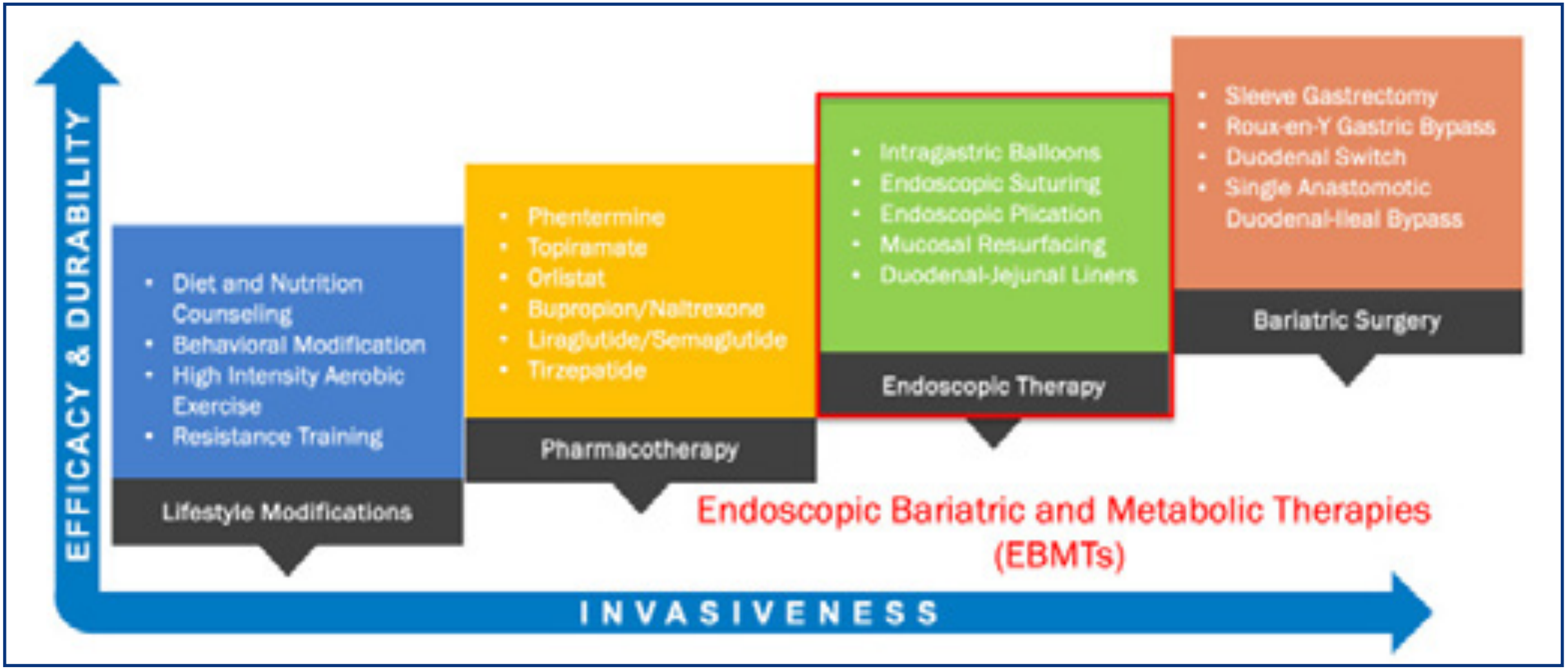


RAZIONALE BIOLOGICO DELLA SINERGIA FARMACOLOGICO–ENDOSCOPICA

Prof. M. Nannipieri
Dip. Medicina Clinica e Sperimentale
Università di Pisa

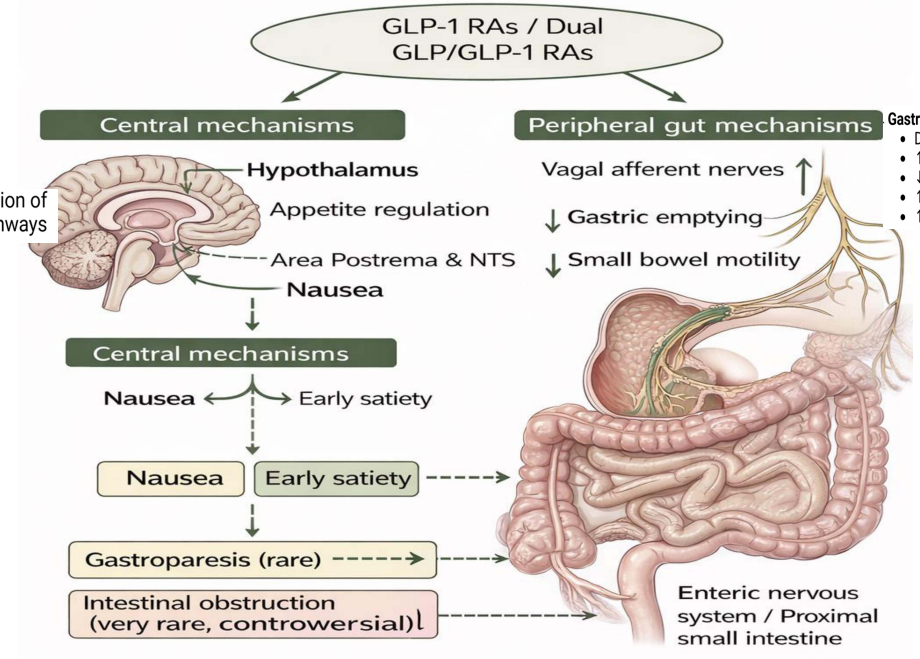
Obesity treatments in order of advanced invasiveness and durability.



Allencherril, RP, Methodist DeBakey Cardiovascular Journal 2025

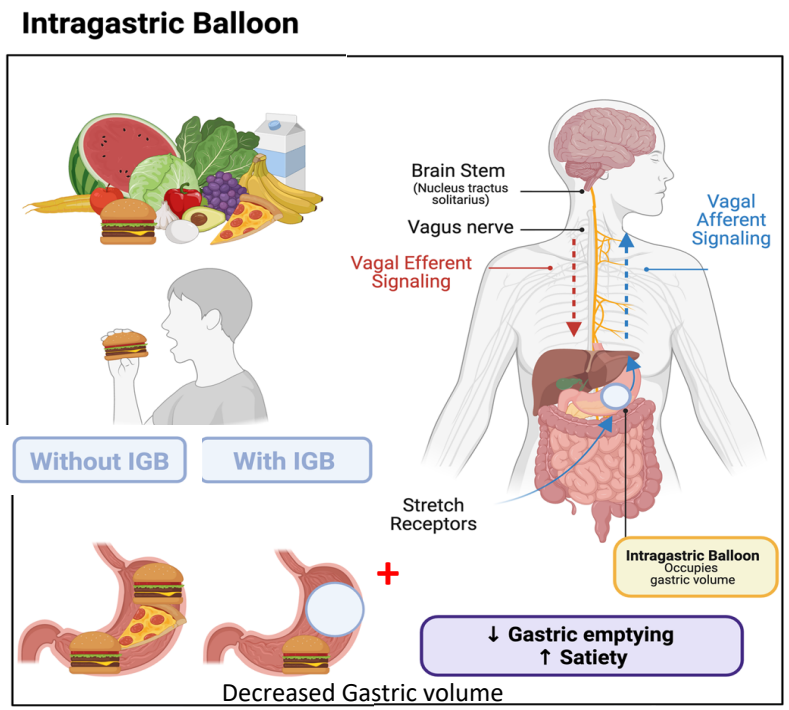
Gastrointestinal Effects of GLP-1 and Dual GLP-1/GIP Receptor Agonists

Yılmaz N, Diabetes, Metabolic Syndrome and Obesity 2026

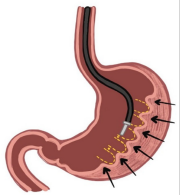


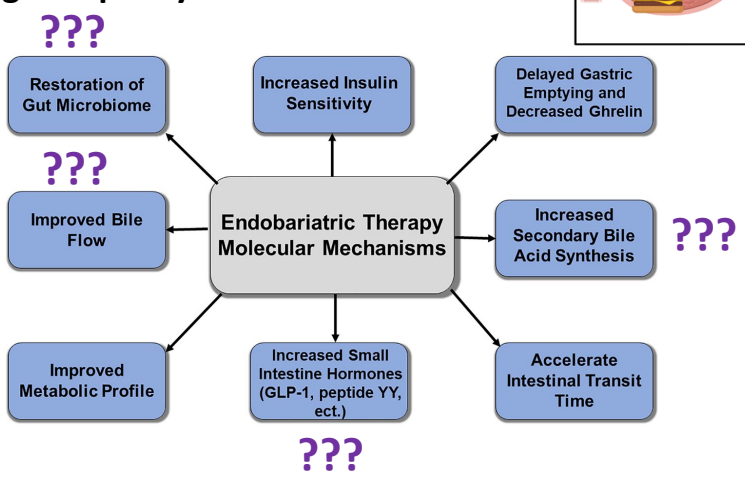
Mechanism of Action
Intragastric balloons

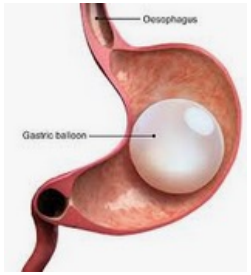
Barakat KE, Obesity Surgery 2025



Endoscopic sleeve gastroplasty mechanism of action.

	ESG
	
TBWL at 12 months	17.57%
Length of Hospital Stay (Days)	0.34 ± 0.73
Complications	2.20%
New-onset GORD	1.9%

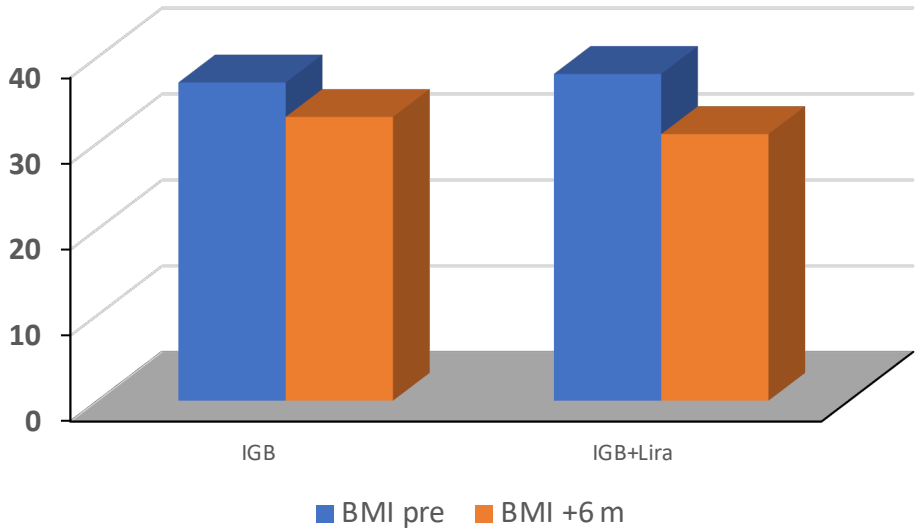




Does Combining Liraglutide with Intragastric Balloon Insertion Improve Sustained Weight Reduction?

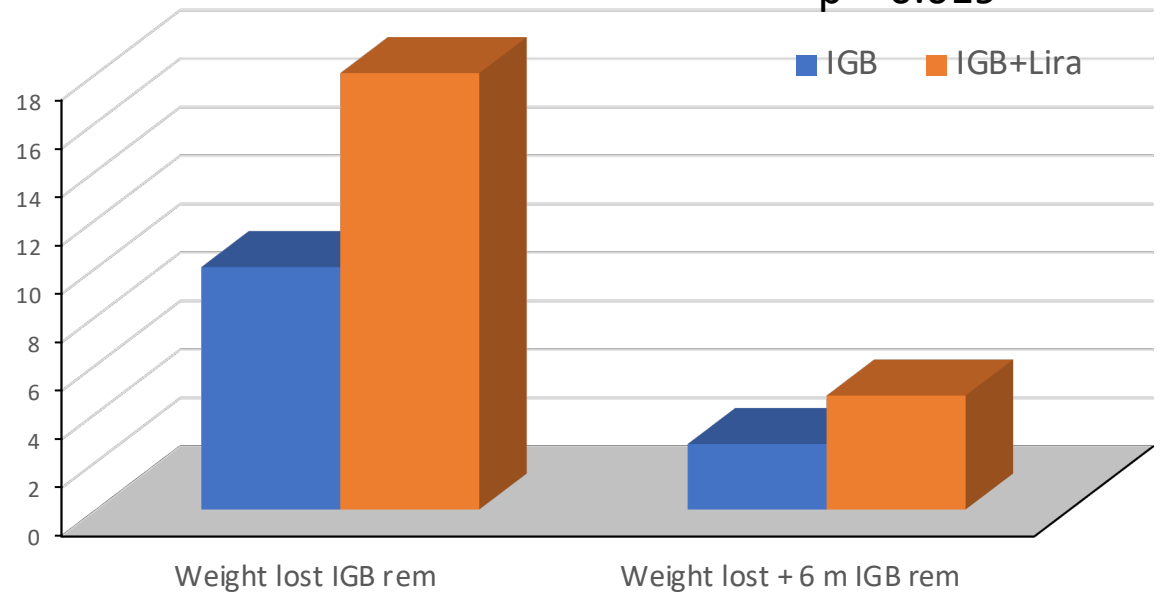


IGB 64 pz (6 months FU)
IGB+Lira 44 pz (Lira after 1 m IGB)



p <0.0001

p = 0.019



no significant differences were observed between the two groups with regards to pain, nausea, GERD, need for early IGB removal, IGB migration

Mosli MM, Saudi Journal of Gastroenterology 2017

Efficacy of Adjunctive Semaglutide Injections in Patients Undergoing Gastric Ballooning for Weight Reduction

Introduction

Given the global increase in obesity prevalence, there has been an emergence of a multitude of treatment options, specifically less invasive operations, like intragastric balloons, and pharmaceutical treatments like Semaglutide.

The aim of this study is to evaluate the synergistic effects of intragastric balloon and Semaglutide on weight reduction and weight regain.

Methods



Eligible Participants:
18-65 years old with a
BMI ≥27 kg/m²

Randomization



Group A:
20 patients



IGB (removed at
6 months)



Group B:
20 patients



IGB (removed at
6 months)



Semaglutide: 0.5 mg/
wk (month 2), 1 mg/
wk (months 3-4, 7-8)



Standard Diet &
Lifestyle Counseling





Regular Follow-up
& Weight/BMI at 3, 6,
& 12 months

Results

Group A: IGB



Significant weight
regain than Group B

Group B: IGB & Semaglutide



Significantly
greater TBWL &
EWL than Group A

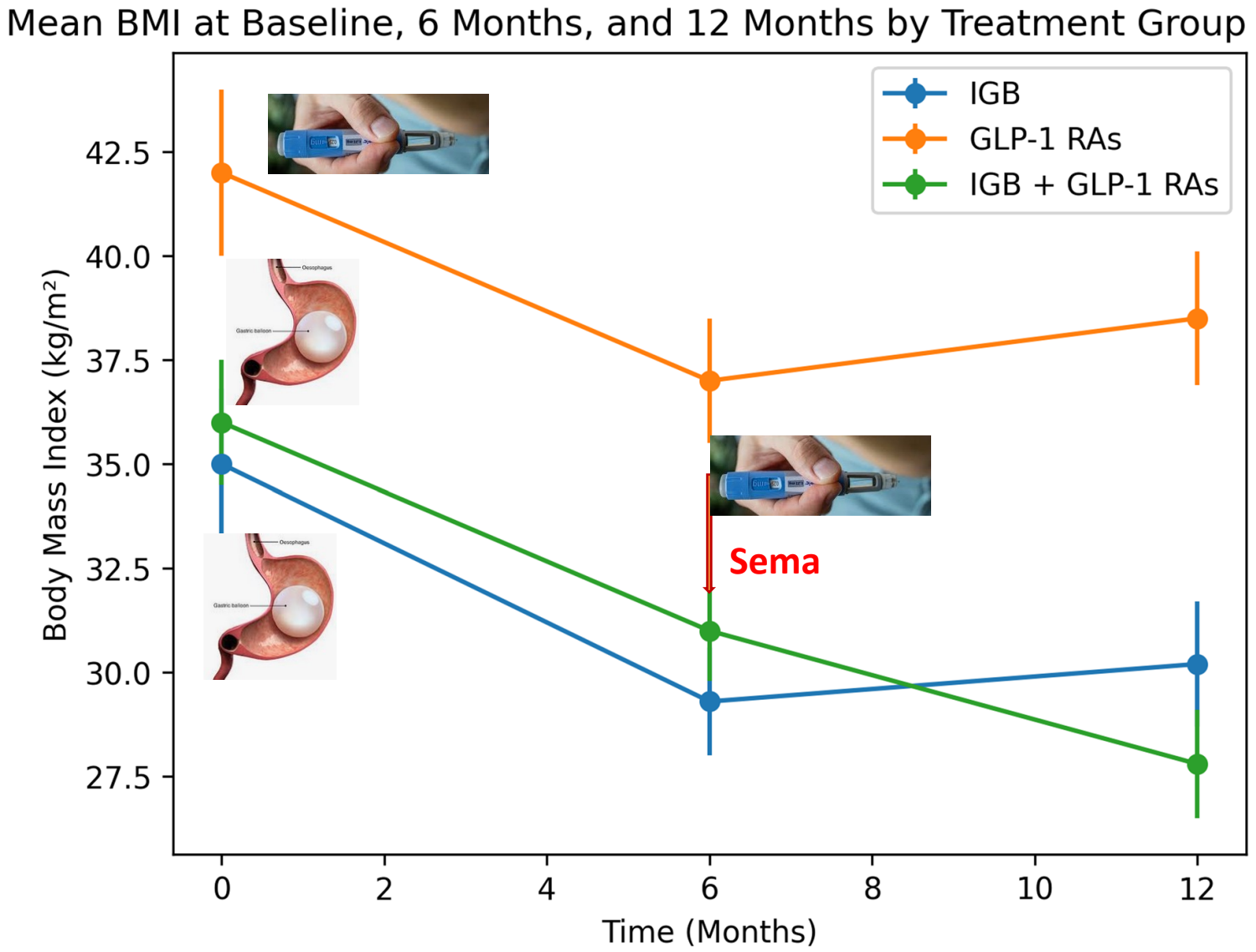
Conclusion

This study demonstrates that adjunctive Semaglutide with intragastric balloon enhances the magnitude of short-term weight loss, while enhancing the sustainability achieved with intragastric ballooning alone.

Barakat, Abuhasan, Mahmoud, Asal, Elsayed, Guy, Safadi, Basson

Barakat KE, Obesity Surgery 2025

Sequential Intragastric Balloon Followed By Semaglutide in Obesity: A Comparative Study of 12-Month Weight Loss Outcomes

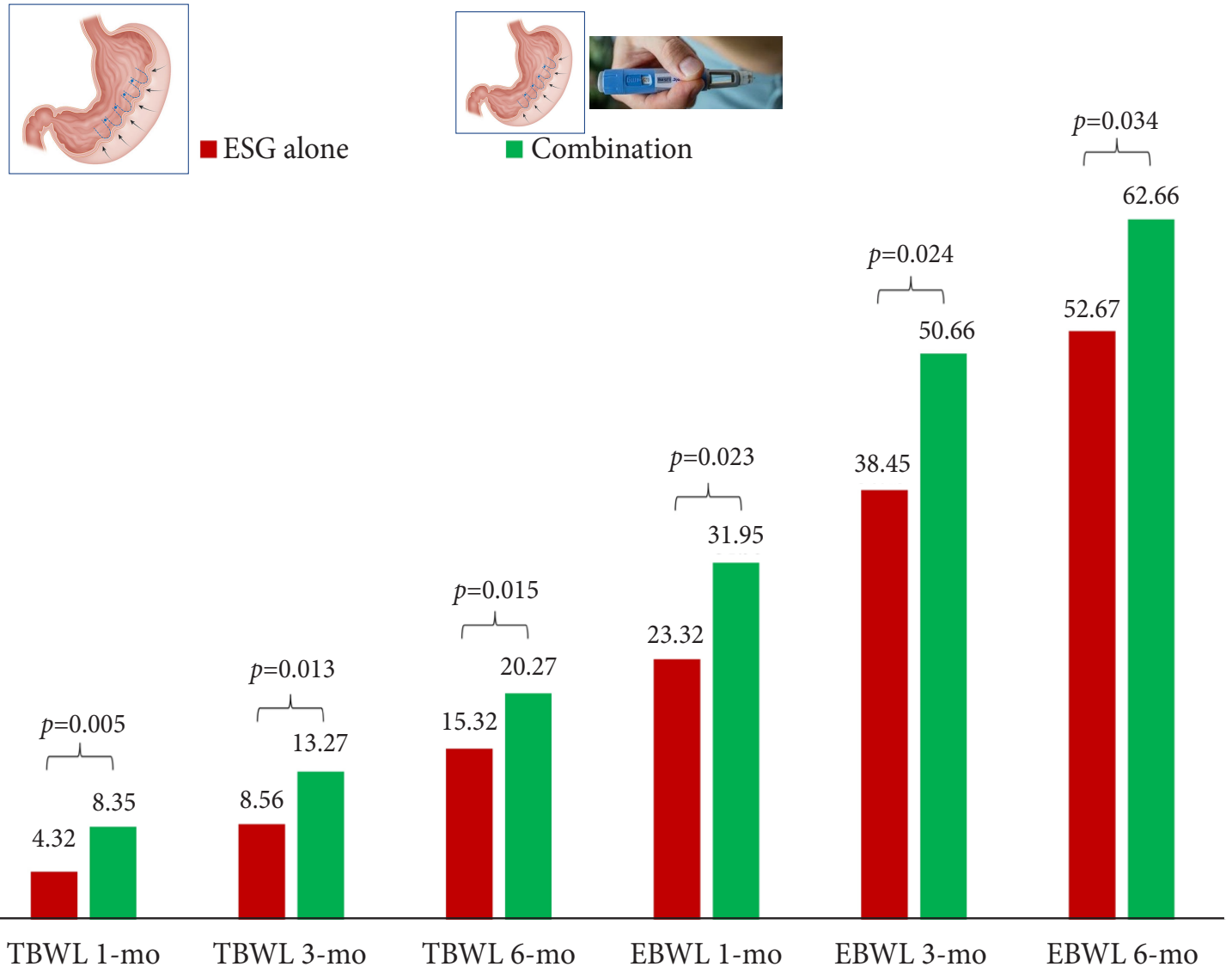


Conclusions:

- Sequential administration of **Sema after intragastric balloon removal was associated with greater weight loss than either therapy alone.**
- These findings suggest that **strategic timing of combination therapy, rather than concurrent use**, may optimize efficacy in non-surgical obesity management.

Teke E, Obesity Surgery 2026

Endoscopic Sleeve Gastroplasty combined with oral Semaglutide (2 wk after) for better control of weight and diabetes



Variable	ESG alone (*n*=10)	ESG combining AOM (*n*=8)	*p*-value
Age (yr)	42.90±8.81	43.13±5.57	0.95
Sex (female/male)	6 (60.0)/4 (40.0)	4 (50.0)/4 (50.0)	0.67
BMI before ESG (kg/m^2)	35.18±3.83	33.15±2.16	0.20
BMI at 6-mo after ESG (kg/m^2)	28.95±0.97	26.43±0.78	<0.001
TBWL (%)			
1-mo	4.32	8.35	0.005
3-mo	8.56	13.27	0.01
6-mo	15.32	20.27	0.02
EBWL (%)			
1-mo	23.32	31.95	0.02
3-mo	38.45	50.66	0.02
6-mo	52.67	62.66	0.03
HbA1c reduction (%)	1.2±0.13	1.4±0.19	0.02
Dyslipidemia improvement	4 (40.0)	4 (50.0)	0.67
Procedure-related complication			
Abdominal pain	2 (20.0)	1 (12.5)	0.67
Nausea	2 (20.0)	2 (25.0)	0.80
Bleeding	1 (10.0)	0 (0)	0.36
Perforation	0 (0)	0 (0)	NA

Values are presented as mean±standard deviation or number (%) unless otherwise indicated.
ESG, endoscopic sleeve gastroplasty; AOM, anti-obesity medication; BMI, body mass index; TBWL, total body weight loss; EBWL, excess body weight loss; HbA1c, hemoglobin A1c; NA, not applicable.

Chung CS, Clin Endosc 2025

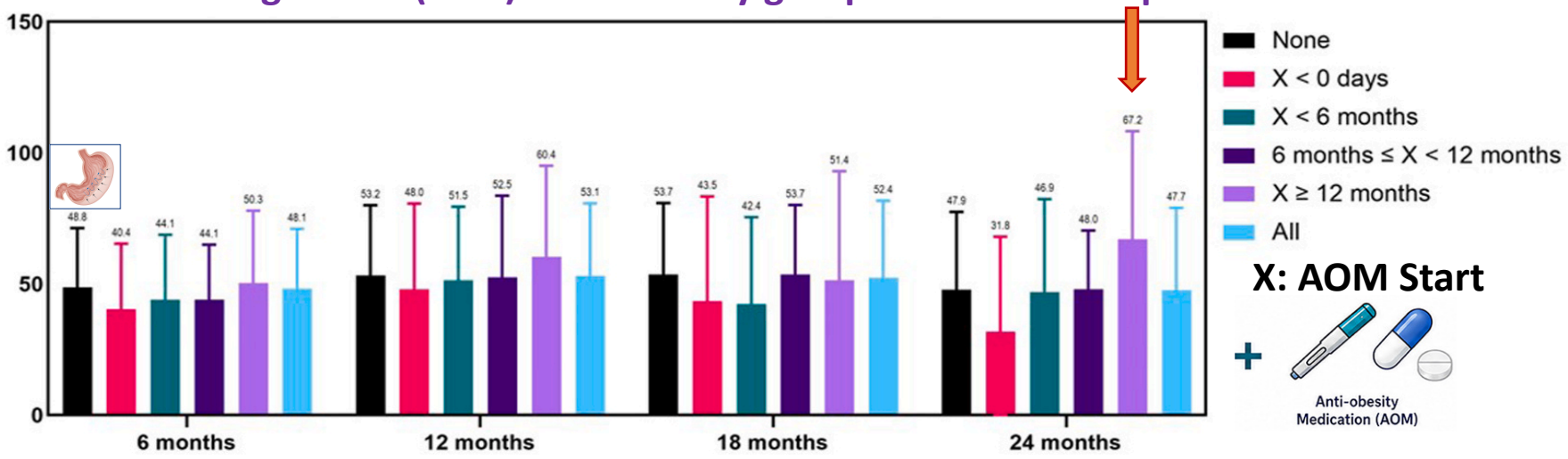
Outcomes of concomitant antiobesity medication use with Endoscopic Sleeve Gastroplasty in clinical US settings

Real Word

1359 (90.2 %) no AOM use

147 (9.8 %) AOM use

%Excess Weight Loss (EWL) outcomes by group and time from procedure.



X: AOM Start

%TBWL at 24 mo

No AOM: 15.4% ± 9.6

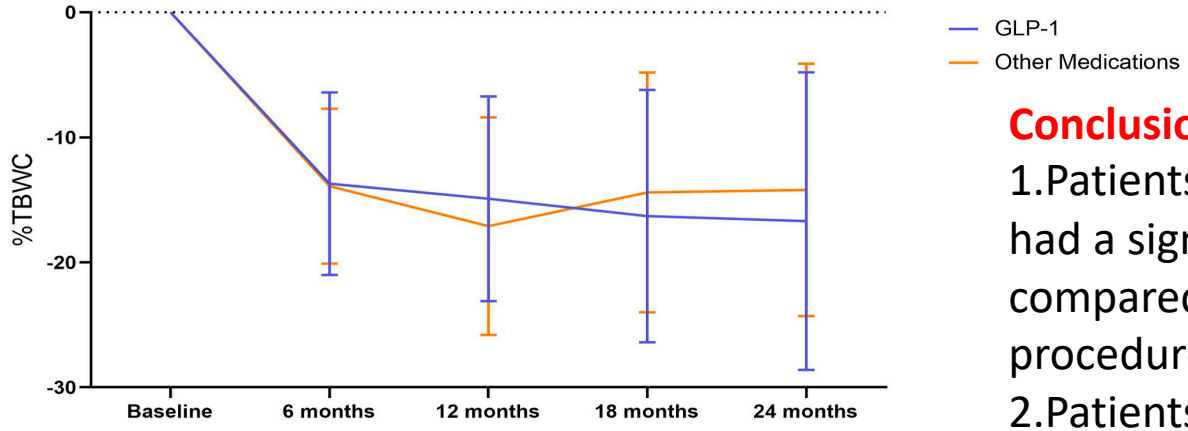
AOM <6 mo from ESG: 10.4 ± 10.8

AOM 6-12 mo from ESG: 14.8 ± 10.1

AOM 12 mo from ESG

21.1 ± 10.0*

%Total Body Weight Change (TBWC) outcomes by type of AOM.



Conclusions

1.Patients who were prescribed AOMs **after the 12-month visit** had a significantly higher TBWL% and EWL% at 24 months, as compared to patients who were on active AOM at the time of the procedure.

2.Patients on a GLP-1RA had a trend towards improved weight loss at 18 and 24 months.

Gala K, Obesity Pillars 2024

Endoscopic Bariatric and Metabolic Therapies Combined with Anti-Obesity Medications

A Systematic Review and Meta-analysis

11 STUDIES
2,609 PATIENTS

78% EGR/ESG alone

PRIMARY ENDOSCOPIC BARIATRIC AND METABOLIC THERAPY (EBMT)

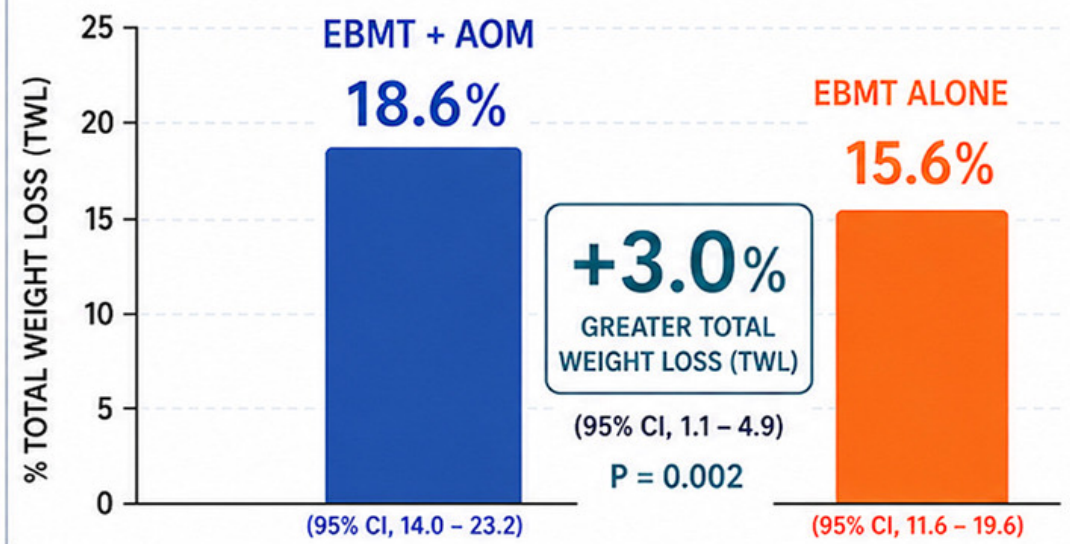
Intragastric Balloon (IGB)

Endoscopic Gastric Remodeling (EGR/ESG)

+

Anti-obesity Medication (AOM)

→ Weight loss at 12 months



BENEFIT OBSERVED IN BOTH SUBGROUPS

IGB + AOM > IGB Alone

EGR/ESG + AOM > EGR/ESG Alone

TIMING OF AOM INITIATION

AFTER EBMT — Weight loss

BEFORE EBMT — No significant benefit

IMPROVED METABOLIC OUTCOMES WITH COMBINATION THERAPY

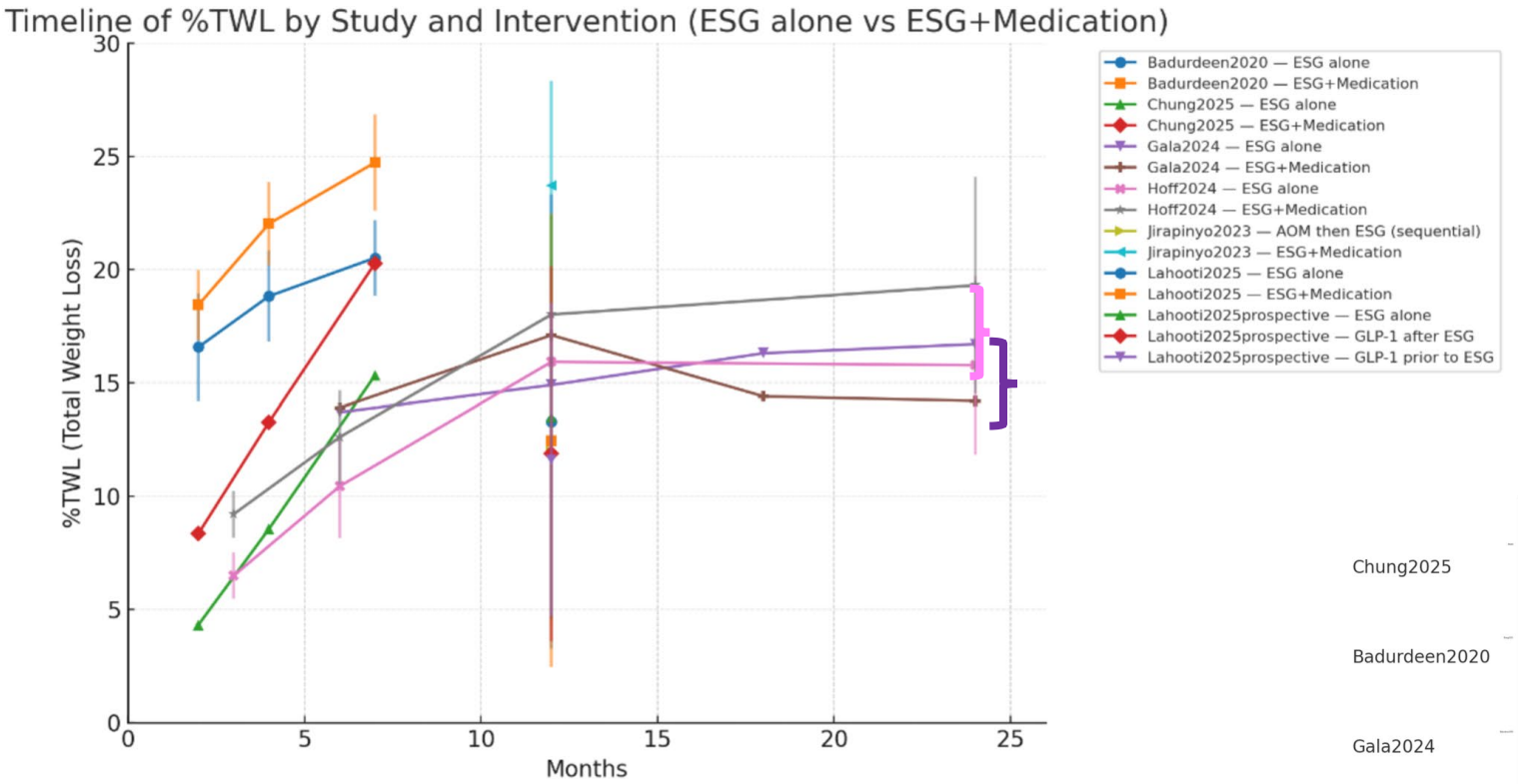
Greater reduction in HbA1c

Greater reduction in fibrosis NITs

CONCLUSION: Combination therapy with EBMT and AOMs results in greater weight loss and improved metabolic outcomes compared with EBMT alone. Initiation of AOM following EBMT may represent the optimal sequencing strategy.

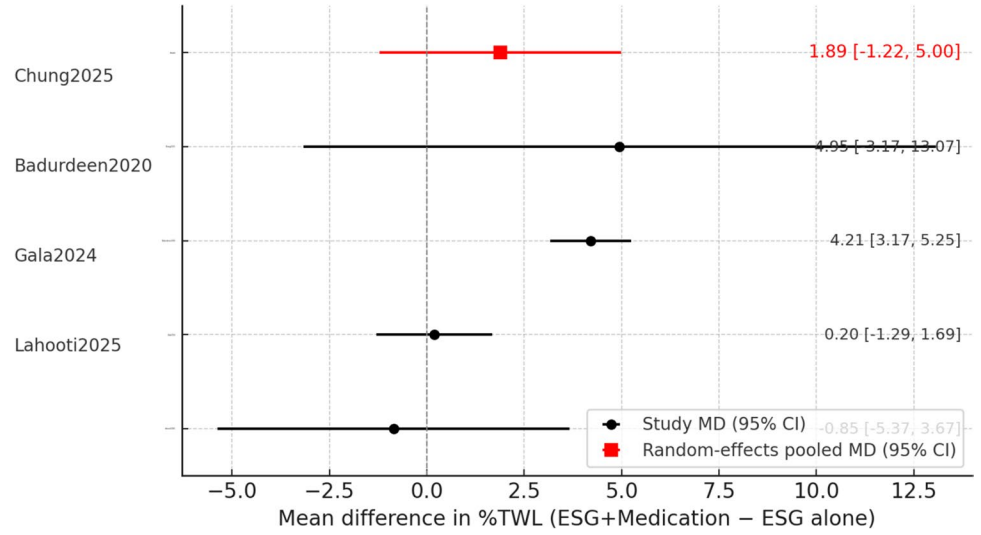
Gopakumar H, Gastrointestinal Endoscopy 2026

Comparison of the concomitant use of anti-obesity medications with endoscopic sleeve gastroplasty versus endoscopic sleeve gastroplasty alone: a systematic review and meta-analysis



Conclusions

ESG combined with AOMs **may enhance early weight loss in selected settings**; however, **current evidence does not support** consistent long-term superiority over ESG alone for weight or glycemic outcomes. Although the available data remain limited and heterogeneous, **concomitant therapy may be considered in selected patients rather than as a universally superior strategy**.

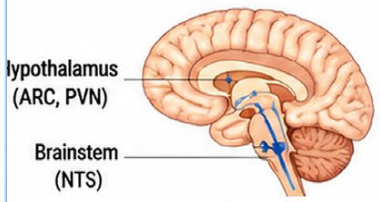


de Quadros LG, Surgical Endoscopy 2026

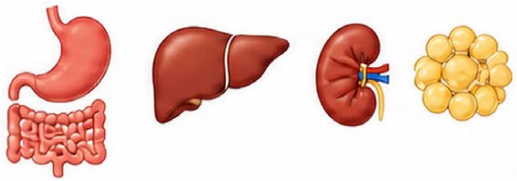
Combination Pharmacotherapies for Obesity—Current Evidence and Future Directions

Homeostatic appetite control

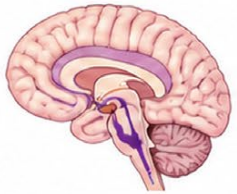
Central appetite and satiety regulation



Peripheral and metabolic targets



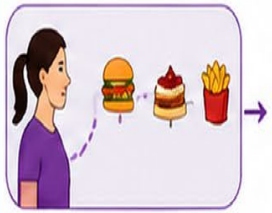
Reward/hedonic and impulse-control pathways



Mesolimbic reward circuit
(VTA → NAc,
PFC, Amygdala)

GLP-1 receptor agonists → Enhance satiety via hypothalamic pathways; slow gastric emptying; reduce food intake.

GCG ± GLP-1 agonists → Increase energy expenditure; improve glucose metabolism and insulin sensitivity; increase satiety.



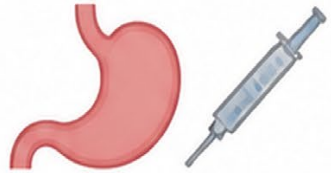
→ Modulates cue reactivity and impulse control; reduces binge eating and relapse risk.

Cravings, binge eating, and relapse control

Combination obesity pharmacotherapy

Complementary mechanisms across pathways → greater efficacy, sustained weight loss, and cardiometabolic improvement

4 Multimodal strategies with procedures



Integrate medications with bariatric and endoscopic procedures for **superior and sustained** outcomes.

- **Pre-bariatric:** medications to optimize weight and reduce surgical risk
- **Post-bariatric:** medications to enhance weight loss and prevent regain
- **Endoscopic procedures plus GLP-1 RA**

Requires multidisciplinary care and long-term follow-up

FOUNDATIONAL MEDICAL NUTRITION THERAPY AND LIFESTYLE INTERVENTION

Energy-restricted diets, physical activity, and behavioral/psychological support across all strategies.

Energy-restricted, higher-protein diets
Higher-protein, energy-restricted eating; prioritize whole, nutrient-dense foods.

Physical activity
≥150 minutes/week moderate–vigorous activity plus resistance training.

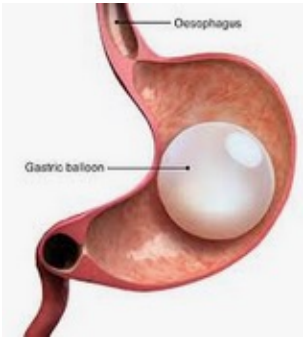
Behavioral support
Counseling, goal setting, self-monitoring, and relapse-prevention strategies.

Kamrul-Hasan ABM, Endocrinology, Diabetes & Metabolism, 2026

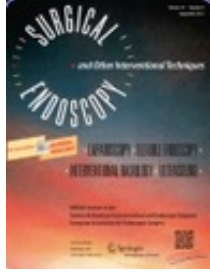
Conclusions

- ESG combined with AOMs may enhance early weight loss in selected settings with **strategic timing of combination therapy, rather than concurrent use**.
- However, **current evidence does not support consistent long-term superiority over ESG alone** for weight or glycemic outcomes.
- Although the **available data remain limited and heterogeneous**, combination therapy may be considered in selected patients rather than as a universally superior strategy.
- Multicenter randomized trials with standardized pharmacotherapy protocols, longer follow-up, and improved patient stratification are needed to clarify durability, cost-effectiveness, and the subgroups most likely to benefit.

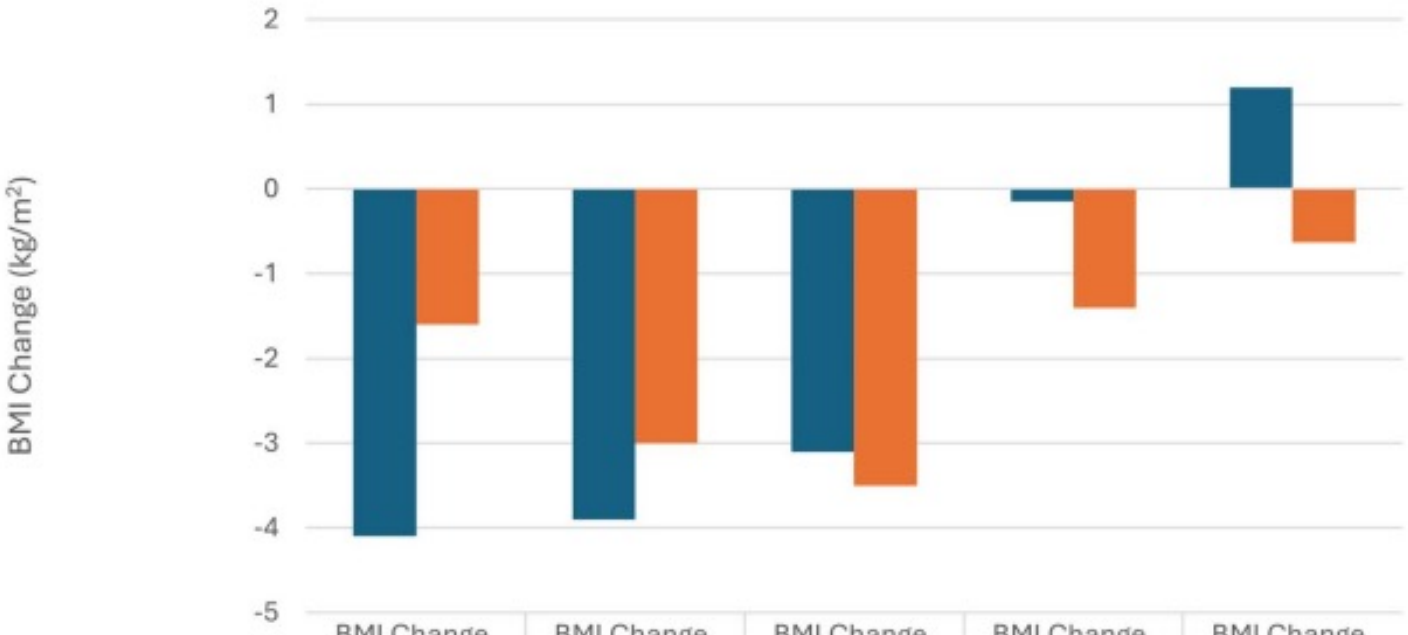
Weighing your options—intragastric balloon versus semaglutide







➢ All patients were enrolled in a multidisciplinary weight management program for 12 weeks. Outcomes measured were patients' weights at 0, 3, 6, and 12 months and weight change for these intervals. Mean initial BMI was 37 ± 5.9 kg/m^2.



	BMI Change, 0-3 months (kg/m2)	BMI Change, 0-6 months (kg/m2)	BMI Change, 0-12 months (kg/m2)	BMI Change, 3-6 months (kg/m2)	BMI Change, 6-12 months (kg/m2)
Intragastric Balloon	-4.1	-3.9	-3.1	-0.15	1.2
Semaglutide	-1.6	-3	-3.5	-1.4	-0.63

➢ 17 patients: Intragastric balloon (IGB) placement;

➢ 96 patients: Semaglutide up to 2.4 mg

Choy K, et al. Surg Endosc August 2024

Primary endoscopic sleeve and anti-obesity medicine.

Study	Drug	Endoscopic intervention	Intervention	Patient profile	Time since surgery	Results
2025 Chung et al. Endoscopic sleeve gastroplasty combined with anti-obesity medication for better control of weight and diabetes	N=18 10 ESG monotherapy 8 ESG + semaglutide	18 ESG using the OverStitch Sx suturing system (Apollo Endosurgery Inc.)O	Retrospective study; ESG alone or in combination with semaglutide	Patients with obesity who underwent ESG	Semaglutide in the combination group started the second week after ESG	% TWL 6 months: ESG monotherapy: 15.32 ESG + semaglutide: 20.27 (p = 0.02)
2024 Jirapinyo et al. Efficacy of anti-obesity medication (AOM) and endoscopic gastric remodeling (EGR) Analysis of combination therapy with optimal timing and agents	N=208 65 EGR monotherapy 19 EGR + GLP-1RA 42 EGR + other AOM 21 EGR then AOM after six months 61 AOM then EGR after six months	208 EGR using the Overstitch endoscopic suturing device (Boston Scientific, Marlborough, Massachusetts, United States) or the Incisionless Operating Platform (USGI Medical, San Clemente, Calif, USA)	Retrospective review of prospectively collected data; EGR as monotherapy or in combination with AOM started within or after 6 months prior to or after EGR and concomitant moderate lifestyle modification after the procedure.	Patients with obesity, defined as BMI ≥30kg/m², or who are overweight, defined as BMI ≥ 27kg/m² with at least one obesity-related comorbidity such as hypertension, hyperlipidemia, diabetes/ prediabetes and metabolic dysfunction-associated liver disease.	AOM within or after 6 months of EGR	% TWL 12 months EGR monotherapy: 17.3 ± 10.0 EGR + GLP1-RA: 23.7 ± 4.6 (p = 0.04) EGR + AOM: 18 ERG followed by AOM: 14.7 AOM followed by EGR: 12.0 ± 7.7 (p = 0.03)
2024 Gala et al. Outcomes of concomitant antiobesity medication use with endoscopic sleeve gastroplasty in clinical US settings	N=1.506 1.302 ESG monotherapy 58 GLP-1RA 146 Others (phentermine, phentermine-topiramate, bupropion-naltrexone, orlistat)	1.506 ESG using the Overstitch™ device (Apollo Endosurgery, Austin, Texas, USA)	Retrospective analysis; start anti-obesity medicine within 2 years after endoscopic sleeve gastroplasty	Patients who started anti-obesity medication after ESG. Reasons for starting are not mentioned.	<6 months after ESG 6–12 months after ESG >12 months after ESG	% TWL 24 months ESG monotherapy: 15.4 CI 14.2 – 16.6 ESG + GLP-1: 16.7 ± 11.9 ESG + other AOM: 14.2 ± 10.1 (p = not mentioned)
2021 Badurdeen et al. Endoscopic sleeve gastroplasty plus liraglutide versus endoscopic sleeve gastroplasty alone for weight loss	N=52 26 ESG monotherapy 26 ESG + liraglutide	56 ESG using the OverStitch; Apollo Endosurgery, Austin, Tex, USA)	Retrospective study; comparing the effect of additional liraglutide after ESG.	Patients aged >18 with a BMI >27kg/m² who were unable to achieve weight loss through intense diet and lifestyle modifications	In months: 5	% TWL 7 months ESG monotherapy: 20.51 ± 1.68 ESG + liraglutide: 24.72 ± 2.12 (p = <0.001)

adjunctive AOM following ESG improves weight loss outcomes from 15 –21% TWL with ESG alone to 17 – 25% TWL when combined with GLP-1 RAs

De Vaal JR, Front. Endocrinol. 2026

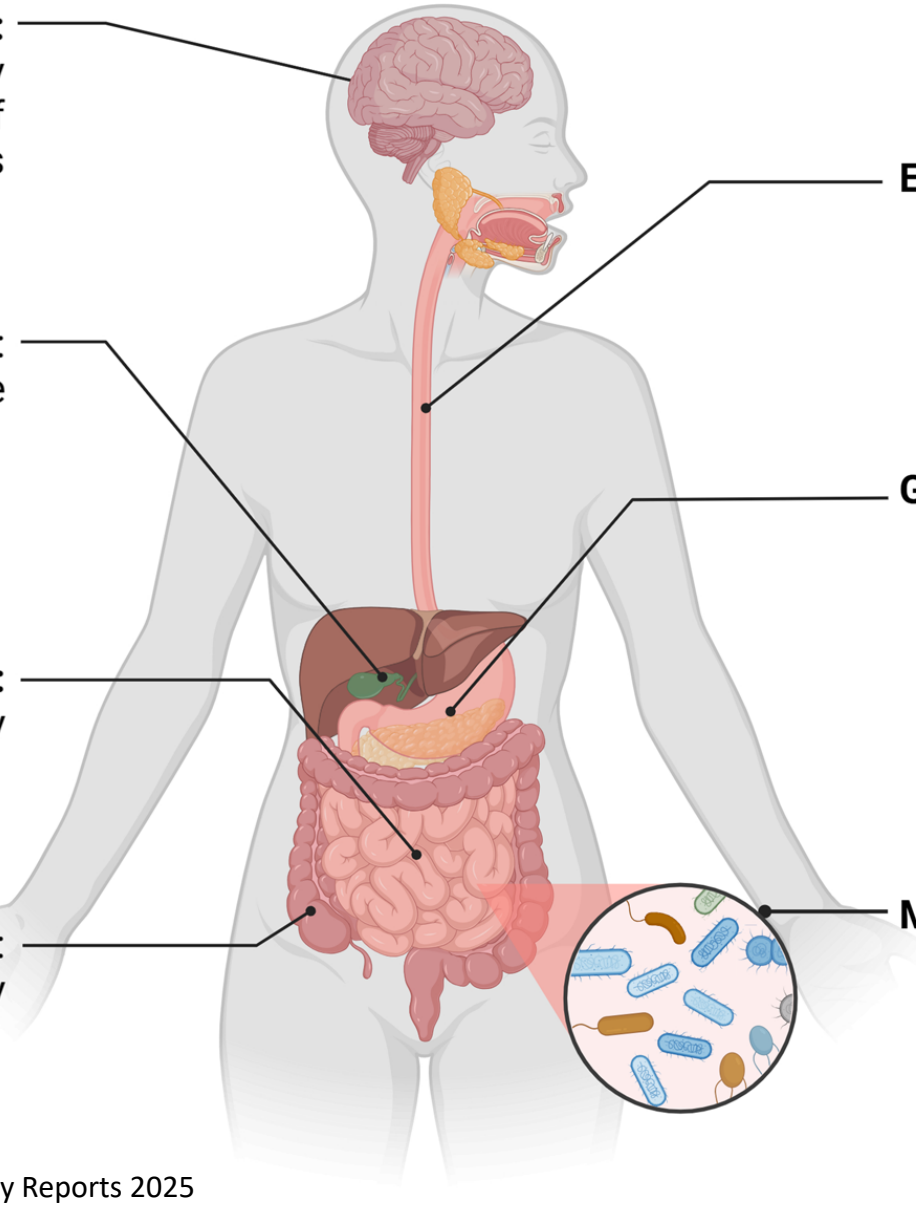
GI motility effects of GLP-1 RAs at each level of the GI tract

Neurologic:
- ↑ Satiety
- Modulation of reward pathways

Biliary:
- ↓ CCK release

Small Bowel:
- ↓ Motility

Large Bowel:
- ↓/↑ Motility



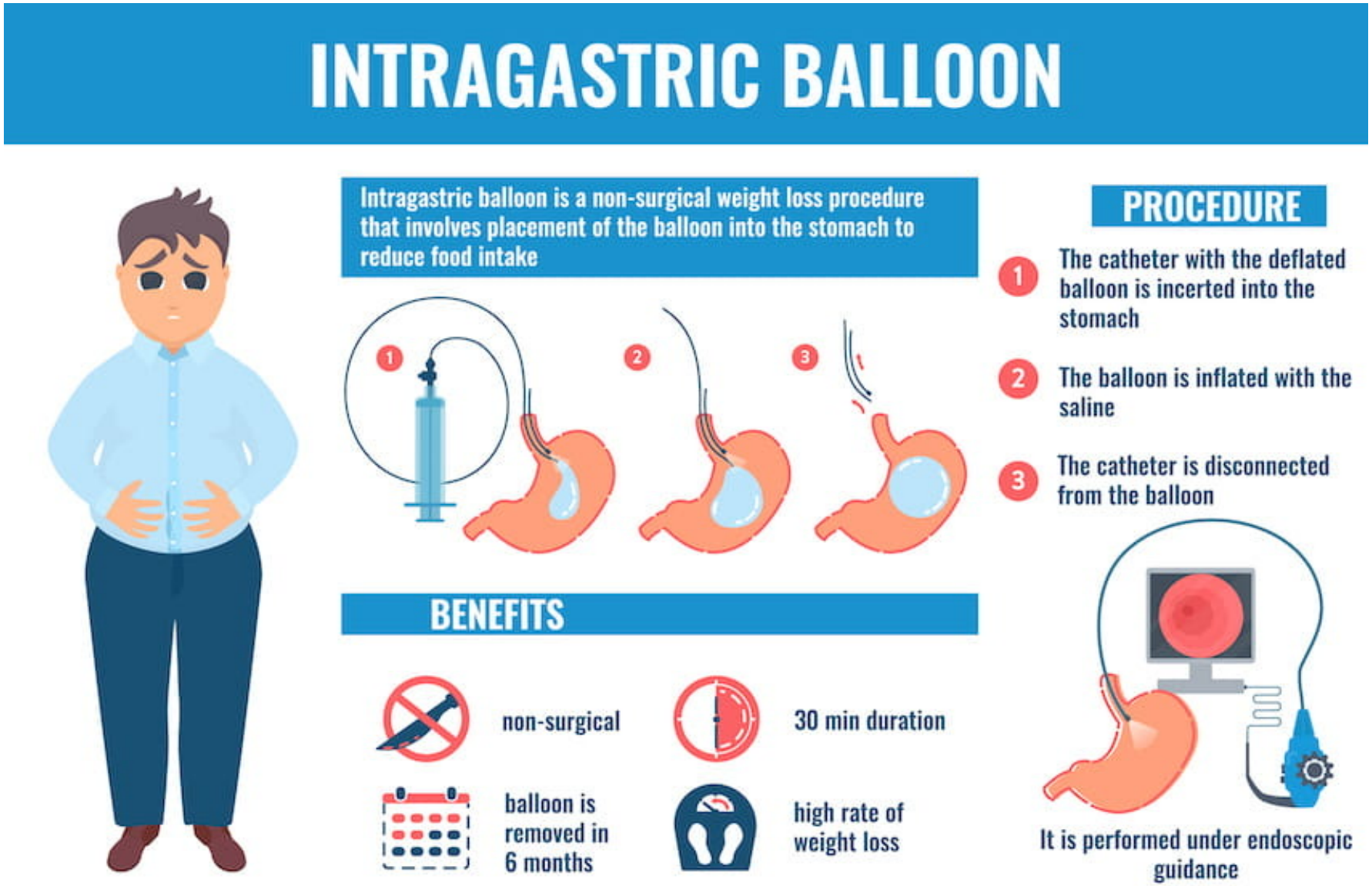
Esophageal:
- ↑ Reflux events
- ↑ LES sphincter relaxation frequency

Gastric:
- Delayed gastric emptying
- ↑ Accomodation
- ↓ Antral motility
- ↑ Pyloric tone
- ↑ Sympathetic tone
- ↓ Vagal tone

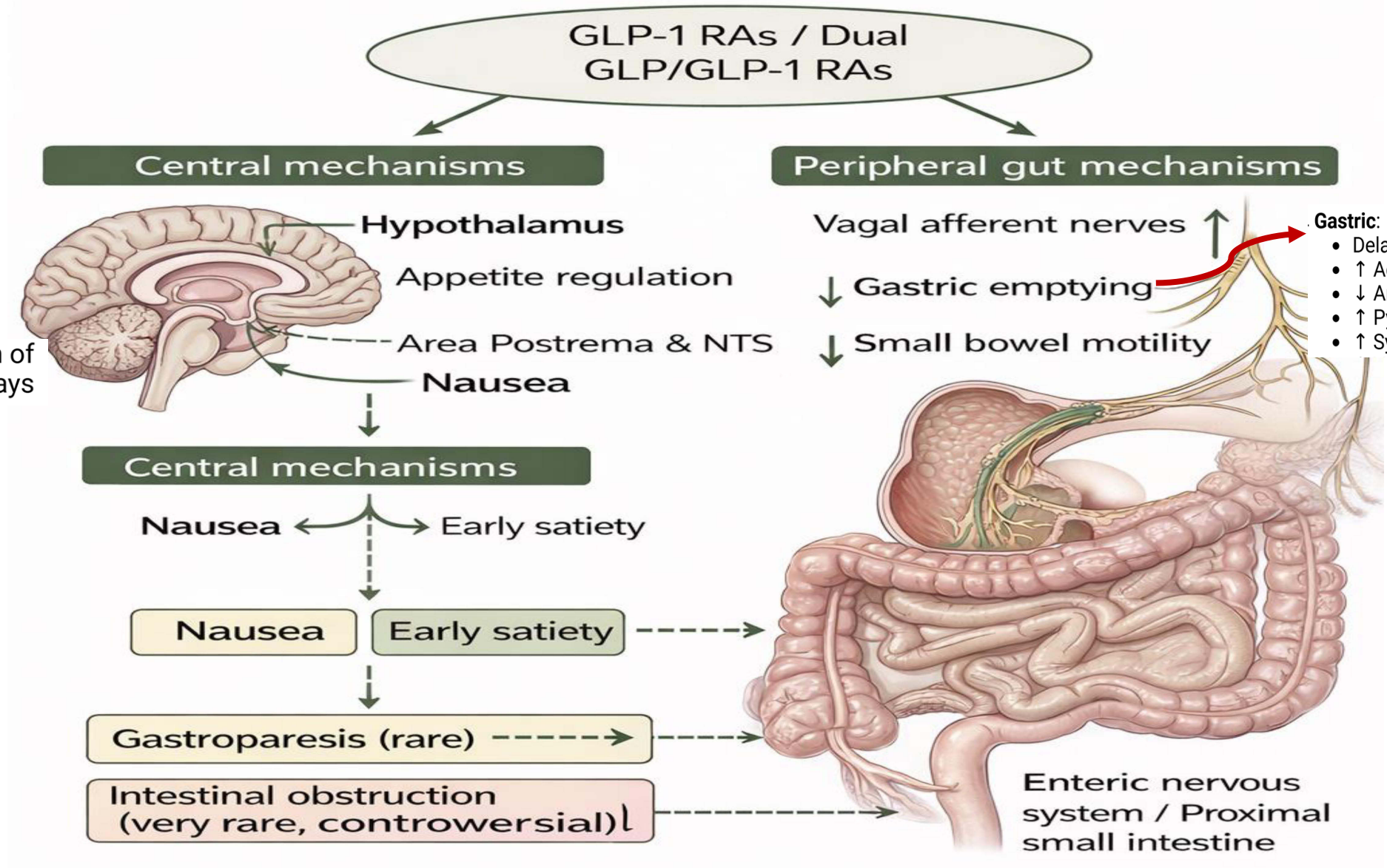
Microbiome:
- ↓ Phyla associated with obesity
- ↑ Phyla associated with lean body mass
- ↑ SCFA production
- ↑ Serotonin production

Bellavance D, Current Gastroenterology Reports 2025

Intragastric Balloons (IGBs)

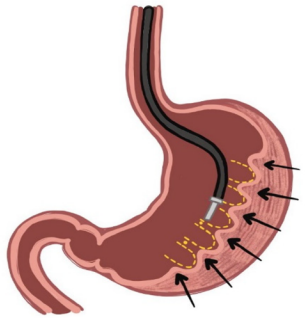


Gastrointestinal Effects of GLP-1 and Dual GLP-1/GIP Receptor Agonists

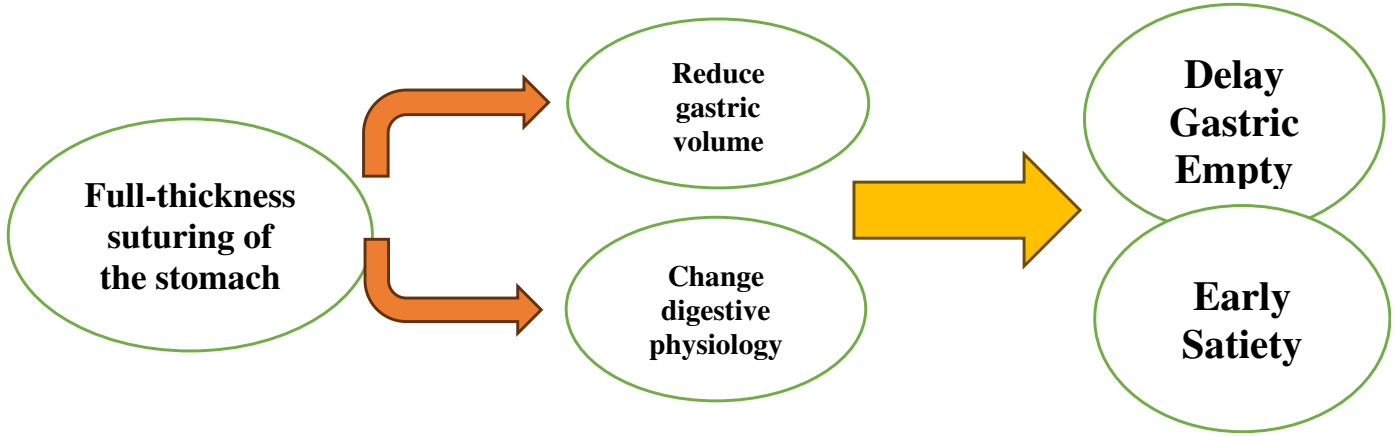


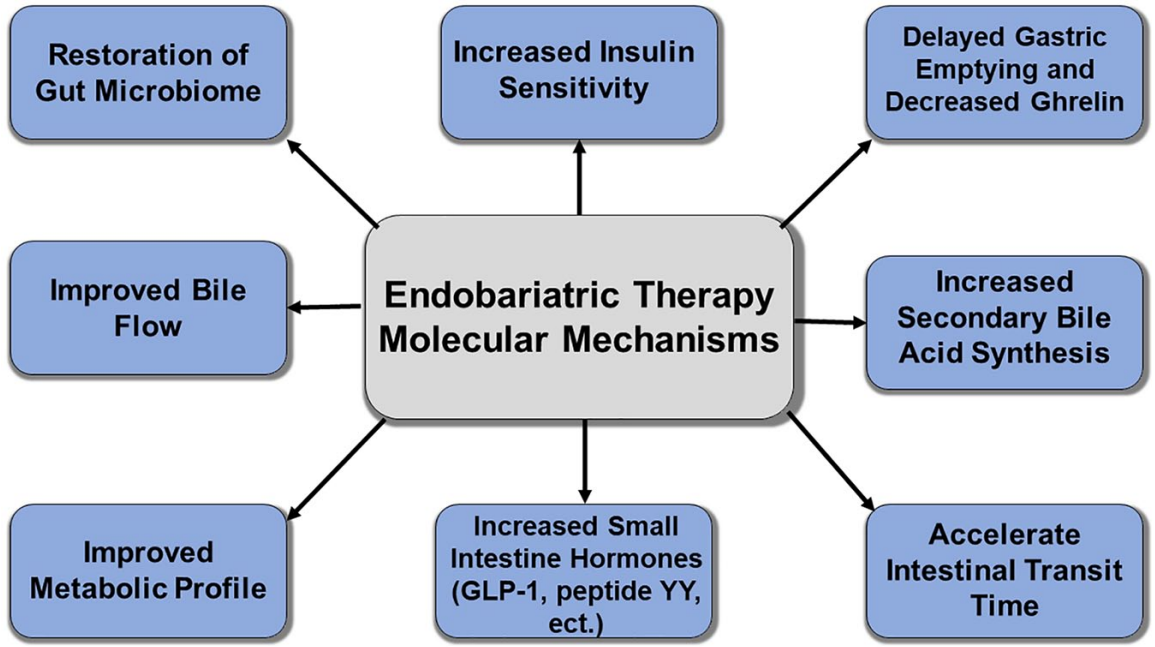
Yılmaz N, Diabetes, Metabolic Syndrome and Obesity 2026

Endoscopic sleeve gastroplasty mechanism of action.

	ESG
	
TBWL at 12 months	17.57%
Length of Hospital Stay (Days)	0.34 ± 0.73
Complications	2.20%
New-onset GORD	1.9%







GLP-1-Based Combination Strategies for Weight Loss

From single-agent multi-target agonists to multi-drug combinations

1 Clinical need



- Approximately 650 million people worldwide are affected by obesity.
- The safe and effective medications are an urgent clinical priority.
- GLP-1-based combination strategies have advantages in efficacy, durability, and personalization.

2 Two major GLP-1-based combination strategies

A Single-agent multi-target agonists



- **GLP-1R/GIPR** — GLP-1R/GIPR dual agonists: tirzepatide, VK2735, MarTide, CT-388
- **GLP-1R/GCGR** — GLP-1R/GCGR dual agonists: mazdutide, survodutide, cotadutide
- **GLP-1R/AMYR** — GLP-1R/AMYR dual agonists: amycretin
- **GLP-1R/GIPR/GCGR** — GLP-1R/GIPR/GCGR triple agonists: retatrutide, UBT251

B Multi-drug combinations



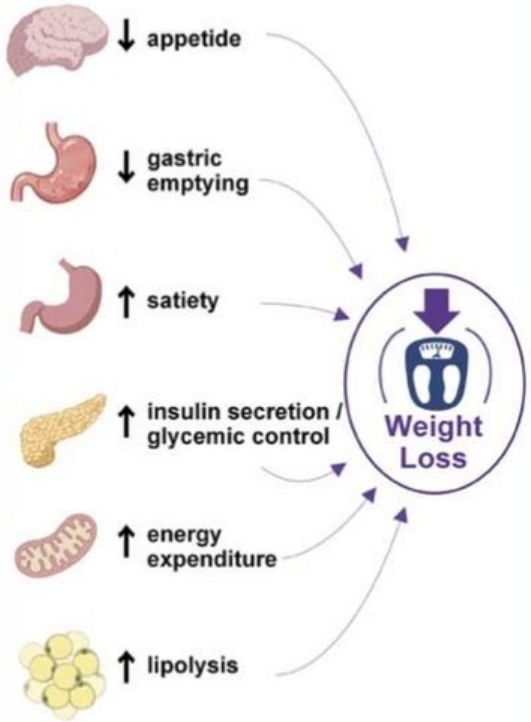
Free combinations
- exenatide + dapagliflozin
- liraglutide + B11820237
- semaglutide + PYY1875

Fixed-dose combination
- CagriSema

Free combinations: flexibility

Fixed-dose combinations: improved convenience and adherence

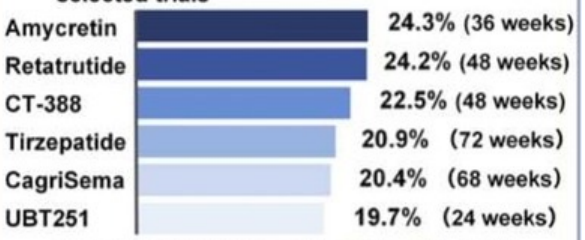
3 Synergistic mechanisms



1 + 1 > 2
synergistic effect

4 Clinical impact and outlook

Representative and top-tier weight loss in selected trials*



*Cross-trial, illustrative only; not head-to-head

Benefits
- Substantial weight loss
- Improved cardiometabolic profile
- Potential reduction in hepatic fat

Key challenges
- Gastrointestinal events are most common
- Potential heart-rate increase and hypoglycemia
- Long-term muscle and psychiatric safety need monitoring
- High cost and limited accessibility

Future directions
- Individualized therapy
- Head-to-head comparisons
- Oral formulations
- Long-term maintenance strategies

GLP-1-based therapies are evolving toward complementary mechanisms, stronger efficacy, and more comprehensive obesity management.

Wang X, Pharmacological Research 2026

Efficacy of Adjunctive Semaglutide Injections in Patients Undergoing Gastric Ballooning for Weight Reduction

Comparison between the two groups studied according to anthropometric measurements at baseline, 3, 6, and 12 months

		IGB-only (n=20)	IGB+semaglutide (n=20)	Test of Sig.	p	Effect size	Difference (95% C.I)
After 6 months	Weight						
	Min. – Max.	81.33–119.8	76.25–106.9	t=3.297*	0.002*	d=1.044	9.40 (3.63–15.18)
	Mean±SD.	97.41±9.38	88.00±8.64				
	Median (IQR)	95.64 (90.91–105.5)	87.38 (82.24–93.60)				
	BMI						
	Min. – Max.	29.47–35.19	27.65–31.62	t=7.066*	<0.001*	d=2.232	3.05 (2.18–3.93)
	Mean±SD.	32.59±1.49	29.54±1.23				
	Median (IQR)	32.80 (31.87–33.60)	29.43 (28.68–30.55)				
After 12 months	Weight						
	Min. – Max.	83.24–120.3	72.97–98.74	t=6.022	<0.001*	d=1.905	16.13 (10.71–21.55)
	Mean±SD.	100.2±9.27	84.07±7.58				
	Median (IQR)	97.73 (95.71–109.13)	82.44 (79.24–89.28)				
	BMI						
	Min. – Max.	30.37–35.38	26.61–30.26	t=14.259	<0.001*	d=4.517	5.29 (4.54–6.04)
	Mean±SD.	33.53±1.26	28.23±1.08				
	Median (IQR)	33.48 (32.96–34.39)	28.10 (27.44–28.97)				

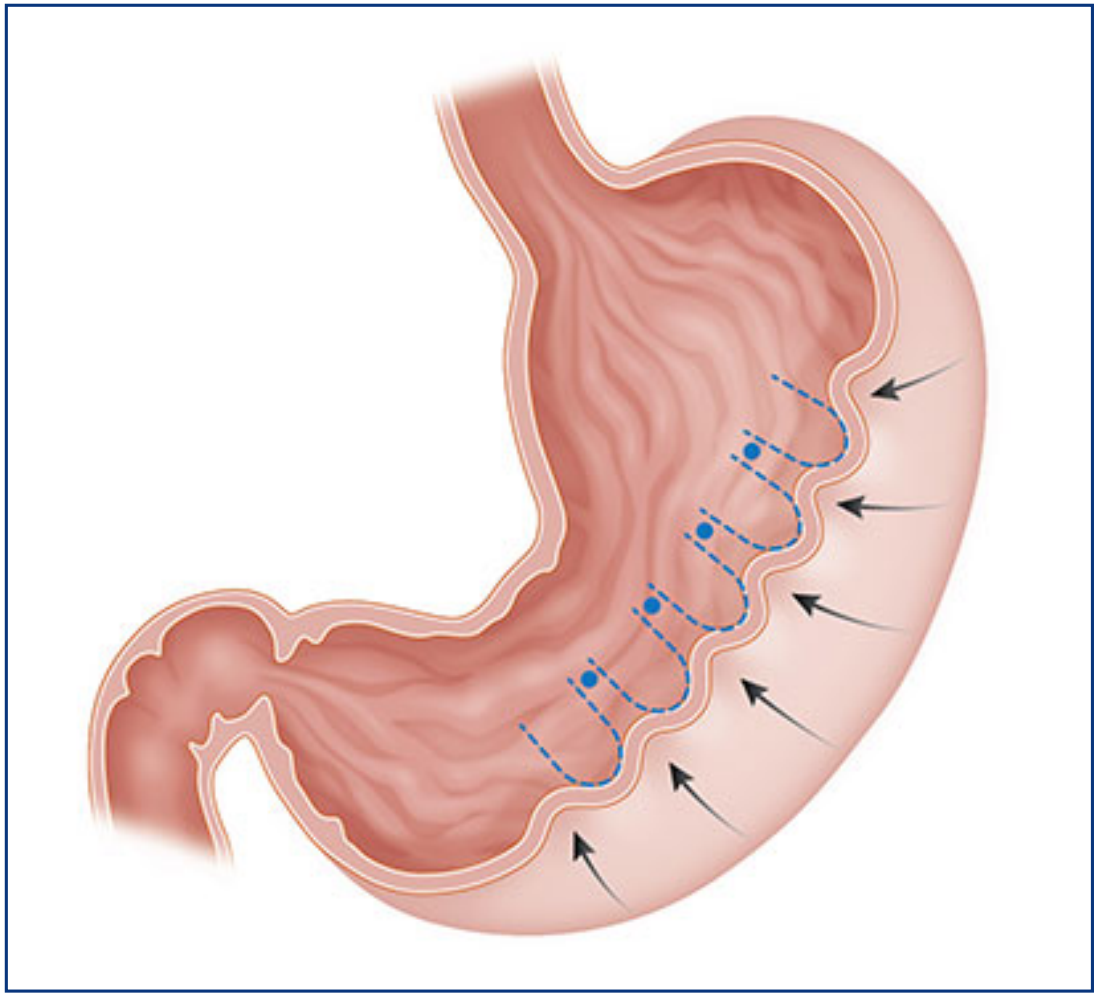
	IGB-only (*n*=20)	IGB+semaglutide (*n*=20)	Test of Sig.	*p*	Effect size	Difference (95% C.I)
Serious complications	0 (0.0%)	0 (0.0%)	–	–	–	
Nausea & vomiting	7 (35.0%)	10 (50.0%)	χ^2=0.921	0.337	φ=0.152	0.15 (0.10–0.20)

χ^2 Chi-square test, *P* p-value for comparing the two studied groups

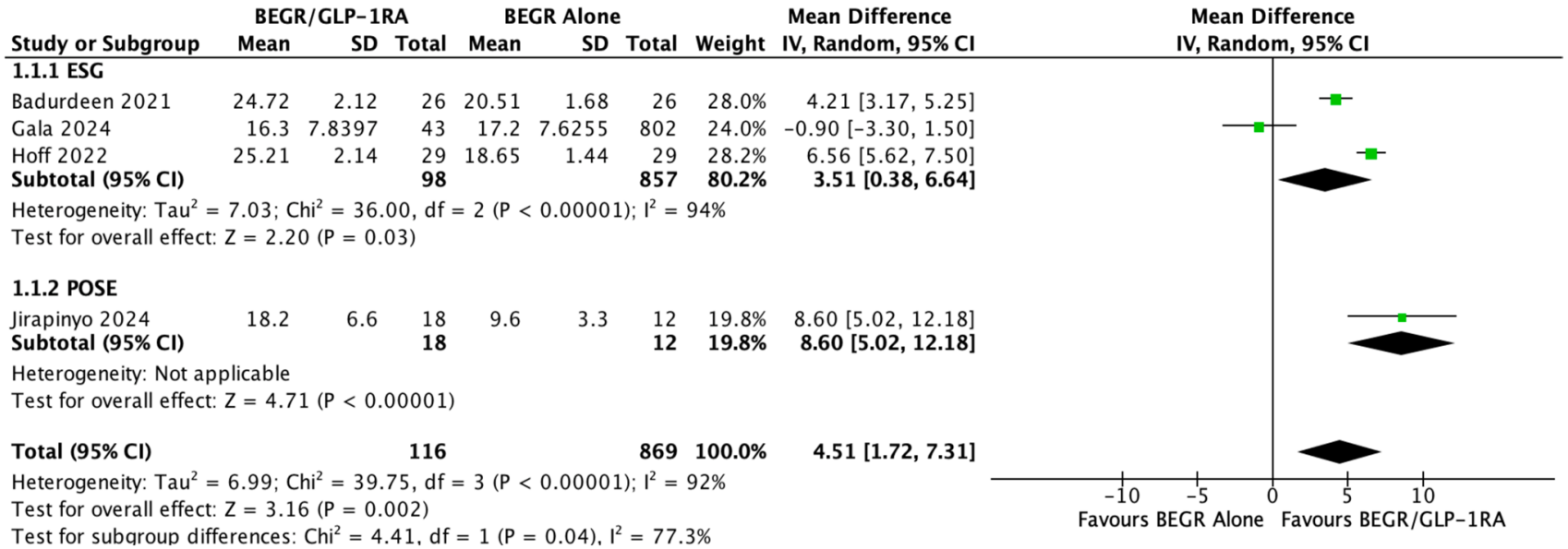
φ Phi

Barakat KE, Obesity Surgery 2025

Endoscopic Sleeve Gastroplasty



Effectiveness of Pharmacotherapy and Technical Modifications as Adjunctive Tools for Enhancing Weight Loss After Bariatric Endoscopy (Endoscopic Gastric Remodeling and Transoral Outlet Reduction): A Meta-analysis

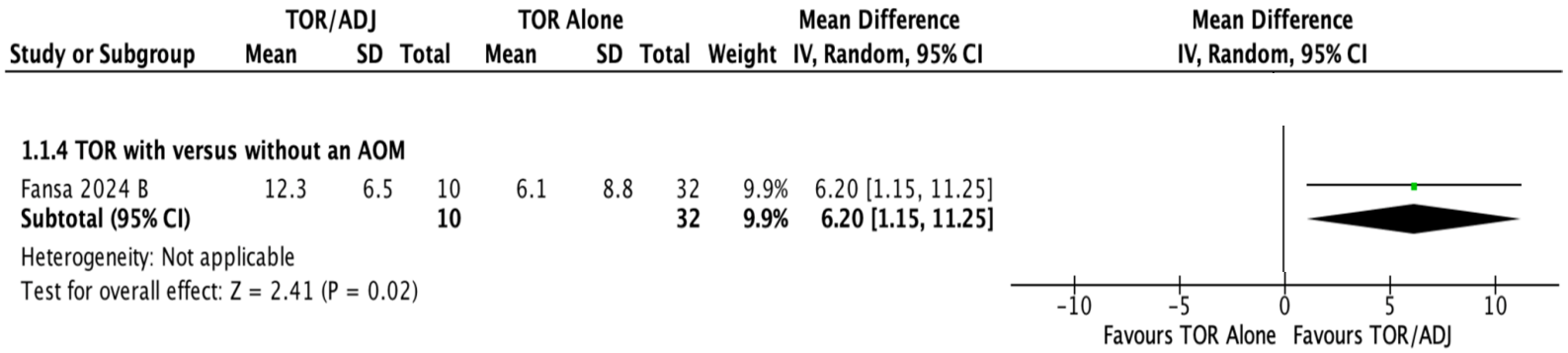


Study or Subgroup	BEGR/GLP-1RA Mean	SD	Total	BEGR Alone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 ESG								
Badurdeen 2021	24.72	2.12	26	20.51	1.68	26	28.0%	4.21 [3.17, 5.25]
Gala 2024	16.3	7.8397	43	17.2	7.6255	802	24.0%	-0.90 [-3.30, 1.50]
Hoff 2022	25.21	2.14	29	18.65	1.44	29	28.2%	6.56 [5.62, 7.50]
Subtotal (95% CI)			**98**			**857**	**80.2%**	**3.51 [0.38, 6.64]**
Heterogeneity: $Tau^2 = 7.03$; $Chi^2 = 36.00$, df = 2 ($P < 0.00001$); $I^2 = 94\%$								
Test for overall effect: Z = 2.20 (P = 0.03)								
1.1.2 POSE								
Jirapinyo 2024	18.2	6.6	18	9.6	3.3	12	19.8%	8.60 [5.02, 12.18]
Subtotal (95% CI)			**18**			**12**	**19.8%**	**8.60 [5.02, 12.18]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.71 (P < 0.00001)								
Total (95% CI)			**116**			**869**	**100.0%**	**4.51 [1.72, 7.31]**
Heterogeneity: $Tau^2 = 6.99$; $Chi^2 = 39.75$, df = 3 ($P < 0.00001$); $I^2 = 92\%$								
Test for overall effect: Z = 3.16 (P = 0.002)								
Test for subgroup differences: $Chi^2 = 4.41$, df = 1 (P = 0.04), $I^2 = 77.3\%$								

Mean Difference IV, Random, 95% CI

-10 -5 0 5 10

Favours BEGR Alone Favours BEGR/GLP-1RA

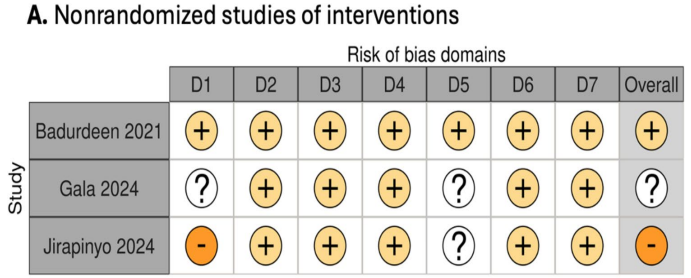


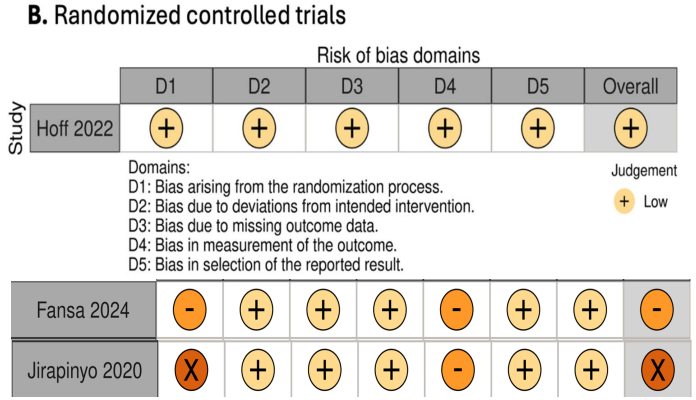
Study or Subgroup	TOR/ADJ Mean	SD	Total	TOR Alone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.1.4 TOR with versus without an AOM								
Fansa 2024 B	12.3	6.5	10	6.1	8.8	32	9.9%	6.20 [1.15, 11.25]
Subtotal (95% CI)			**10**			**32**	**9.9%**	**6.20 [1.15, 11.25]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.41 (P = 0.02)								

Mean Difference IV, Random, 95% CI

-10 -5 0 5 10

Favours TOR Alone Favours TOR/ADJ





Fadi Diab AR, Obesity Surgery 2025