)	18.83 (2.09)	18.85 (2.11)	19.29 (2.31)	18.27 (1.75)	.386
Absolute weight at 5 mo, mean (SD)	87.38 (8.23)	88.65 (8.81)	82.78 (5.53)	89.73 (7.82)	.023

Values are n (%) unless otherwise defined.
SD, Standard deviation.