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Research Article

Endoscopic Sleesve Gastroplasty Plus Semaglutide Versus Endoscopic Sleeve Gastroplasty Alone for Weight Loss: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study

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Abstract

Endoscopic sleeve gastroplasty (ESG) is effective for inducing weight loss and treating metabolic co-morbidities of obesity. Semaglutide, a long-acting glucagon-like peptide-1 receptor agonist (GLP-1), produces significant weight loss when combined with lifestyle intervention. In this study, we aim to assess whether adults with overweight and obesity can achieve superior weight loss and metabolic improvement with ESG and semaglutide (ESG-S) compared to ESG alone.

Methods: In this prospective randomized, double-blind, placebo-controlled trial, we enrolled 61 patients with overweight or obesity undergoing ESG at three outpatient clinics in Brazil between June to October 2019. Patients were randomly assigned to treatment with once-weekly injectable semaglutide or an identical placebo pen within 1-month after ESG. 58 patients completed the study. The primary outcome was percent total body weight loss (%TBWL) 12 M after ESG (11 M after initiation of semaglutide). Secondary outcomes were change in percent body fat and hemoglobin A1c (HbA1c) 11 M after initiation of semaglutide.

Results: Comparisons between the two groups showed that patients who received injectable semaglutide within one month of ESG had a superior mean% TBWL at 12 m compared to those who received placebo, 25.21% (SD 2.14%) versus 18.65% (SD 1.44%) ($p < 0.001$). Additionally, the ESG-S group had a significantly greater reduction in percent body fat mass, 12.69% (SD 4.84%) vs. 9.04% (SD 6.38%), $p < 0.001$), and lower mean hemoglobin A1c, (4.93 [SD 0.45] vs. 5.33 [SD 0.60]), compared to the ESG group at 12 M.

Conclusion: Combination therapy utilizing injectable semaglutide at 1-month following ESG results in superior weight loss and co-morbidities compared to ESG alone, as demonstrated by the decrease in%TBWL, percent body fat and HbA1c at 12m.

Key points

- Endoscopic bariatric therapies, while effective, have not achieved bariatric surgery outcomes on their own.
- Endoscopic sleeve gastroplasty and semaglutide (ESG-S) approached bariatric surgery weight loss outcomes at 12 months.
- Combination therapy has potential as a less-invasive alternative to bariatric surgery for managing obesity and its complications.

Keywords: *Weight Loss; Metabolic Endoscopy; Combination Therapy; Bariatric Endoscopy; Diabetes; Obesity*

Introduction

Obesity is a chronic relapsing disease that has become a global pandemic, and its prevalence continues to increase [1]. Endoscopic Sleeve Gastroplasty (ESG) is a safe and effective therapy for obesity and its associated comorbidities [2]. It results in a% TBWL between

14.6%-19.7% at 18 - 24 months [3,4], and improvements in systolic blood pressure (SBP), HbA1c, and dyslipidemia at 12 months [3,5]. We recently demonstrated that liraglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA), augmented weight loss and improved metabolic parameters when commenced five months after ESG [6]. More generally, recent studies have demonstrated that GLP-1 RAs lead to sustained weight reduction, improvement of metabolic outcomes such as hemoglobin A1c (HbA1c) and body fat mass, and reduction in cardiovascular mortality [7,8]. However, their widespread use has been impeded by their short duration of action and the need for frequent injections [9]. Semaglutide is a long-acting GLP-1 RA that, unlike liraglutide, requires only once-weekly injections [10]. Recent clinical trials have demonstrated that semaglutide induces substantial and clinically relevant weight loss in adults with overweight or obesity without diabetes [8]. In 2021, semaglutide received FDA approval for chronic weight management in adults with obesity or overweight with at least one weight-related condition [11].

To our knowledge, no study has investigated the effect of semaglutide after ESG to augment weight loss and improve metabolic outcomes. In this prospective, randomized, double-blind, placebo-controlled study, we evaluate the efficacy of combined ESG and semaglutide (ESG-S) for weight loss compared to ESG alone (ESG).

Methods

ESG study cohort

This prospective, randomized, double-blind, placebo-controlled study was conducted at three obesity clinics in Brazil with the institutional review board's approval. Patients who were at least 18 years at the time of the procedure, had a pre-procedure BMI ≥ of 27 kg/m^2 and at least one or more obesity-related co-morbidities or a BMI ≥ of 30 kg/m^2, unable to achieve weight loss through intense diet and lifestyle modification attempts, and who subsequently underwent ESG between June and October 2019 were included. These patients were not included in previous studies, and none were taking other weight loss medications during the study period. Exclusion criteria were previous gastric surgery, gastric ulceration, hiatal hernia > 5 cm, use of anticoagulant medications, pregnancy, or lactation. All patients gave consent for off-label use of semaglutide for weight loss. Patients who had a contraindication to initiating semaglutide, such as personal or family history of medullary thyroid carcinoma and multiple endocrine neoplasia syndrome type 2, were excluded from the study. None of the patients had a history of previous intragastric balloon insertion for weight loss. Demographic data, including age, sex, comorbid illnesses, baseline height, weight, and percent body fat (via Inbody370 body composition analyzer) were collected before ESG and 12 months after ESG. 75.86% of patients had at least one comorbidity, such as hypertension, obstructive sleep apnea, dyslipidemia, non-alcoholic fatty liver disease, or diabetes mellitus type 2.

ESG-S study design

Eligible patients who underwent ESG were randomized 1:1 to receive either semaglutide (ESG-S) or an identical placebo pen (ESG) sham injection one month after ESG, using randomization generated by Research Randomizer (Research Randomizer Version 4.0, Lancaster, Pennsylvania). Novo Nordisk provided demonstrative placebo pens identical in appearance to the active drug free of charge. Blinding was maintained by the clinic director. All investigators were blinded from the onset of enrollment to completed analysis of primary and secondary outcomes. Participants were followed in their respective weight loss clinics by a medical weight loss specialist, dietician, and exercise physiologist for a total of 12 months. Weight (kg), BMI, and HbA1c before initiation of semaglutide were recorded. Changes in mean percent body fat mass (measured by Inbody 370 body composition analyzer [Ottoboni]) [12] and %TBWL were recorded 1-month post-ESG and then monthly for 11 months after initiation of semaglutide or placebo. HbA1c was measured at 3, 6, 9, and 12 months post-ESG. The pre-and post-procedure follow-up was identical at all three clinics. All authors had access to the study data and reviewed and approved the final manuscript.

Endoscopic sleeve gastroplasty

ESG is an incisionless, minimally invasive technique that involves remodeling of the greater curvature of the stomach by the placement of full-thickness sutures. The technique has been described in previous publications [13]. 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 (Over Stitch; Apollo Endosurgery, Austin, Tex, USA) along the stomach's greater curvature 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. All patients paid for their procedure out-of-pocket.

Two bariatric endoscopists performed the ESG using an identical technique. A rectangular-shaped pattern was used with an average of 9 to 14 bites per suture. The gastric fundus was not sutured. Patients received cefazolin 1 mg, ondansetron 4 mg, and tramadol 100 mg intravenously intraoperatively. Dexlansoprazole 40 mg was initiated two weeks before the procedure and continued for eight weeks after ESG with sucralfate every 8 hours for 14 days after ESG. Patients were discharged home the same day with ondansetron 8 mg and dimenhydrinate 50 mg every 8 hours for five days as needed for nausea. Patients were given paracetamol 500 mg every 6 hours and codeine 30 mg daily for three days as needed for pain control.

Post-ESG follow-up

The first post-procedure visit was one week after ESG. Patients then had follow-ups scheduled bi-monthly for the first two months and then monthly for the remaining ten months. 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. In addition to close follow-up, all patients were added to a WhatsApp group that included a specialized weight loss coach, personal trainer, dietician, program coordinator, nurse, and physician.

Patients met with a trainer before their procedure at the clinic's private gym, where they were prescribed a personalized workout program in addition to YouTube home-workout video links. Patients were instructed to undergo high-intensity interval training (HIIT) for at least 15 minutes a day for four days per week.

After ESG, all patients followed a diet tailored to their basal metabolic rate (BMR), which was calculated using the Inbody370 body composition analyzer (Ottoboni) [12]. The first week after ESG, patients consumed a clear liquid diet, followed by a full-liquid diet for the second week based on 50% of their BMR. They were transitioned to a soft diet based on 66% of their BMR for weeks 3 and 4. Whey protein supplementation was recommended from weeks 1 to 4. Subsequently, patients were encouraged to eat a low-carbohydrate, high-protein diet consisting of 25% carbohydrates, 60% protein, and 15% fat. At week 6, patients were transitioned to a regular diet consisting of a caloric intake of 80% of their BMR.

Semaglutide

Injectable semaglutide (Ozempic, Novo Nordisk, Bagsvaerd, Denmark) dosed at 2.4 mg once weekly for 68 weeks has been shown to lower HbA1c, decrease systolic blood pressure, and induce significant weight loss [8]. It was approved by the US Food and Drug administration for type 2 diabetes in 2017 and obesity or overweight with one weight-related condition in 2021 [11]. The most common adverse reactions include nausea, vomiting, diarrhea, abdominal pain, and constipation, seen in 5% of patients. Pancreatitis, thyroid cancer, and diabetic retinopathy are serious but rare associated side effects [14].

Patients were randomized to semaglutide or placebo during the first month following ESG to further augment weight loss. All patients were initiated on semaglutide (n = 31) or placebo (n = 30) per protocol at 0.25 mg/week for four weeks and then increased incrementally by 0.25 mg every 4 weeks based on tolerance and side effects to a maximal tolerated dose of 1.5 mg/weekly. If patients had side effects upon increasing the dose, the previous dose was maintained for a further 4 weeks. Subjects were trained to self-administer the injection.

A total of five patients, 3 in the ESG group and 2 in the ESG-S group, were on additional diabetes medications such as metformin, glyburide, canagliflozin, and dapagliflozin. No other weight loss medications were initiated during the study period, and none of the patients were taking insulin.

Statistical analysis

We hypothesized that at the end of follow-up, mean% TBWL from ESG alone would be 20% and %TBWL from ESG and semaglutide would be 25%. In order to observe a 5% difference between these two interventions with an 80% power, 10% loss to follow-up, and a type 1 error of 0.05, we estimated that we would need 60 participants (30 in each arm).

Categorical variables were presented as percentages. They were analyzed with Fisher's exact test or Chi-squared test. Continuous data were presented as mean value ± standard deviation (SD) or median (interquartile range). Continuous variables were analyzed with the Student t-test or Mann - Whitney U test. Associations were considered statistically significant at a two-tailed p-value of < 0.05. All analyses were performed with the R software (online at http://www.R-project.org, the R Foundation for Statistical Computing, Vienna, Austria). A subgroup analysis of patients with diabetes mellitus was not performed due to the small sample size.

Results

Baseline characteristics

Sixty-one patients who underwent ESG were randomized to receive semaglutide or placebo. Two patients in the ESG-S group and one patient in the ESG group were lost to follow up, and thus were excluded from the study. None of the patients discontinued injections due to side effects. This resulted in 29 patients available for analysis in each group. There was no substantial difference in baseline characteristics between the two groups (Table 1). The average patient BMI prior to ESG was 36.87 kg/m^2 (SD 2.30 kg/m^2). None of the patients had a BMI below 30 kg/m^2. At baseline 41.4% of patients had diabetes mellitus Type 2 and 5 patients (8.62%, 3 from ESG group, 2 from ESG-S group) were on medications for glucose control. The 3 patients in the ESG group were taking glucose-lowering regimens that consisted of glibenclamide and metformin, canagliflozin and metformin, and dapagliflozin and metformin. The regimens of the two patients in the ESG-S consisted of dapagliflozin and metformin and metformin alone. The mean baseline HbA1c was 5.86 (SD 0.71). The mean percent body fat mass before initiation of semaglutide/placebo was 43.63% (SD 5.33%). Co-morbidities observed in the study population before semaglutide were dyslipidemia (51.7%), obstructive sleep apnea (36.2%), and coronary artery disease (20.7%).

	ESG	ESG Plus Semaglutide	P Value
Age, years, mean (SD)	36.62 (9.65)	33.31 (9.87)	0.20
Female, age (%)	21 (72.4)	21 (72.4)	>0.99
Initial Weight, kg, mean (SD)	103.71 (12.89)	101.58 (14.95)	0.57
Height, m, mean (SD)	1.67 (0.08)	1.66 (0.09)	0.49
Initial body mass index, kg/m^2(SD)	36.88 (1.78)	36.86 (2.76)	0.98
Dyslipidemia, n (%)	15 (51.72)	15 (51.72)	>0.99
Diabetes Mellitus Type 2, n (%)	12 (41.37)	12 (41.37)	>0.99
Obstructive Sleep Apnea, n (%)	11 (37.93)	10 (34.48)	>0.99
Coronary Artery Disease, n (%)	7 (24.13)	5 (17.24)	0.75
Baseline body fat percentage, mean (SD)	44.61 (4.47)	42.61 (6.01)	0.17

Table 1: *Baseline characteristics of patients.*

Decrease in percent total body weight loss, BMI, and percent body fat mass

The %TBWL, BMI loss, and change in percent body fat mass after initiation of semaglutide are shown in figure 1 and table 2 and 3. Mean %TBWL were significantly higher in the ESG-S group as early as month 2, and then consistently from month 4 of follow-up onwards compared to the ESG alone group. At 12-months after ESG (11-months after the initiation of semaglutide/placebo), patients in the ESG-S group experienced a cumulative %TBWL of 25.21% (SD 2.14%) compared to 18.65% (SD 1.44%) in the ESG group ($p < 0.001$). When stratified by dose of semaglutide (0.50 mg, 1.0 mg, and 1.5 mg/weekly), there was no significant difference in %TBWL at 12 months (Figure 2 and 3) (26.73% [SD 1.87%], 25.59% [SD 0.43%], 27.72% [SD 1.84%], respectively, $p = 0.06$).

	Esg	**Esg-S**	**P Value**
N	**29**	**29**	
%TBWL by Month			
2	4.83 (1.99)	6.01 (1.35)	0.01
3	7.01 (3.00)	7.71 (1.49)	0.27
4	8.40 (2.31)	9.75 (1.46)	0.01
5	10.16 (2.51)	11.43 (1.51)	0.03
6	11.60 (2.69)	12.88 (1.71)	0.04
7	12.82(2.57)	14.74 (1.87)	0.003
8	14.12 (2.57)	17.04 (1.94)	<0.001
9	15.28 (2.35)	19.55 (1.99)	<0.001
10	16.36 (2.08)	21.76 (2.06)	<0.001
11	17.56 (1.75)	23.53 (2.13)	<0.001
12	18.65 (1.44)	25.21 (2.14)	<0.001

	ESG	**ESG-S**	**P Value**
N	**29**	**29**	
BMI loss by month (kg/m^2)			
2	2.59 (1.10)	2.84 (0.59)	0.28
3	3.10 (0.84)	3.60 (0.60)	0.01
4	3.75 (0.93)	4.22 (0.67)	0.04
5	4.28 (0.99)	4.75 (0.75)	0.05
6	4.74 (0.99)	5.44 (0.87)	0.007
7	5.23 (1.03)	6.29 (0.96)	<0.001
8	5.66 (1.00)	7.22 (1.02)	<0.001
9	6.06 (0.94)	8.04 (1.11)	<0.001
10	6.50 (0.85)	8.70 (1.24)	<0.001
11	6.90 (0.72)	9.32 (1.26)	<0.001
12	7.27 (0.71)	9.88 (1.22)	<0.001

Table 2A: *%TBWL by month 12 months after ESG.*

Table 2B: *BMI loss by month 12 months after ESG.*

	ESG	ESG-S	P Value
N	**29**	**29**	
HbA1c, mean (SD)			
Baseline	5.86 (0.79)	5.86 (0.63)	0.99
Month 3	5.66 (0.70)	5.62 (0.56)	0.80
Month 6	5.48 (0.62)	5.39 (0.53)	0.57
Month 9	5.45 (0.59)	5.18 (0.50)	0.08
Month 12	5.33 (0.60)	4.93 (0.45)	0.006
Percent Body Fat Mass %, mean (SD)			
Baseline	44.61 (4.47)	42.61 (6.01)	0.17
Month 12	35.57 (1.88)	29.92 (2.16)	<0.001

Table 3: *Hemoglobin A1c and percent body fat mass 12 months after ESG.*

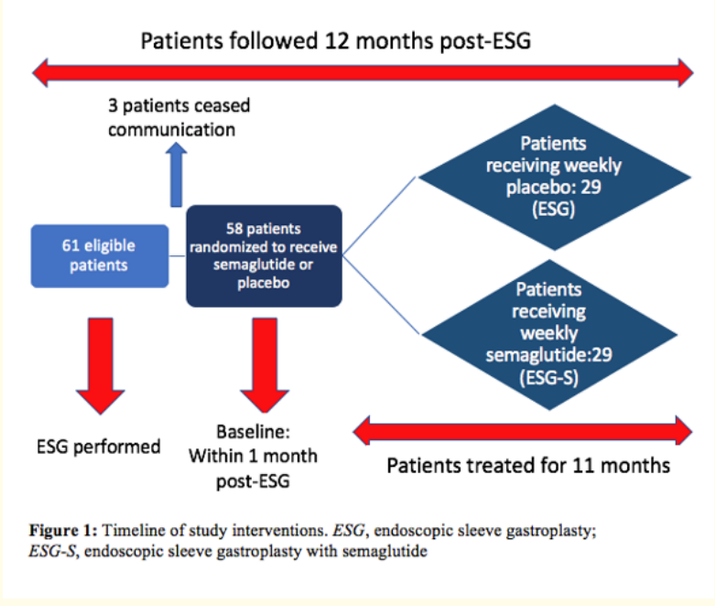

Figure 1: Timeline of study interventions. *ESG*, endoscopic sleeve gastroplasty; *ESG-S*, endoscopic sleeve gastroplasty with semaglutide

Figure 1

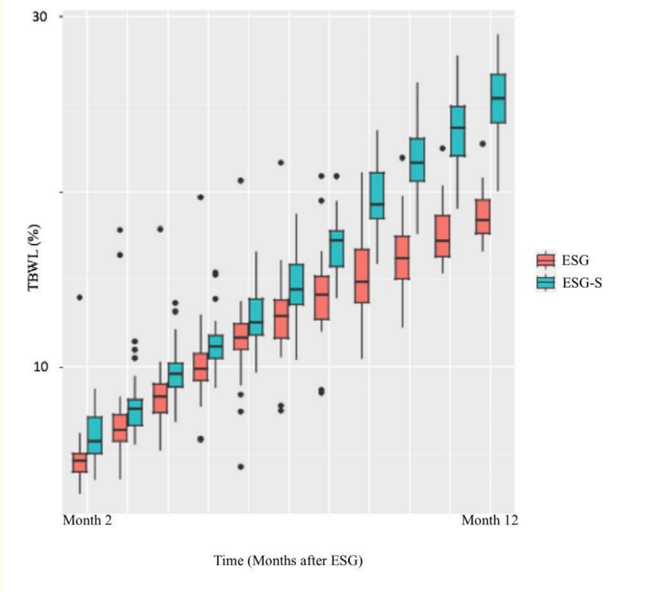

Figure 2: *Change in %TBWL after ESG and and placebo (ESG) versus semaglutide (ESG-S).*

Figure 3: *Change in %TBWL after 12 months, stratified by dose of semaglutide.*

Patients in the ESG-S group experienced a statistically significant greater BMI decrease from month 3 onwards (Table 2B). At the 12-month post-ESG mark, patients receiving semaglutide experienced a more significant BMI reduction compared to patients receiving placebo (9.88 [SD 1.22] versus 7.27 [SD 0.71], $p < 0.001$). The ESG-S group also achieved a significantly higher loss of percent body fat mass when compared to the ESG group (29.92% [SD 2.16%] versus 35.57% [SD 1.88%], $p < 0.001$).

Decrease in hemoglobin A1c

Changes in HbA1c at 3-, 6-, 9-, and 12-month after ESG are shown in table 3. The baseline HbA1c was 5.86 (SD 0.79) in the ESG group and 5.86 (SD 0.63) in the ESG-S group. Mean HbA1c values did not differ significantly until 12 months. At the end of 12 months, the mean HbA1c in the ESG-S group was significantly lower than the ESG group (4.93 [SD 0.45] vs. 5.33 [SD 0.60], $p = 0.006$).

Adverse events

No serious adverse events were encountered after ESG. Overall, 4 patients in the ESG-S group tolerated a dose of 0.5 mg/weekly, 13 patients tolerated 1.0 mg/weekly, and 11 patients tolerated 1.5 mg/weekly. Side effects were mild and limited to nausea and vomiting. None of the patients experienced serious adverse events from semaglutide. A higher percentage of patients who received semaglutide experienced nausea compared to patients receiving placebo (85.21% vs. 14.36%, $p < 0.001$). Semaglutide was not discontinued in any patient due to side effects.

Patients lost to follow-up

A total of three patients, two in the ESG-S group and one in the ESG group, were lost to follow-up. Patients in the ESG-S group ceased communication at months 1 and 3, with last recorded %TBWL of 5.85% and 9.34%, respectively. One patient in the ESG group ceased communication after month 2, after 17.82% TBWL. All 3 patients were excluded from the study.

Discussion

In this prospective, randomized, double-blind, placebo-controlled trial we found that combination therapy of ESG with weekly semaglutide was superior to ESG alone in terms of %TBWL and BMI reduction beginning at 4-months. Furthermore, mean %TBWL at one-year post-intervention was approximately 25% for those on combination therapy, closely matching %TBWL outcomes seen in bariatric surgeries such as the laparoscopic sleeve gastrectomy [15,16].

Overweight (Body Mass Index (BMI) ≥ 25 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) lead to numerous clinical co-morbidities. It is challenging to achieve significant and sustained weight loss with diet and lifestyle modification alone [17-19]. Additionally, reversal of obesity-related co-morbidities and improvement in quality of life entails a percent total body weight loss (%TBWL) between 5 - 10%, which is rarely achieved with medications alone [20-22].

ESG has recently emerged as an effective and minimally invasive modality for managing obesity. Recent trial data suggests that ESG may be associated with hormonal weight loss through decreased secretion of ghrelin without impacting GLP-1 or peptide YY levels [23,24]. ESG results in superior weight loss compared to diet and lifestyle [25], and studies demonstrate fewer adverse events compared to LSG [26,27].

LSG is one of the most commonly performed bariatric surgeries. Although different hypotheses have been proposed, the exact mechanism by which it induces weight loss is unknown. Previous studies have shown that LSG improves insulin sensitivity, decreases ghrelin, and improves glucose homeostasis [28,29]. These hormonal changes are thought to contribute to a higher weight loss observed with LSG compared to ESG [26]. This might be due to the fact that even though ESG mimics LSG in terms of anatomic alterations, it does not reproduce the hormonal changes induced by LSG [24,30]. Hence, it has been hypothesized that ESG may reach weight loss outcomes similar to LSG if additional therapy is introduced, which aims at reproducing the physiologic and hormonal changes seen with LSG [31-34]. In an attempt to achieve weight loss and metabolic outcomes similar to LSG, endoscopists have investigated the impact of procedural modifications to enhance ESG, such as suture pattern, use of argon plasma coagulation, and extending suturing into the fundus. However, these aforementioned modifications have not shown significant benefit [35-37]. The addition of a medication that reproduces the physiologic and hormonal changes seen with LSG, has been hypothesized to increase the efficacy of ESG [31-34].

Recently, semaglutide, a long-acting once-weekly GLP-1 agonist, has been FDA approved for the treatment of adults with obesity. It is more cost-effective than liraglutide [38], has milder gastrointestinal side effects, induces greater weight loss, and leads to more significant improvement in weight-related secondary outcomes such as hypertension, HbA1c, and nonalcoholic fatty liver disease (NAFLD) [38,39] Since previous studies determined that weight loss at six months predicted both weight maintenance and long-term weight loss [40], we initiated semaglutide within one month after ESG to maximize cumulative weight loss and metabolic benefits over a longer period. We observed a statistically significant greater mean %TBWL in the ESG-S group as early as 2 months after treatment with semaglutide, followed by sustained weight loss between 5 and 12 months. These results suggest that the addition of semaglutide assists in overcoming the weight loss deceleration observed 4 - 6 months after ESG [30].

While this study has a strong randomized, double-blind, placebo-controlled design, we also acknowledge as a limitation the small sample size and short follow up of 12 months. ESG is a relatively new procedure with few referrals due to lack of insurance coverage thus limiting a larger sample size. It is unknown whether the beneficial effects of the combined intervention would be maintained beyond 12 months or if semaglutide should be continued for a longer duration. Additionally, further large studies are needed to determine the optimal timing and duration of semaglutide post-ESG. Considering that ESG is currently less expensive than bariatric surgery [41], it is plausible that with further adjustment of dose and timing that this combination approach may be more palatable as a less invasive alternative with fewer adverse events and long-term complications. We recognize that our study's intensive lifestyle interventions were achieved by highly motivated patients, and that outcomes observed in the general population may differ to some degree. While none of our patients

discontinued semaglutide due to nausea, we suspect some degree of medication nonadherence in larger populations based on data from larger clinical trials [8].

Additionally, assessing patients' baseline gastrointestinal physiology has enhanced treatment tolerance and optimized outcomes [42]. As demonstrated by the promising outcomes of combination endoscopic bariatric and GLP1-RA therapies [43], we predict that in the future personalized combination therapy will be frequently utilized to maximize weight and metabolic outcomes.

Conclusion

In conclusion, our study suggests that the addition of semaglutide to ESG is superior to ESG alone for weight loss, reduction of percent body fat mass, and reduction of HbA1c. Additional larger and longer-term studies are needed to confirm these findings and explore the long-term effects of combined interventions.

Disclosures

Author #1 is a consultant for Apollo Endo Surgery.

Author #3 is a Consultant and Proctor for Fractyl Labs; USGI; GI dynamics;Colubris Mx; Apollo Endosurgery; Ethicon EndoSurgery; OlympusAmerica; Medtronic; Keyron (UK).

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Research Data Policy

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Previous Presentations

None.

Authors Contribution

Anna Hoff: Conduction of Trial, Data collection, analysis and interpretation of data, critical revision, and approval of final draft.

Zadid Haq: Drafting of the article, data collection, analysis and interpretation of data, critical revision, and approval of final draft.

Abdellah Hedjoudje: Data collection, statistical computations, analysis and interpretation of data, critical revision, and approval of final draft.

Manoel Galvao Neto: Conduction of Trial, Data collection, analysis and interpretation of data.

Luiz Gustavo de Quadros: Conduction of Trial, Data collection, analysis and interpretation of data.

Sergio Alexandre Barrichello, Gabriel Cairo Nunes and Dilhana Badurdeen: Conduction of Trial, Data collection, analysis and interpretation of data.

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