DIABETE E CHIRURGIA BARIATRICA: POTENZIALE RUOLO DEI GLP-1 RAS NELLA REAL LIFE

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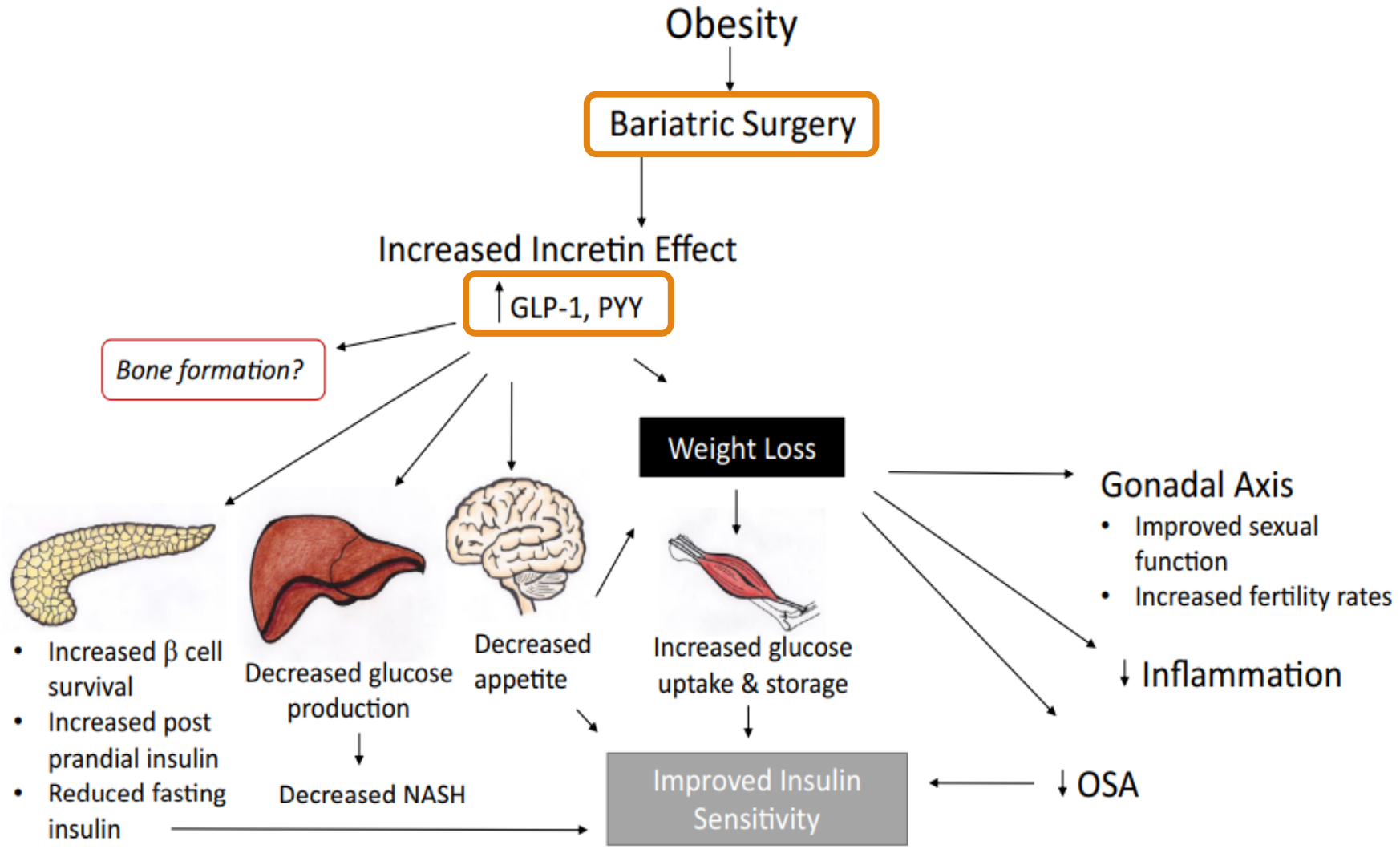
AOSP S. Maria Terni

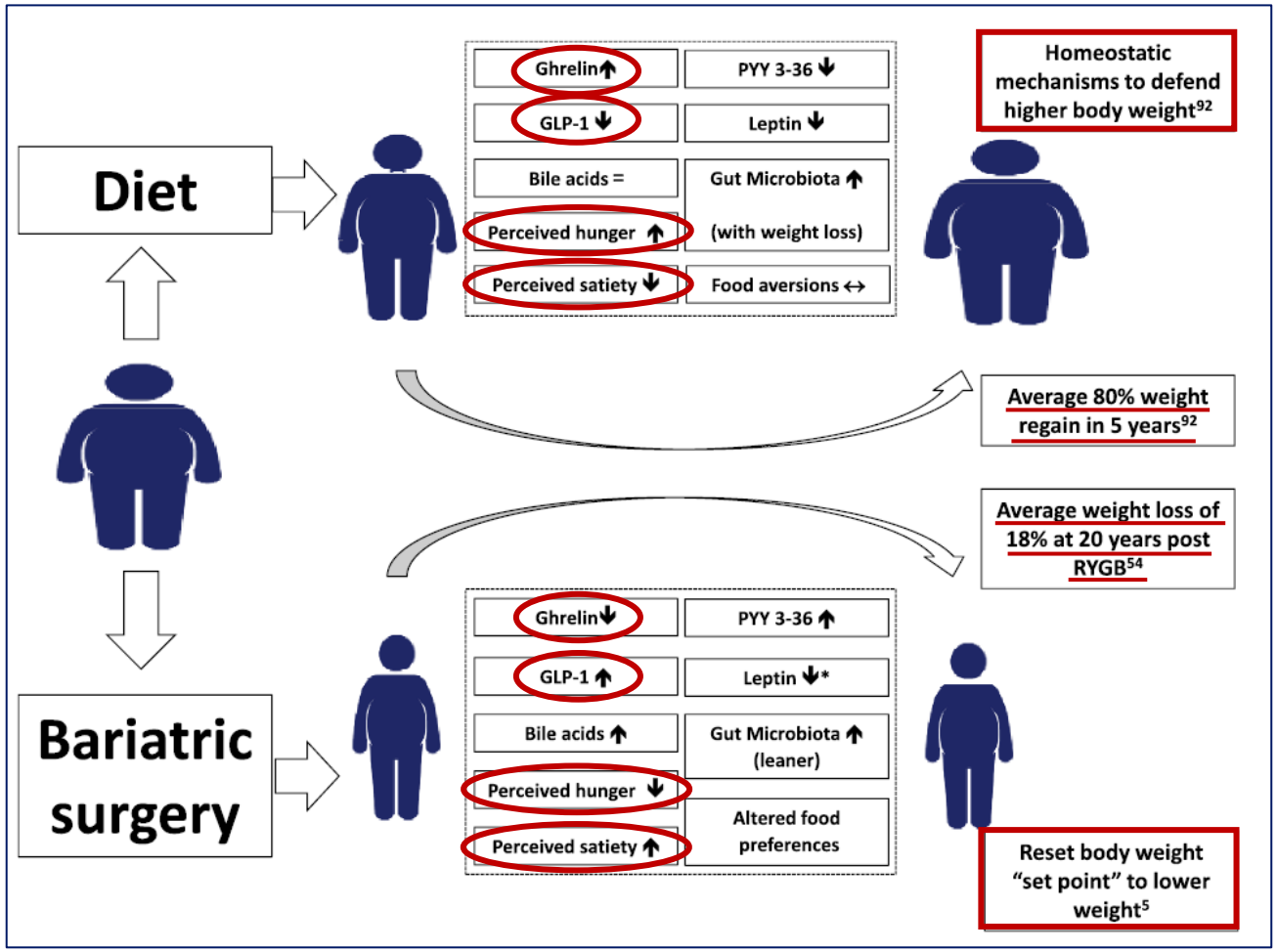
Bariatric surgery is the most effective treatment for sustained weight loss in morbid obesity

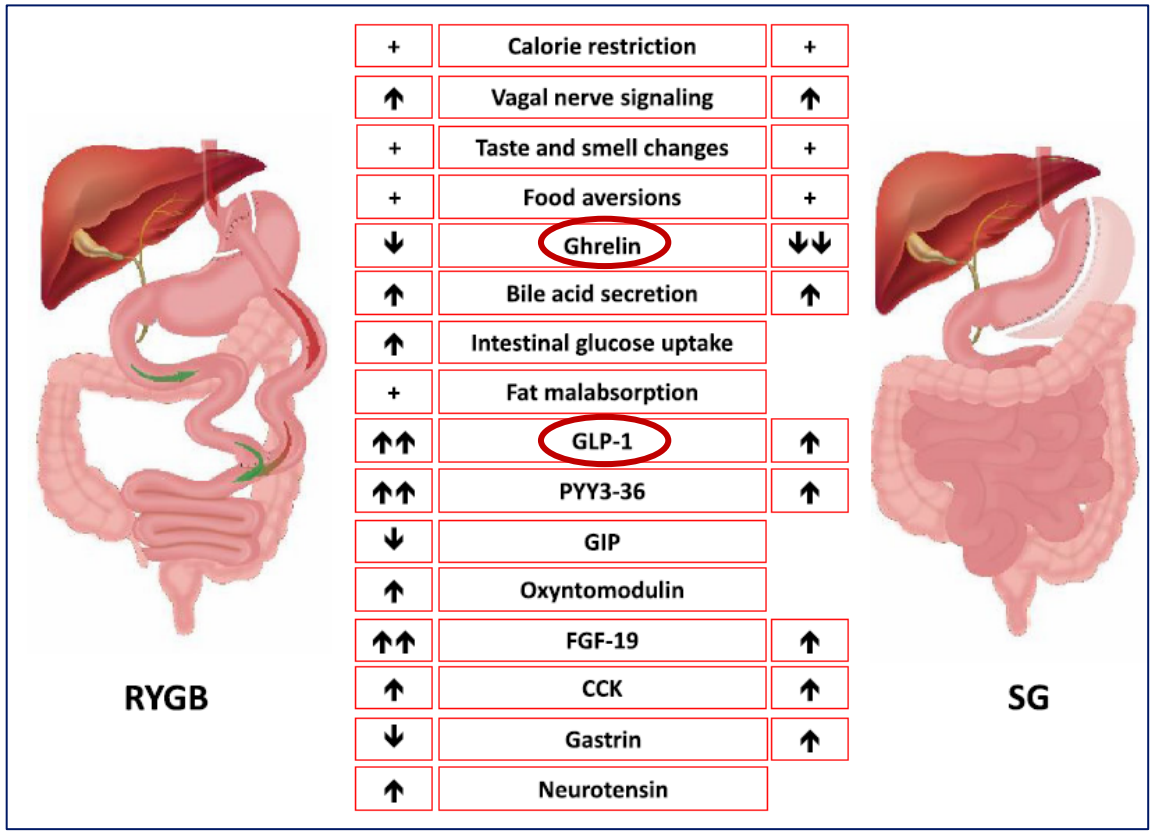


Casimiro I, et al. Physiol Rep. 2019;7(10):e14111.

GLP-1, glucagon-like peptide 1; OSA, obstructive sleep apnea: PYY, peptide YY.

Different biological changes induced by weight loss with diet vs bariatric/metabolic surgery



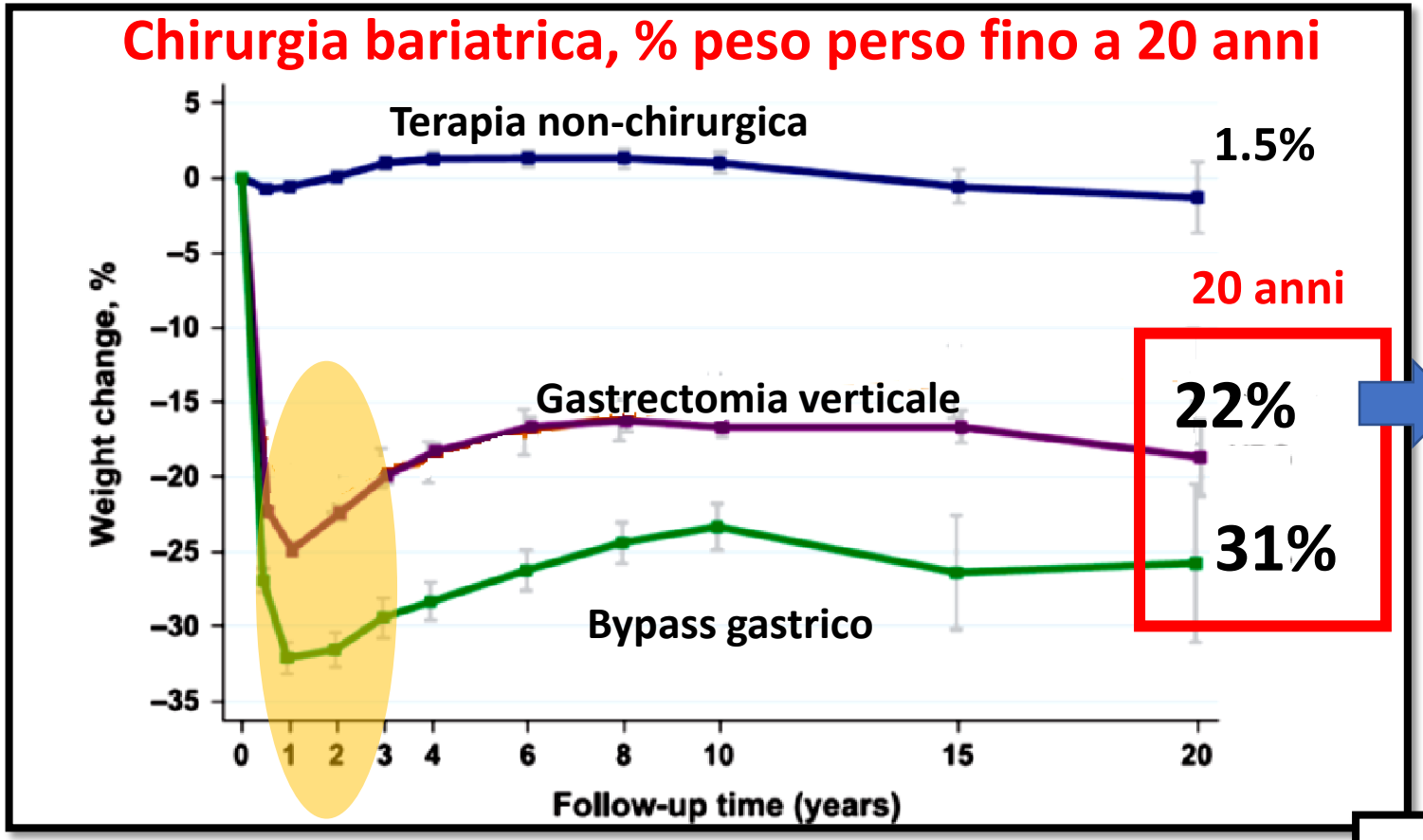


For every mechanism the effect of the procedure is represented with a "↑" when stimulating or "↓" when suppressing. A "+" means that the proposed mechanism is present only after surgery when compared to the pre-operative period.

RYGB Roux-en-Y gastric bypass; SG Sleeve gastrectomy; GLP-1 glucagon-like peptide 1; PYY3-36 peptide tyrosine–tyrosine 3-36; GIP gastric inhibitory polypeptide; FGF-19 fibroblast growth factor-19; CCK cholecystokinin

Pucci A & Batterham RL. J Endocrinol Invest. 2019;42(2):117-128

La chirurgia bariatrica è l'unica terapia per l'obesità in grado di promuovere una perdita di peso significativa e di mantenere una perdita di peso superiore al 20% fino a 20 anni follow-up



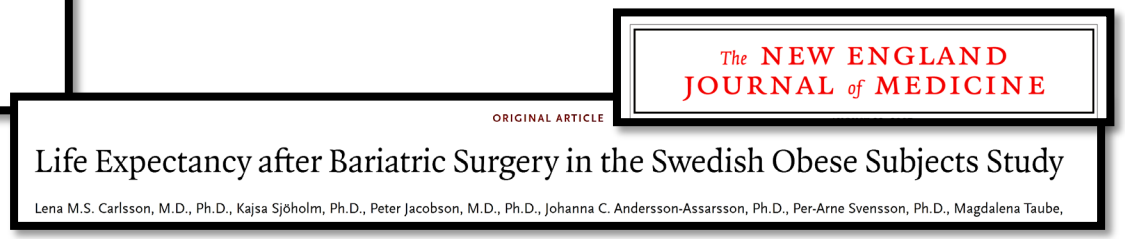
% peso perso a 8 anni :

Cure non-chirurgiche intensive: 4.7%

Cure non-chirurgiche standard: 2.1%

(Look AHEAD study results)

Obesity (Silver Spring). 2014 Jan; 22(1): 5–13



N Engl J Med 2020; 383:1535-1543

CLINICAL EVIDENCE

High Quality (Level I & II-1,2) Studies on Bariatric / Metabolic Surgery in Diabetic Patients

Investigator	Study Type	# Diabetic Patients	Primary Endpoint	Study Duration
Carlsson	Non-randomized, prospective, controlled	3429 pts, 2 arms (1658 surgery)	Rate of incident Type 2 diabetes mellitus	15 years
STAMPEDE (Schauer)*	RCT, single center	150 pts, 3 arms	HbA1c ≤ 6 with or w/o meds	Year 3 of 5-year study
Mingrone	RCT, single center	60 pts, 3 arms	HbA1c ≤ 6.5 without meds	2 years
Buchwald*	Systematic Review & Meta-Analysis	135,000 pts, 621 studies, 888 arms	Effect of bariatric surgery on Type 2 diabetes	N/A
Klein*	Matched Cohort, Claims data	1600 pts, 2 arms	Economic impact & clinical benefits of bariatric surgery	3 years
AHRQ (Segal)*	Matched Cohort, Claims data	8400 pts, 2 arms (2100 surgery)	Impact of surgery to reduce utilization of CV meds	Year 1 of 3-year study
Bolen*	Matched Cohort, Claims data	14,000 pts, 2 arms (6300 surgery)	% Obesity-related co-morbidities between groups	5 years
Cohen	Non-randomized, prospective	66 pts, 1 arm	Safety and % of patients experiencing diabetes remission	5 years (median)

METABOLIC SURGERY

Recommendations

8.17 Metabolic surgery should be a recommended option to treat type 2 diabetes in screened surgical candidates with BMI ≥40 kg/m^2 (BMI ≥37.5 kg/m^2 in Asian Americans) and in adults with BMI 35.0–39.9 kg/m^2 (32.5–37.4 kg/m^2 in Asian Americans) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with nonsurgical methods. **A**

8.18 Metabolic surgery may be considered as an option to treat type 2 diabetes in adults with BMI 30.0–34.9 kg/m^2 (27.5–32.4 kg/m^2 in Asian Americans) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with nonsurgical methods. **A**

8.19 Metabolic surgery should be performed in high-volume centers with multidisciplinary teams knowledgeable about and experienced in the management of obesity, diabetes, and gastrointestinal surgery. **E**

4. CHIRURGIA BARIATRICA

Il ricorso alla chirurgia bariatrica è raccomandato nei pazienti con diabete adulti (età 18-65 anni) con indice di massa corporea >40 Kg/m² indipendentemente dal grado di compenso glicemico e dal tipo di terapia ipoglicemizzante effettuata, o compreso tra 35 e 40 Kg/m² qualora vi sia scompenso glicemico nonostante un'appropriata terapia medica. ***I A***

La chirurgia bariatrica può essere presa in considerazione nei pazienti con diabete adulti con indice di massa corporea tra 35 e 40 kg/m² in buon controllo glicemico, o compreso tra 30 e 35 Kg/m² con scompenso glicemico nonostante un'appropriata terapia medica. ***II C***

I pazienti con diabete sottoposti ad interventi di chirurgia bariatrica necessitano di sorveglianza medico-nutrizionale per tutta la vita da parte del diabetologo, indipendentemente dall'eventuale risoluzione del diabete. ***VI B***

Definition of obesity

Obesity is **chronic relapsing progressive disease**[1]a

Obesity is a **multifactorial** disease[2]

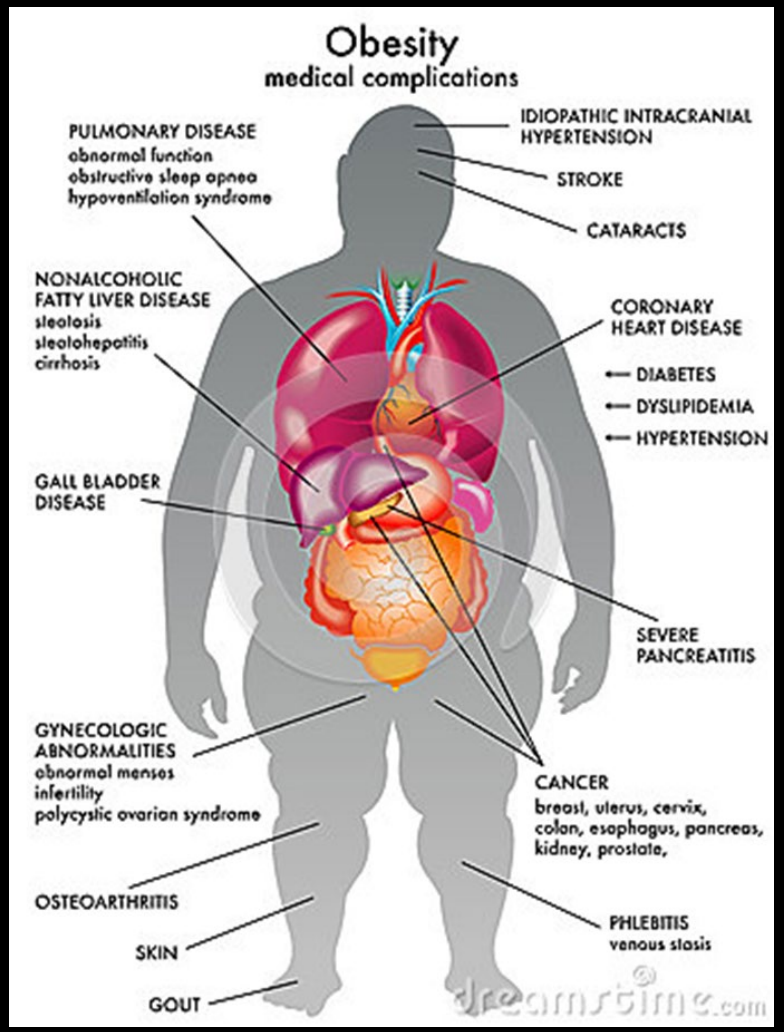
Obesity is a **social** disease, involving the overcoming of **stigma**, discrimination, and generalization[2]

1. WOF Position Statement, G. Brey et al. Obesity Reviews 18, 715–723, July 2017; 2. A. De Lorenzo et al. / Nutrition 71 (2019) 110615

OBESITY AND DISEASES

- ***Raised BMI is a major risk factor for noncommunicable diseases such as:***

- cardiovascular diseases (mainly heart disease and stroke), which were the leading cause of death in 2012;
- **diabetes**;
- musculoskeletal disorders (especially osteoarthritis – a highly disabling degenerative disease of the joints);
- some cancers (including endometrial, breast, ovarian, prostate, liver, gallbladder, kidney, and colon).



World Health Organization, 2015

Il preoperatorio: Scelta del trattamento

DIETETICO

FARMACOLOGICO

COMPORTAMENTALE

DA LCD A VLCKD

A moderato contenuto di CHO : se gli stessi (>130g/die) forniscono dal 26 al 44% dell'energia totale (ET);

A basso contenuto di CHO (low-CHO diet): per valori dal 10 al 25% dell'ET giornaliera (50-130 g/die)

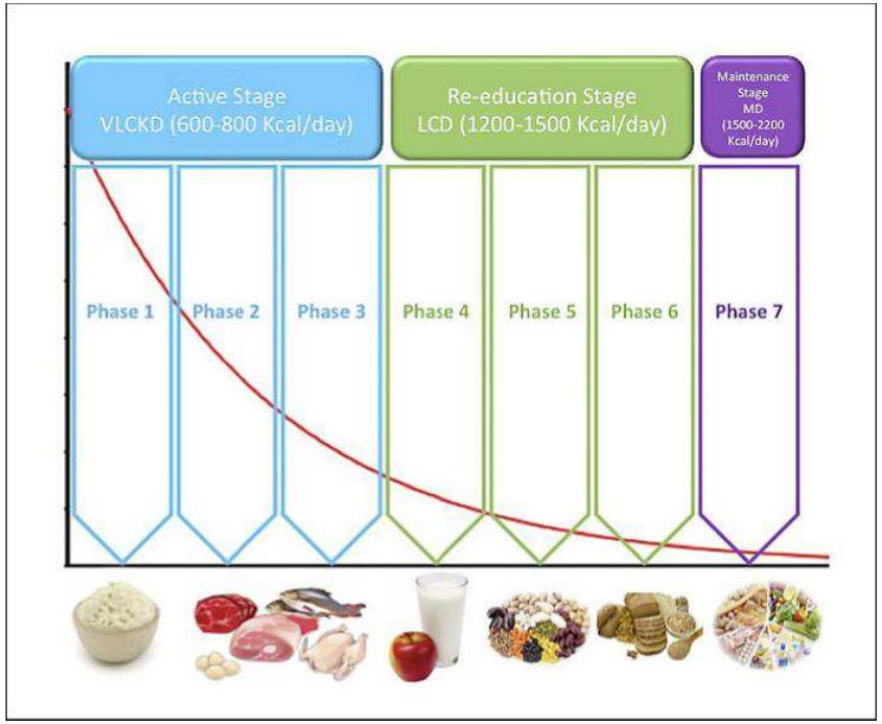
A contenuto molto basso di CHO (very-low CHO diet): i CHO della dieta sono <10% dell'ET e il contenuto assoluto è <50g/die.

LCKD (low calorie ketogenic diet) se le calorie sono >800/die ma inferiori alla spesa energetica giornaliera (TEE)

VLCKD (very low calorie ketogenic diet) se le calorie sono inferiori a 800/die e i CHO <30 gr; le diete VLCKD possono essere utilizzate continuativamente per 12 settimane e comunque sempre sotto controllo medico

Calo ponderale 5-10% nel preoperatorio

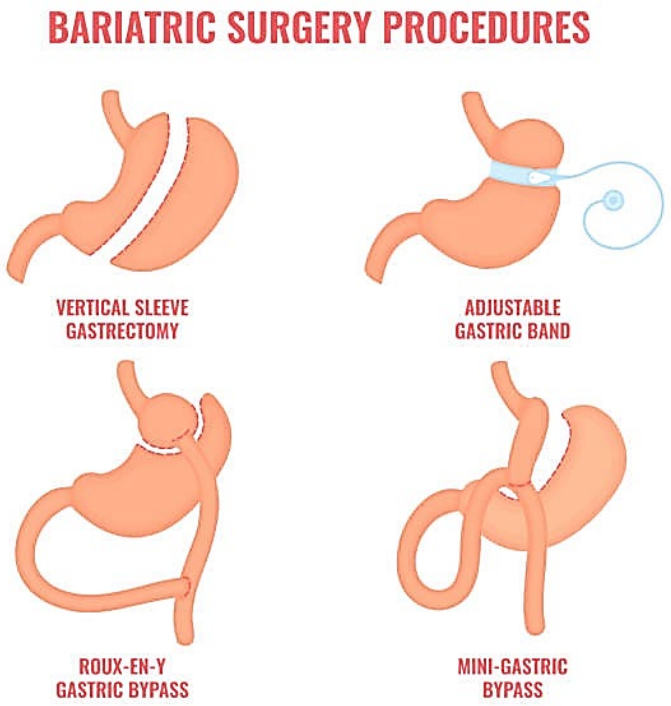
- Per ottenere una perdita di peso >5%, possono essere prescritti interventi a breve termine (3 mesi) che utilizzano diete a bassissimo contenuto calorico (VLCD ≤800 kcal/die) o VLCKD e sostituti del pasto per pazienti attentamente selezionati.
- Per mantenere la perdita di peso, i programmi VLCD e VLCKD devono includere un programma di controllo medico a lungo termine sul mantenimento del peso.
- La dieta VLCKD deve essere presa in considerazione per ottenere una rapida efficacia sul controllo glicemico nei pazienti obesi con prediabete o con breve durata della malattia diabetica.
- Le VLCD e le VLCKD vanno eseguite sempre sotto controllo medico.



The Role of Pharmacotherapy

Pre Bariatric Surgery

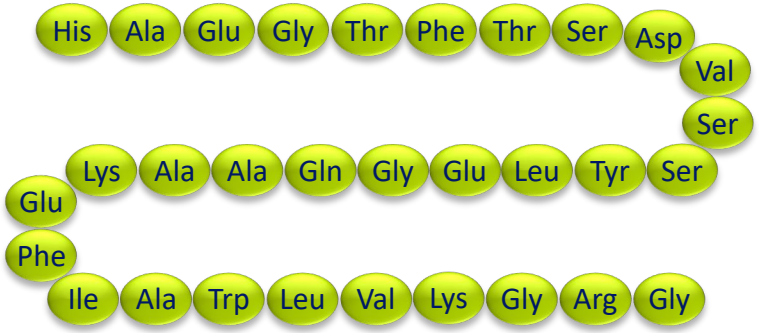
1. **Treat Metabolic Syndrome:**
   - ↑ EWL post-op [1]
   - ↓ Reduce hospital stay [1]
   - ↓ Post-op complications [2]
2. **Reduce Risk in Anesthesia**
3. **BMI > 65*** pre-surgical weight loss is mandatory to **reduce intra-abdominal volume** and **achieve operability** [3]
4. **Patients non-responsive to lifestyle intervention** [4]



* BMI > 55 main risk factor for unfavourable outcomes (SICOB guidelines 2016)

1. Hutcheon DA et al. J Am Coll Surg. 2018;226(4):514-524; 2. Cassie S et al. Surg Obes Relat Dis. 2011;7(6):760-7; 3. Stier et al. Diabetes 2015;64:A43; 4. Malone et al. Ann Pharmacother 2012;46:779–84; 5. Vinciguerra F, et al. 2021 Apr 1. doi: 10.23736/S2724-6507.21.03311-3; 6. Thakur U, et al. Obes Surg. 2021;31(1):84-92; 7. Badurdeen D, et al. Gastrointest Endosc. 2021 Jun;93(6):1316-1324.e1.

Liraglutide is a once-daily, human GLP-1 analogue



Human endogenous GLP-1

$t_{½}$ = ~2 mins

C-16 fatty acid (palmitoyl)

Liraglutide

97% amino acid homology to human GLP-1; improved PK: albumin binding through acylation; heptamer formation

↓

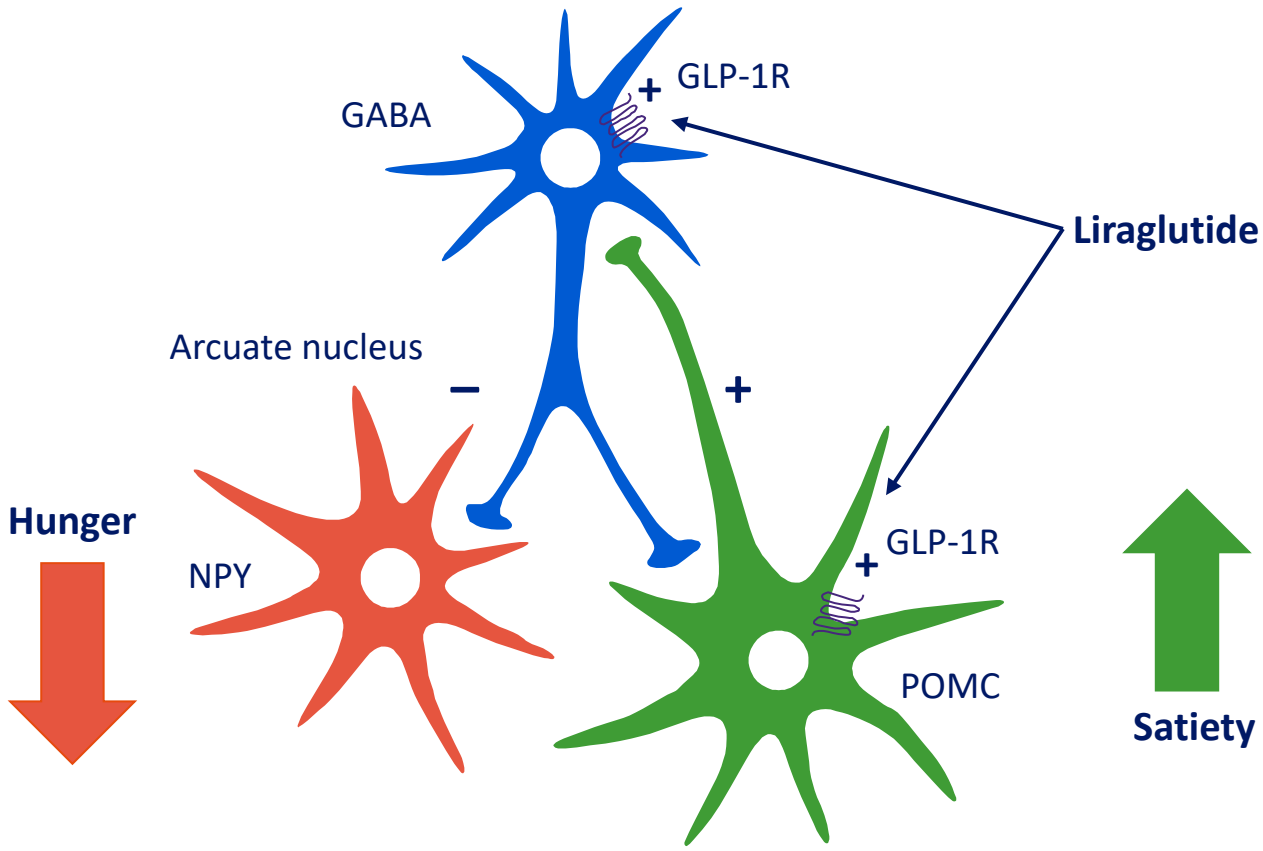
Slow absorption from subcutis
Resistant to DPP-4
Long plasma half-life
($t_{½}$ = 13 h)

DPP-4, dipeptidyl peptidase-4;
GLP-1, glucagon-like peptide-1; PK, pharmacokinetics

Knudsen et al. J Med Chem 2000;43:1664–1669; Degn et al. Diabetes 2004;53:1187–1194

Liraglutide increases satiety and reduces hunger

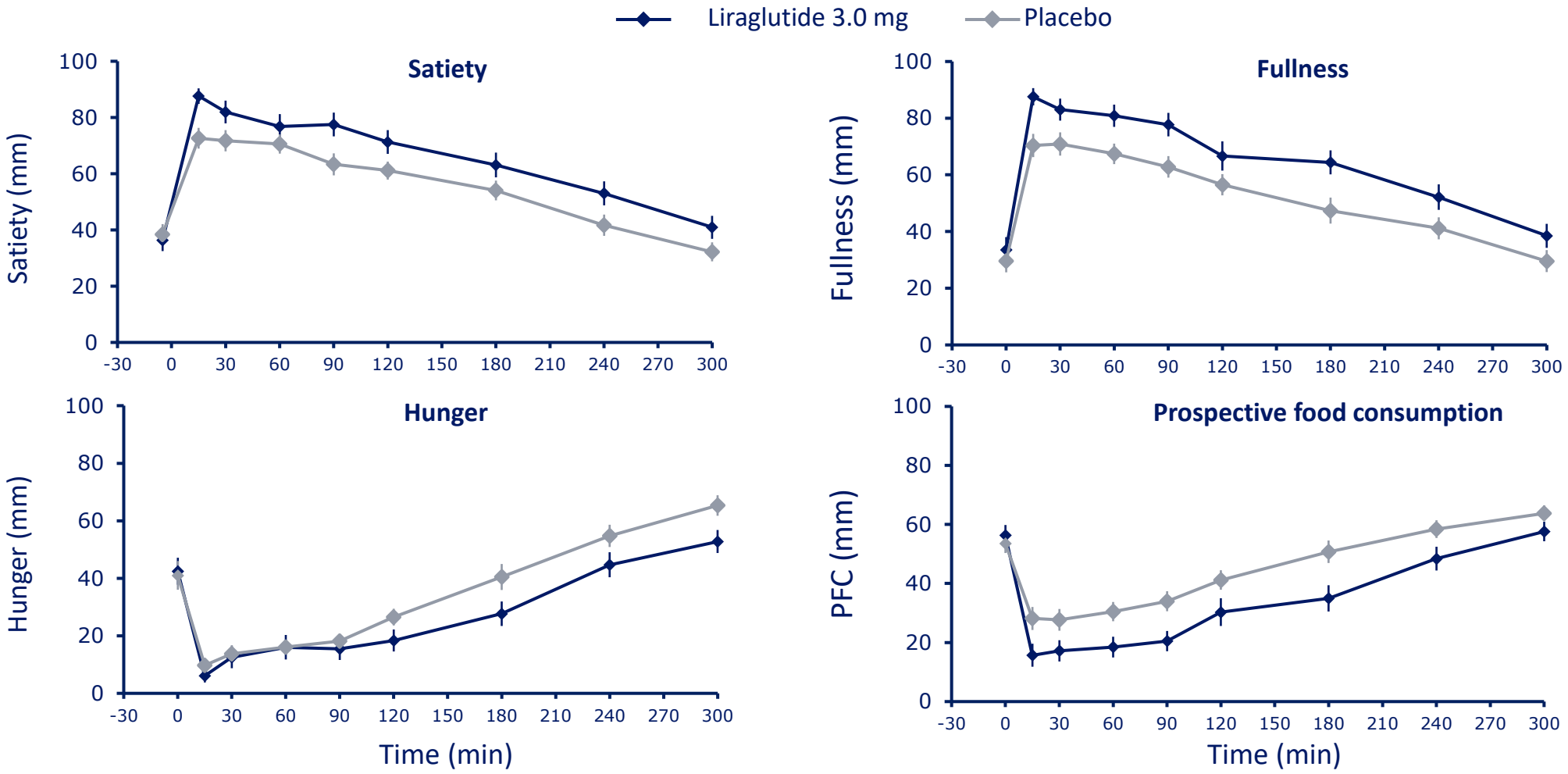
Via neurons in the arcuate nucleus



GABA, gamma-aminobutyric acid; GLP-1R, glucagon-like peptide-1 receptor; NPY, neuropeptide Y; POMC, pro-opiomelanocortin

Secher et al. J Clin Invest 2014;124:4473–88

Liraglutide 3.0 mg influences all dimensions of appetite



Appetite ratings were assessed by visual analog scale. Data are presented as mean ± standard error. PFC, prospective food consumption
Adapted from: van Can et al. Int J Obes 2014;38:784–93

INDICAZIONI LIRAGLUTIDE 3MG

Liraglutide 3 mg è indicato **in aggiunta a una dieta** povera di calorie e a un aumento dell'**attività fisica** per la gestione del peso corporeo in pazienti **adulti e adolescenti dai 12 anni,** con un indice di massa corporea (IMC):

BMI ≥30 kg/m² (obesi),

BMI≥27 kg/m² a <30 kg/m² (sovrappeso) in presenza di **almeno una co-morbidità** correlata al peso quali disglicemia (pre-diabete o diabete mellito di tipo 2), ipertensione, dislipidemia o apnea ostruttiva nel sonno.

Il trattamento con Liraglutide 3 mg deve essere **interrotto dopo 12 settimane** alla dose di **3,0 mg/*die*** se i pazienti **non hanno perso almeno il 5%** del peso corporeo iniziale.

Tabella 1. Schema di aumento della dose

	Dose	Settimane
Aumento della dose - 4 settimane	0,6 mg	1
	1,2 mg	1
	1,8 mg	1
	2,4 mg	1
Dose di mantenimento	3,0 mg	

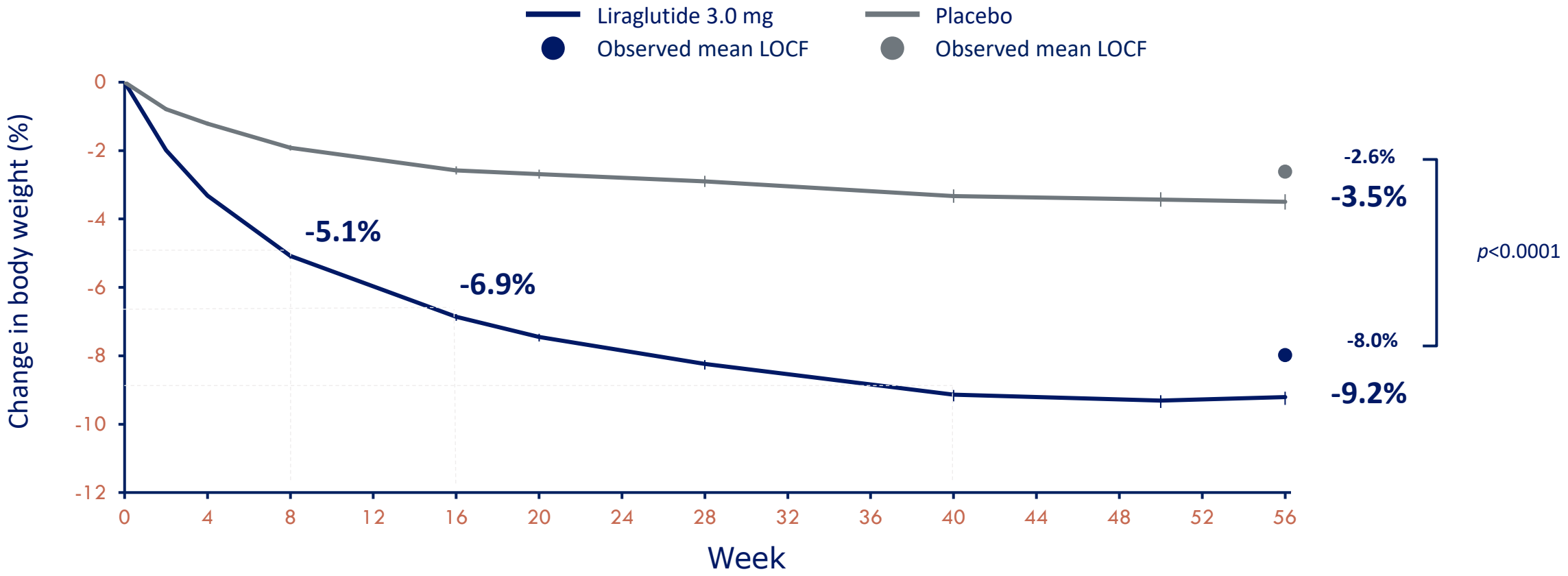
CHANGE IN BODY WEIGHT (%)

SCALE OBESITY AND PREDIABETES: 0-56 WEEKS

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JULY 2, 2015 VOL. 373 NO. 1

A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management

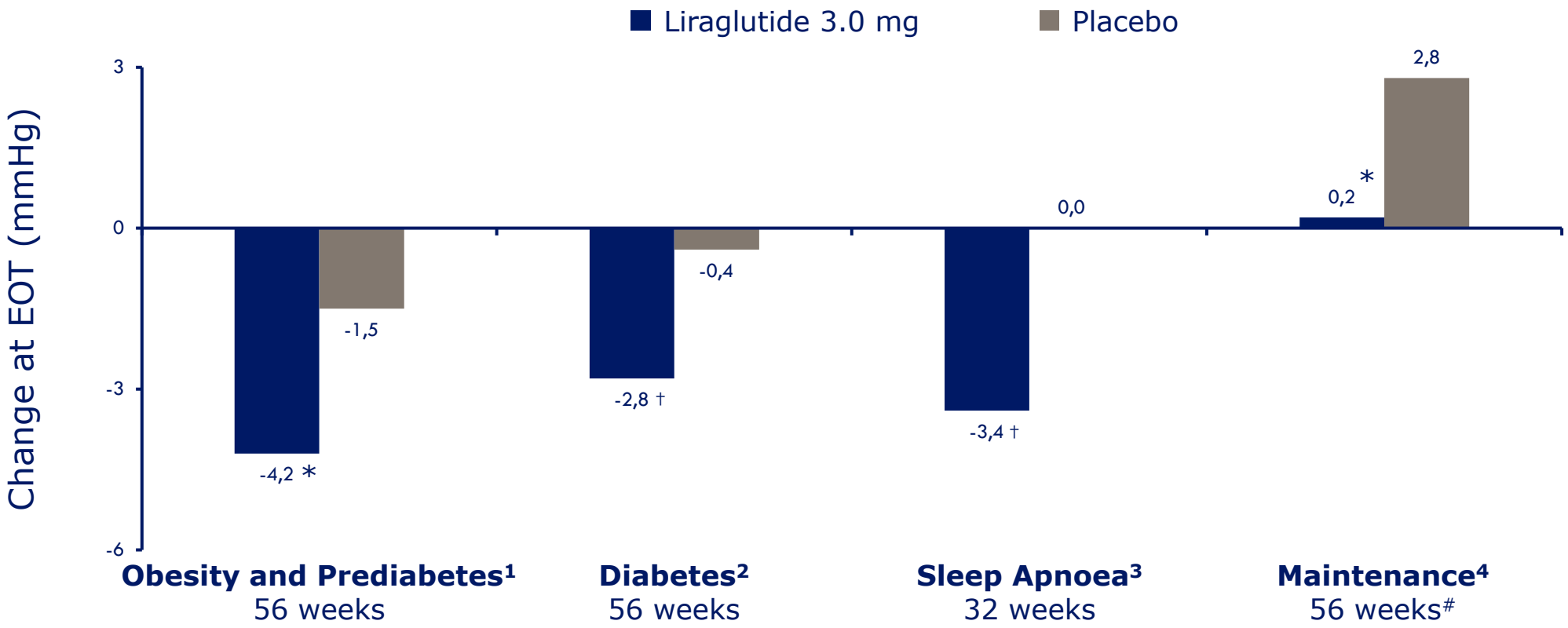
Mean baseline weight: 106 kg



FAS, fasting visit data only. Line graphs are observed means (±SE). Statistical analysis is ANCOVA.
FAS, full analysis set; LOCF, last observation carried forward; SE, standard error

Lifestyle intervention: -500 kcal/day diet + 150 min/week physical activity

CHANGE IN SYSTOLIC BLOOD PRESSURE ACROSS SCALE TRIALS

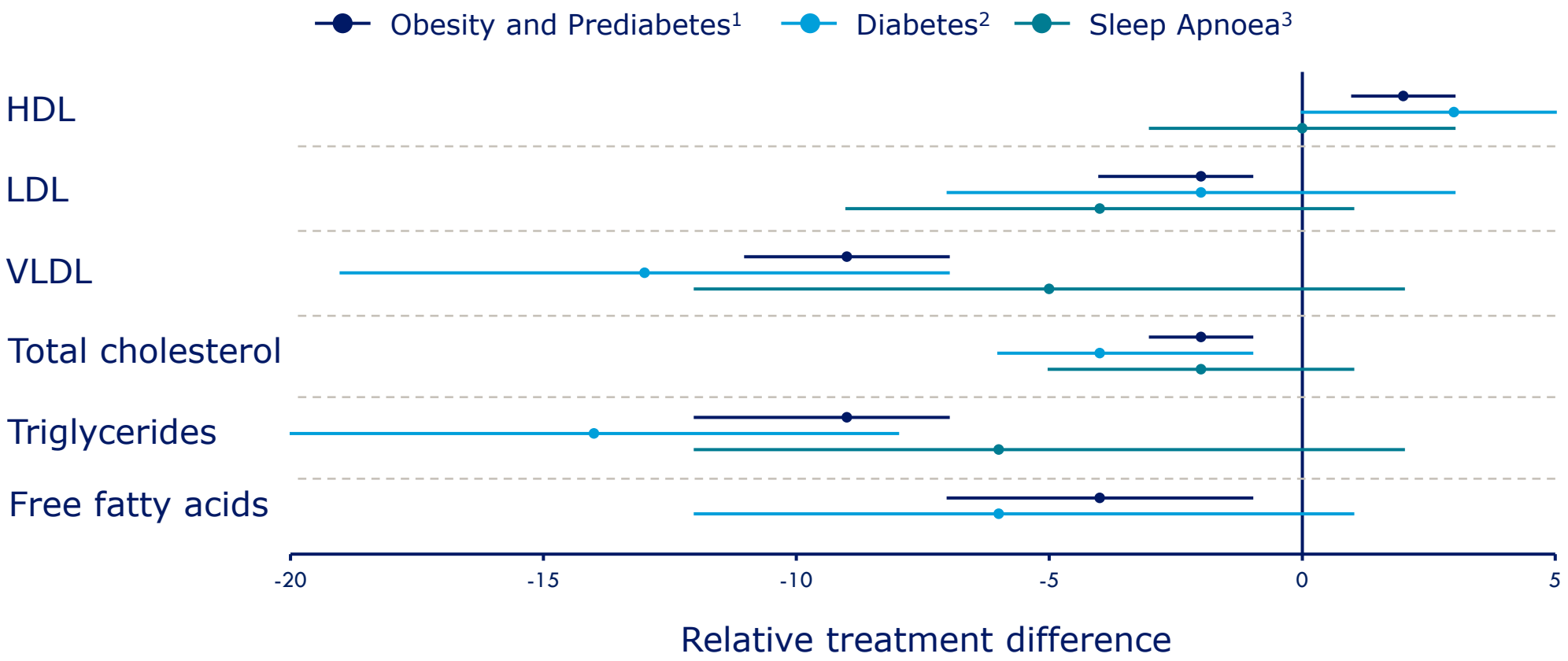


*p<0.001; †p<0.01; vs. placebo. Data are observed means; LOCF at end of trial; EOT, end of treatment
#Followed a 12-week low calorie diet run-in (total energy intake 1200–1400 kcal/day)

1. Pi-Sunyer *et al. N Engl J Med* 2015;373:11–22; 2. Davies *et al*. *JAMA* 2015;314:687–99; 3. Blackman *et al. Int J Obes (Lond)* 2016;40:1310–9;
4. Wadden *et al. Int J Obes (Lond)* 2013;37:1443–51

RELATIVE CHANGE IN LIPIDS ACROSS SCALE TRIALS

OBESITY AND PREDIABETES[1], DIABETES[2] AND SLEEP APNOEA[3]

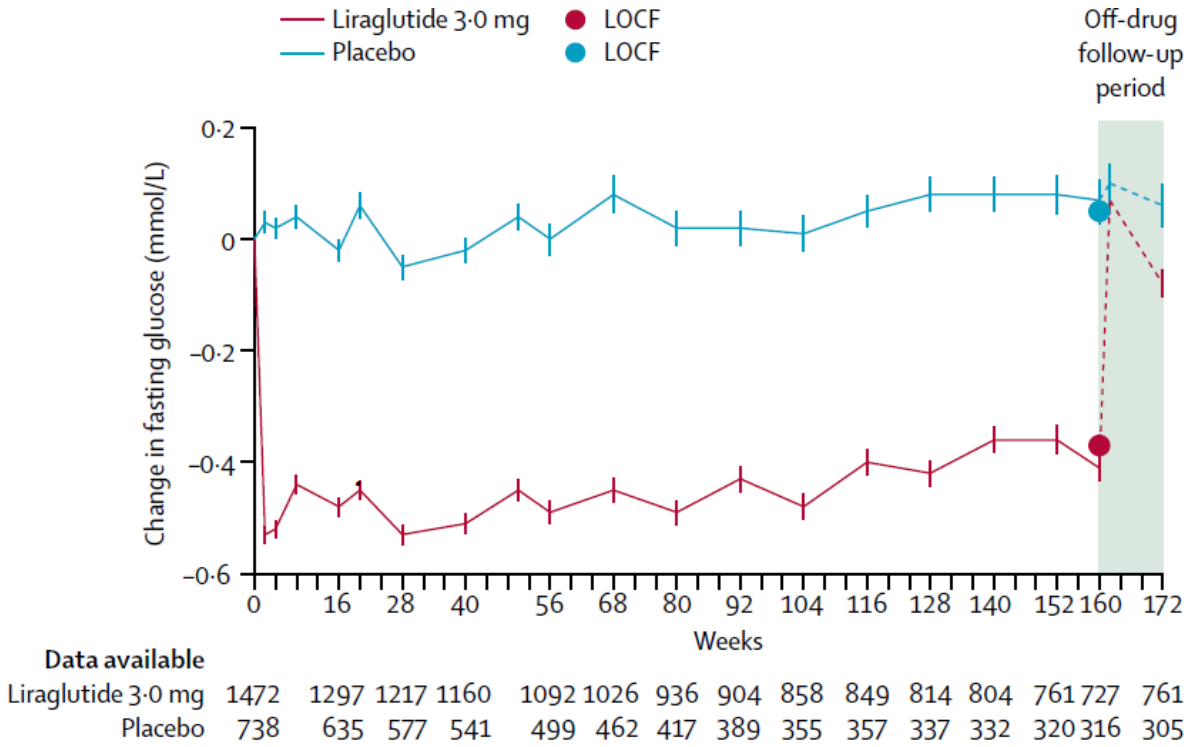


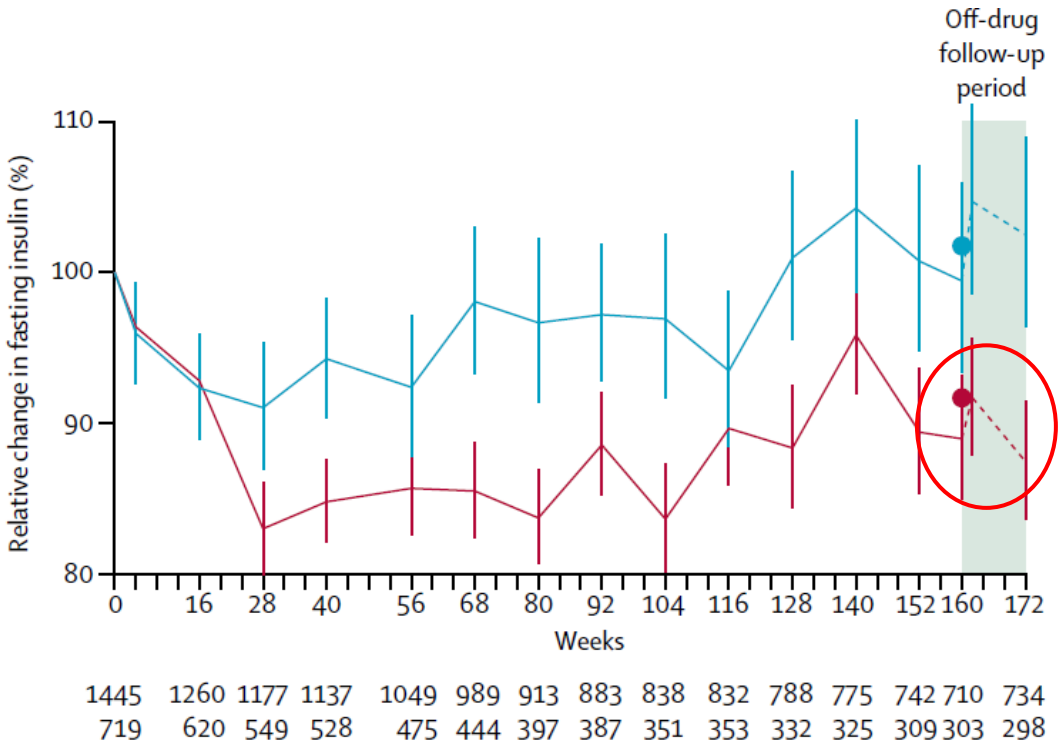
Note: lipids in the SCALE Maintenance publication presented as absolute change in lipids and are not presented here
Figure is relative difference (95% CI). Statistical analyses are ANCOVA. The change from baseline is a relative change given as % of baseline value
ANCOVA, analysis of covariance; CI, confidence interval

1. Pi-Sunyer *et al. N Engl J Med* 2015;373:11–22; 2. Davies *et al*. *JAMA* 2015;314:687–99; 3. Blackman *et al. Int J Obes (Lond)* 2016;40:1310–9

CHANGE IN FASTING GLUCOSE AND FASTING INSULIN

SCALE OBESITY AND PREDIABETES: AT WEEK 172





Glycaemic control parameters				
Glycated haemoglobin (% points)	−0·35 (0·32)	−0·14 (0·34)	−0·21 (−0·24 to −0·18)	<0·0001
Fasting glucose (mmol/L)	−0·37 (0·68)	0·05 (0·62)	−0·41 (−0·46 to −0·36)	<0·0001
Fasting insulin (%)	−8·3%	1·7%	−10·1 (−14·3 to −5·6)	<0·0001

le Roux CW, et al. Lancet. 2017;389(10077):1399-1409.

SCALE Safety Summary

Key safety outcomes with liraglutide 3.0 mg

GI adverse events

93% events

were mild or moderate[1]

Pancreatitis

10 events

vs. 2 events with placebo were recorded over 172 weeks[1]

MTC

0 events

of MTC or confirmed C-cell hyperplasia with liraglutide or placebo[1]

Neuro-psychiatric

Similar rates vs. placebo

observed in the SCALE programme[3]

MACE

0.19 events

per 100 years observation

vs. 0.20 events of adjudication-confirmed MACE with **placebo**[1]

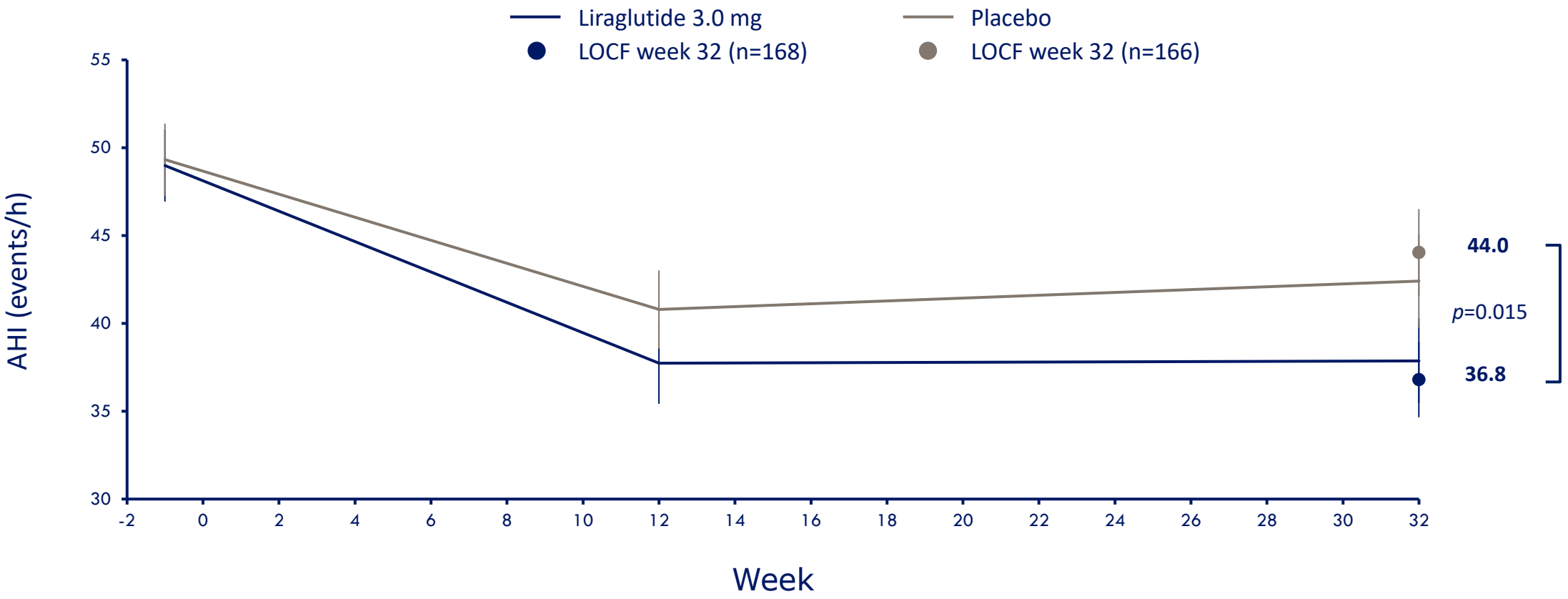
Liraglutide 3.0 mg, n=1505; Placebo, n=749. GI, gastrointestinal; MTC, medullary thyroid carcinoma; ULN, upper limits of normal

1. le Roux *et al*. *Lancet* 2017;389:1399–409

CHANGE IN AHI (EVENTS/H)

0–32 WEEKS

Mean baseline AHI: 49.2 events/h

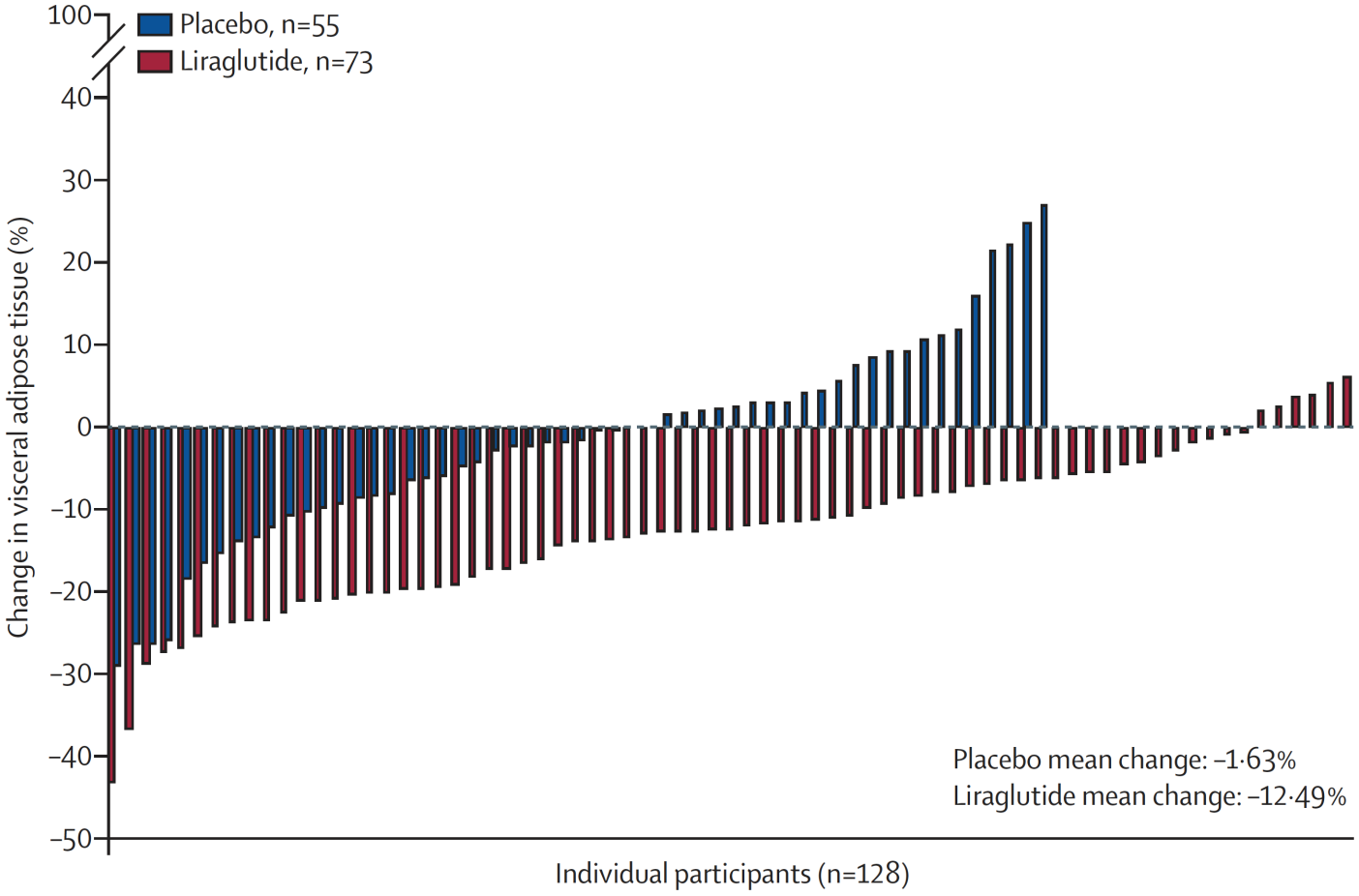


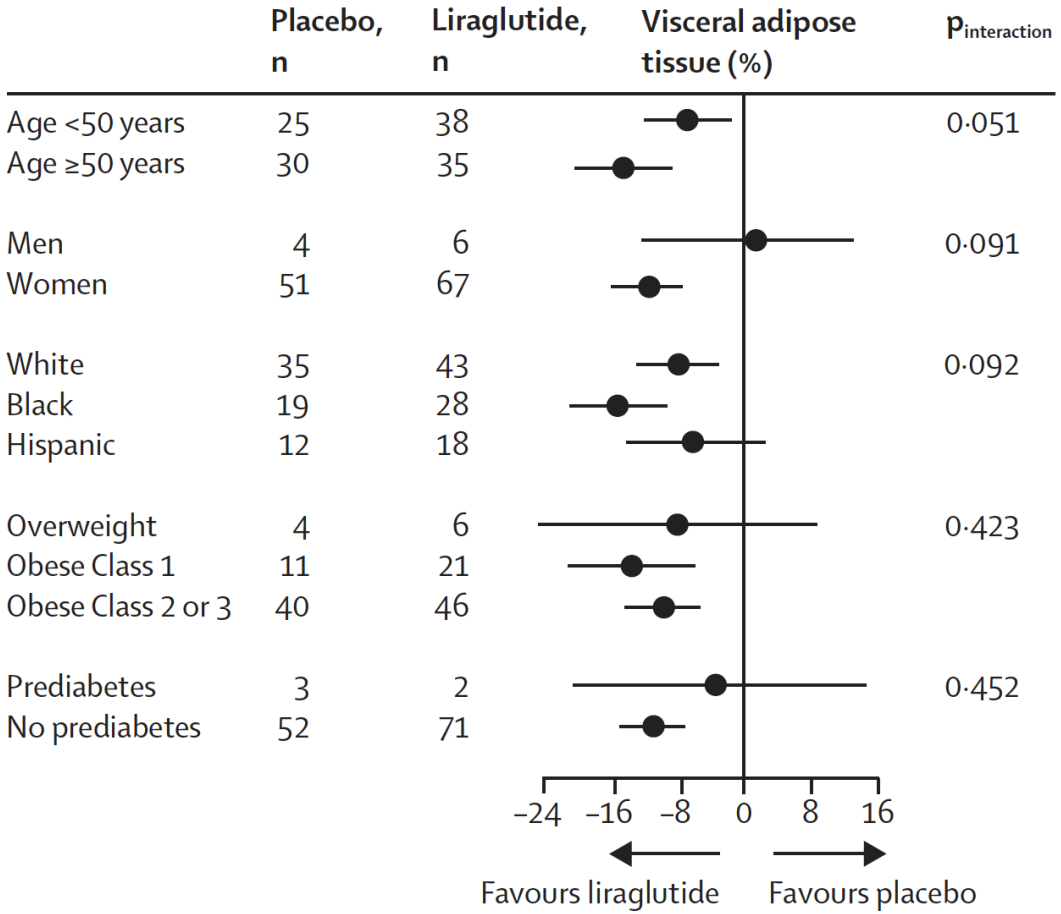
FAS. Line graphs are observed means (±SE). Circles are observed means LOCF. Statistical analysis is ANCOVA.
AHI, apnoea–hypopnoea index; ANCOVA, analysis of covariance; FAS, full analysis set; LOCF, last observation carried forward; SE, standard error

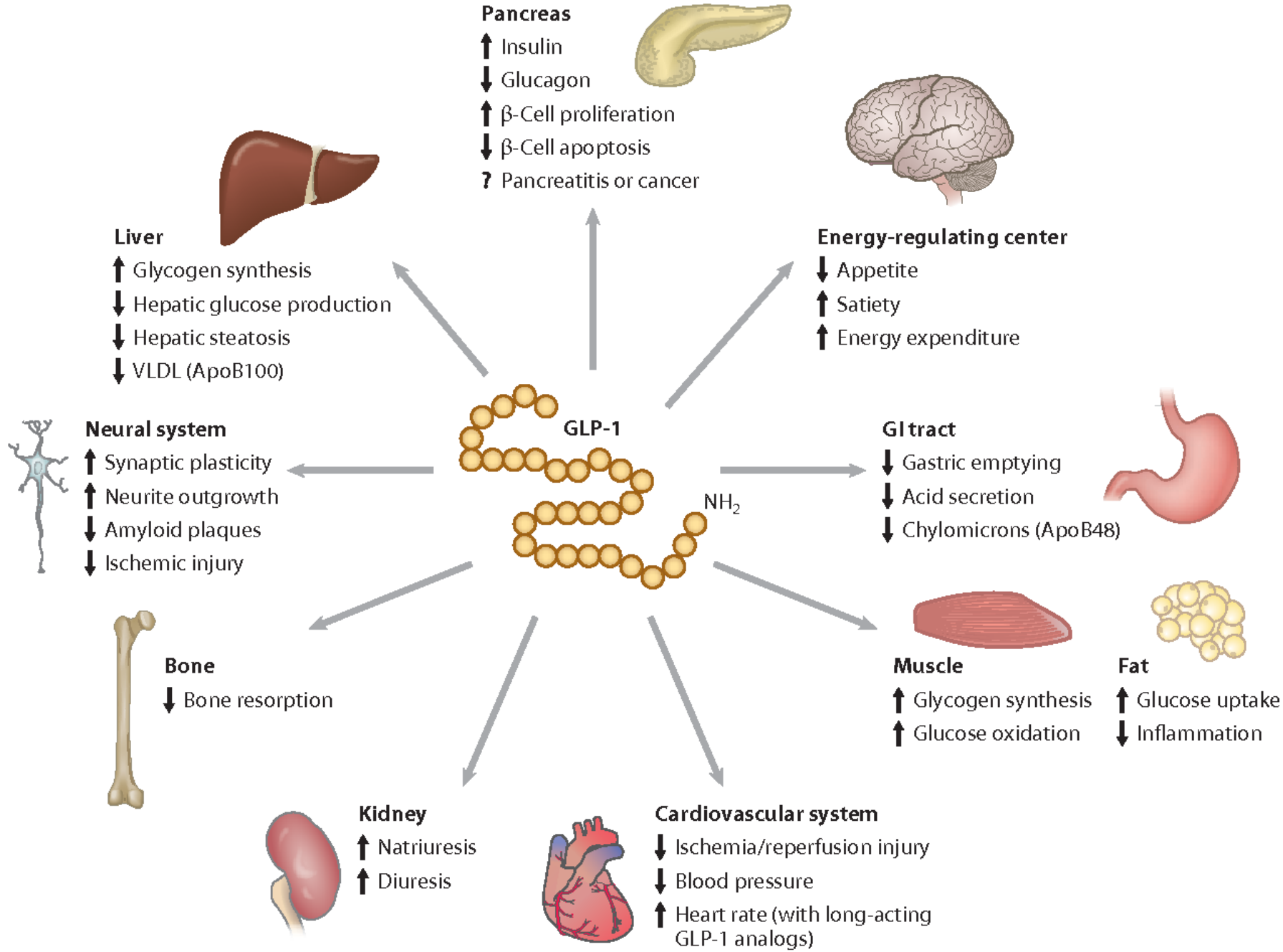
Blackman *et al. Int J Obes (Lond)* 2016;40:1310–9

Effects of liraglutide on visceral and ectopic fat in adults with overweight and obesity at high cardiovascular risk: a randomised, double-blind, placebo-controlled, clinical trial

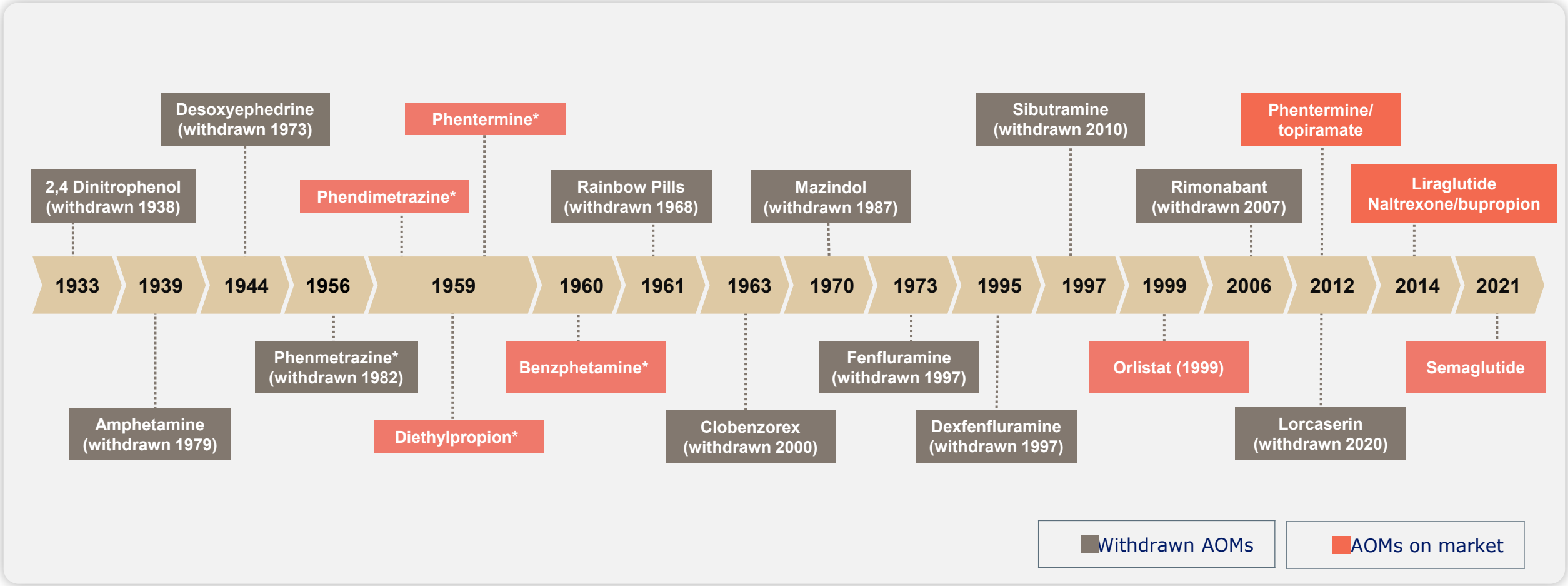
Ian J Neeland, Steven P Marso, Colby R Ayers, Bienka Lewis, Robert Oslica, Wynona Francis, Susan Rodder, Ambarish Pandey, Parag H Joshi






Pancreas
↑ Insulin
↓ Glucagon
↑ β-Cell proliferation
↓ β-Cell apoptosis
? Pancreatitis or cancer
Liver
↑ Glycogen synthesis
↓ Hepatic glucose production
↓ Hepatic steatosis
↓ VLDL (ApoB100)
Energy-regulating center
↓ Appetite
↑ Satiety
↑ Energy expenditure
GLP-1
NH2
Neural system
↑ Synaptic plasticity
↑ Neurite outgrowth
↓ Amyloid plaques
↓ Ischemic injury
GI tract
↓ Gastric emptying
↓ Acid secretion
↓ Chylomicrons (ApoB48)
Bone
↓ Bone resorption
Muscle
↑ Glycogen synthesis
↑ Glucose oxidation
Fat
↑ Glucose uptake
↓ Inflammation
Kidney
↑ Natriuresis
↑ Diuresis
Cardiovascular system
↓ Ischemia/reperfusion injury
↓ Blood pressure
↑ Heart rate (with long-acting GLP-1 analogs)

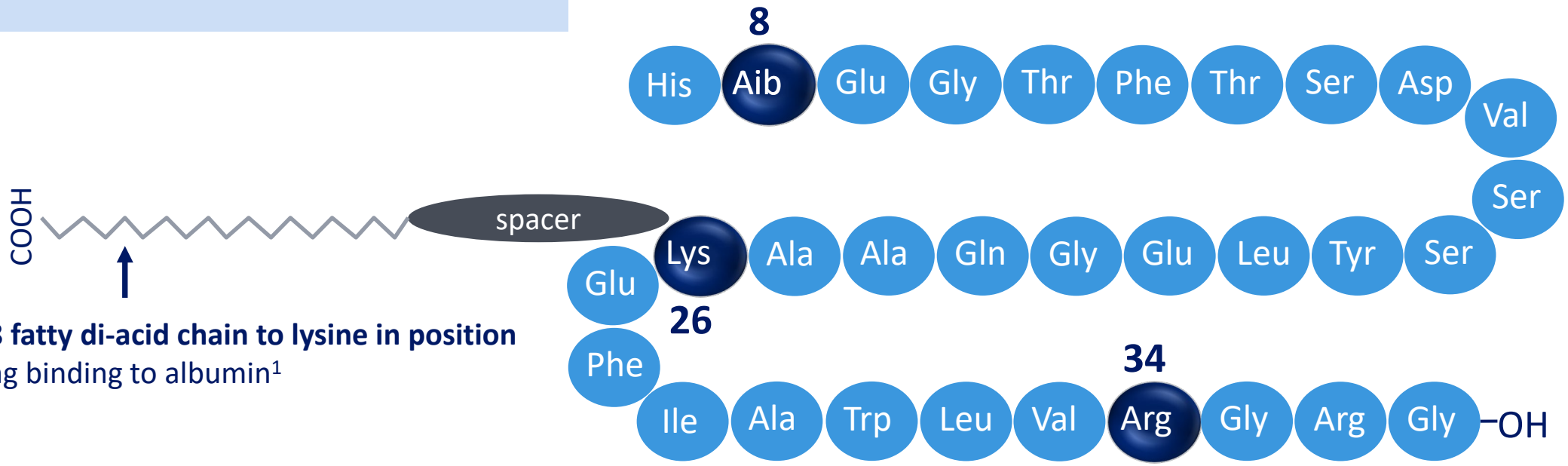
...Guardando al Futuro


2,4 Dinitrophenol (withdrawn 1938)
Desoxyephedrine (withdrawn 1973)
Phendimetrazine*
Phentermine*
Rainbow Pills (withdrawn 1968)
Mazindol (withdrawn 1987)
Sibutramine (withdrawn 2010)
Rimonabant (withdrawn 2007)
Phentermine/ topiramate
Liraglutide Naltrexone/bupropion
1933
1939
1944
1956
1959
1960
1961
1963
1970
1973
1995
1997
1999
2006
2012
2014
2021
Amphetamine (withdrawn 1979)
Phenmetrazine* (withdrawn 1982)
Diethylpropion*
Benzphetamine*
Clobenzorex (withdrawn 2000)
Fenfluramine (withdrawn 1997)
Dexfenfluramine (withdrawn 1997)
Orlistat (1999)
Lorcaserin (withdrawn 2020)
Semaglutide
Withdrawn AOMs
AOMs on market

Semaglutide is a human GLP-1 analogue

- **94%** homology to human GLP-1[1]
- $t_{½}$ of approximately **1 week**[2,3]

Amino acid substitution at position 8
(alanine to alpha-aminoisobutyric acid)
protects against DPP-4 degradation[1]



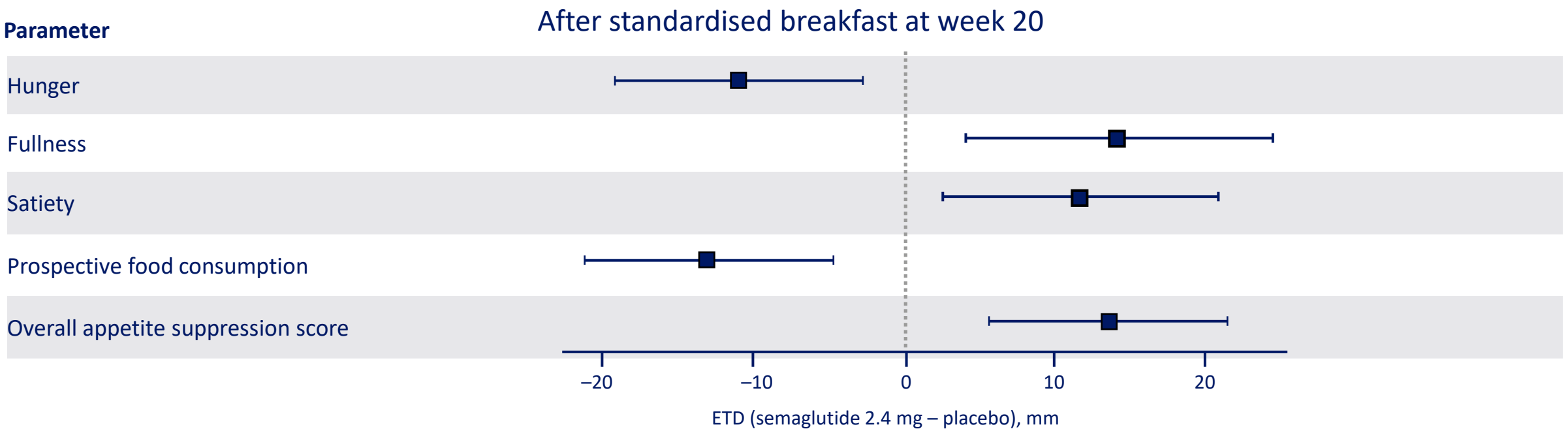
Spacer and C-18 fatty di-acid chain to lysine in position 26 provide strong binding to albumin[1]

Amino acid substitution at position 34
(lysine to arginine) prevents C-18 fatty di-acid binding at the wrong site[1]

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; t½, half-life.
Lau et al. J Med Chem 2015;58:7370–80; Kapitza et al. J Clin Pharmacol 2015;55:497–504; Marbury et al. Clin Pharmacokinet 2017;56:1381–90.

Semaglutide impacts all dimensions of appetite

Participants with obesity



After a standardised breakfast, hunger and prospective food consumption were reduced, and fullness and satiety increased, with semaglutide 2.4 mg vs placebo (all p≤0.01)

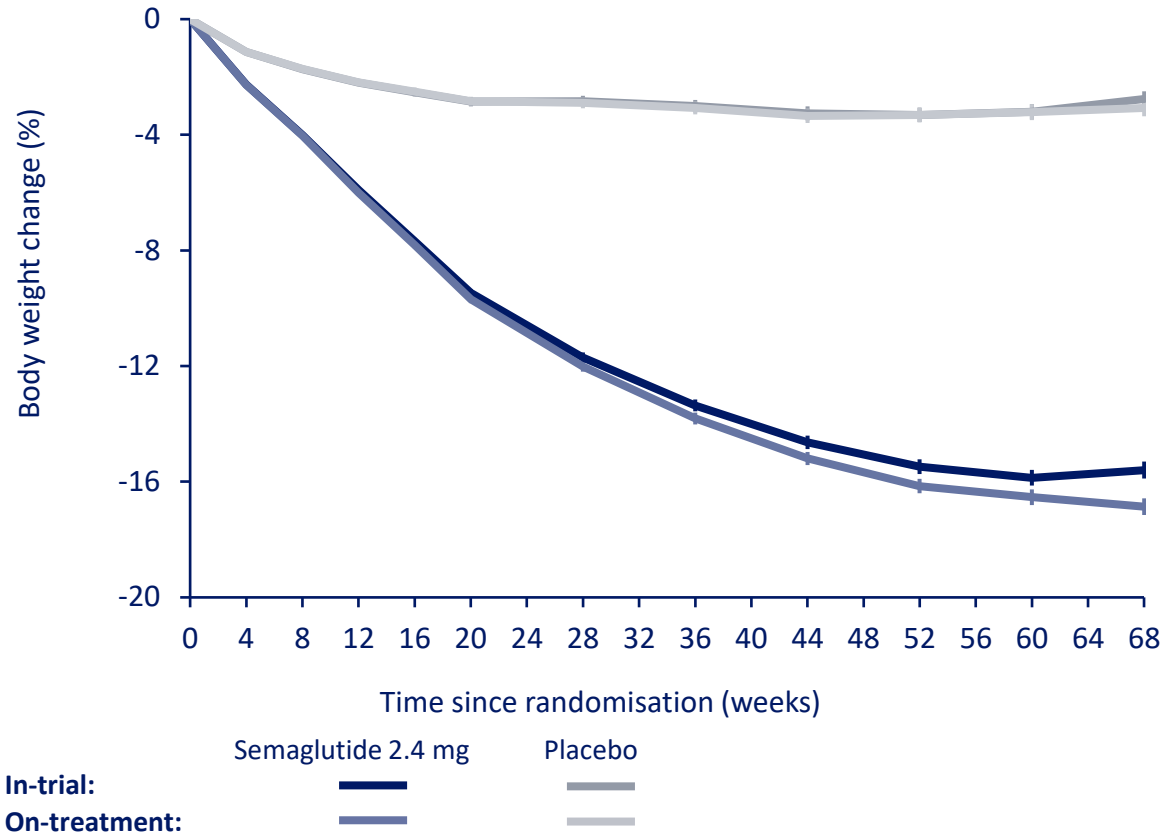
ETD, estimated treatment difference.
Friedrichsen et al. Diabetes Obes Metab 2021;23:754–62.

Change in body weight

STEP 1

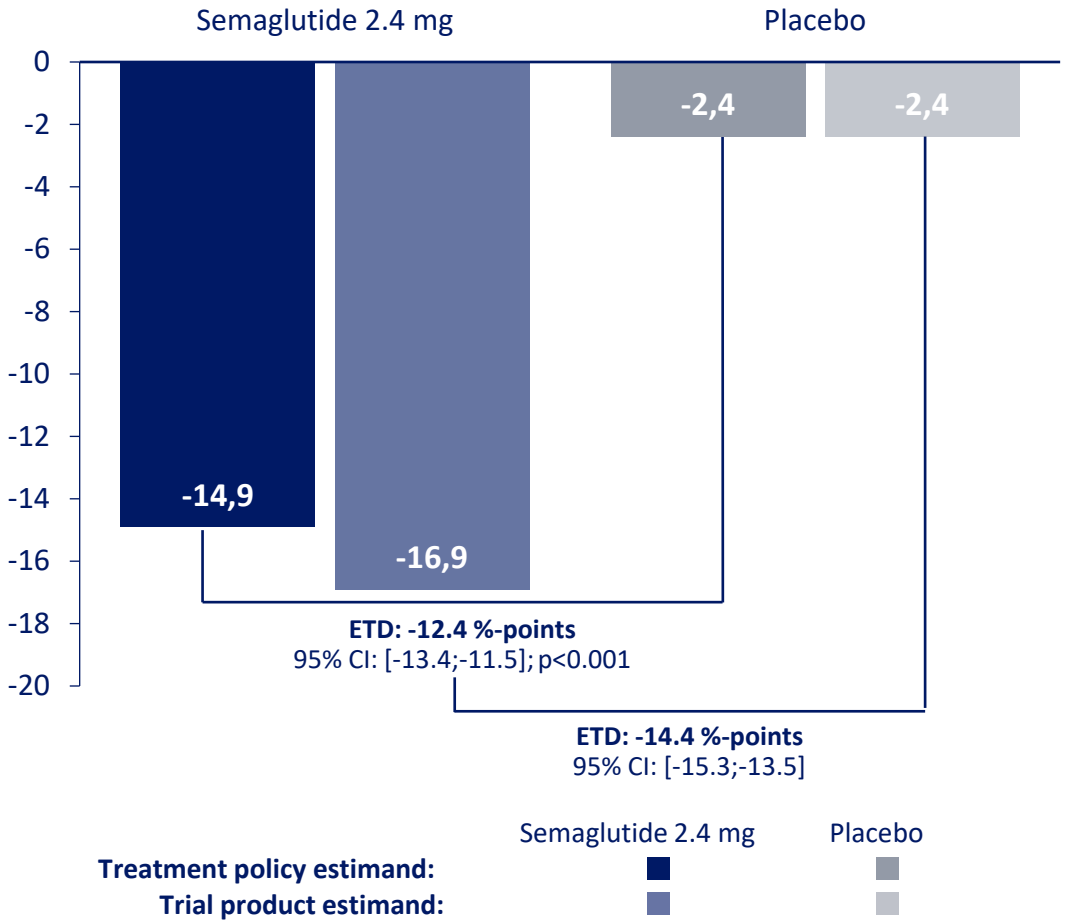
Observed body weight change over time

(Mean at baseline: 105.8 kg)



Error bars are +/- standard error of the mean.
CI, confidence interval; ETD, estimated treatment difference.
Wilding et al. N Engl J Med 2021;384:989-1002;

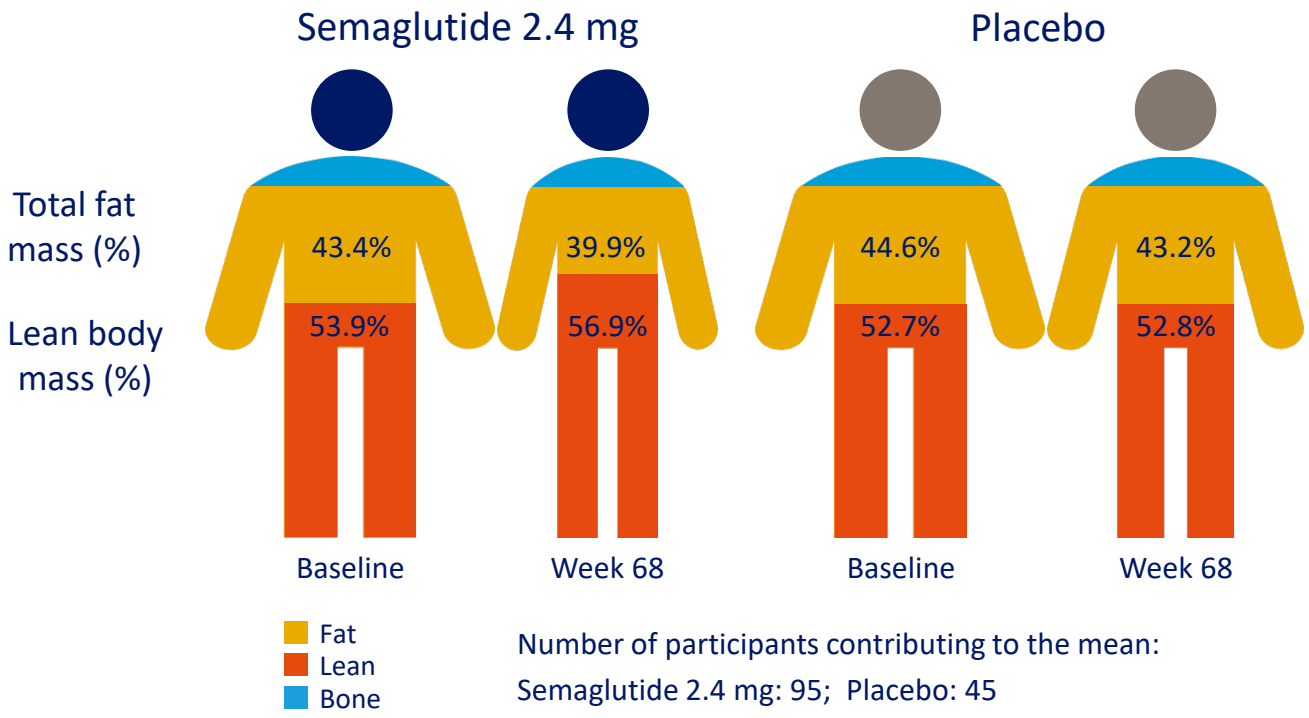
Estimated change from baseline to week 68



Change in body composition (DXA)

STEP 1

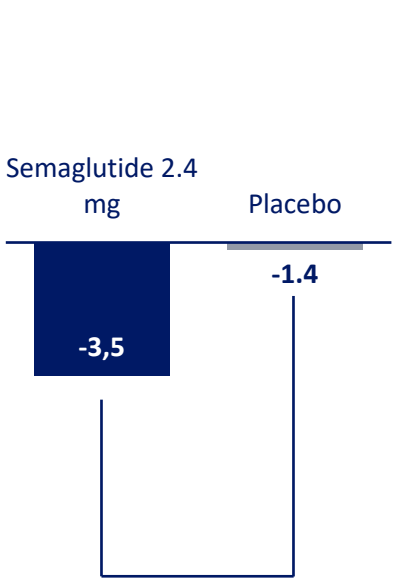
In-trial[§]



Number of participants contributing to the mean:
Semaglutide 2.4 mg: 95; Placebo: 45

Total fat mass (%)[#]

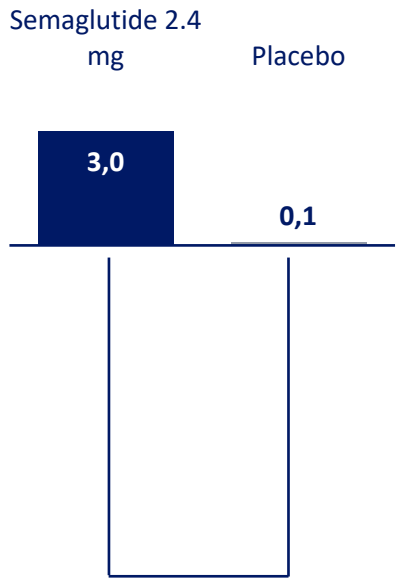
Mean baseline: 43.8 %



ETD: -3.29 %-points
95% CI: [-4.94;-1.65]

Lean body mass (%)[#]

Mean baseline: 53.5 %

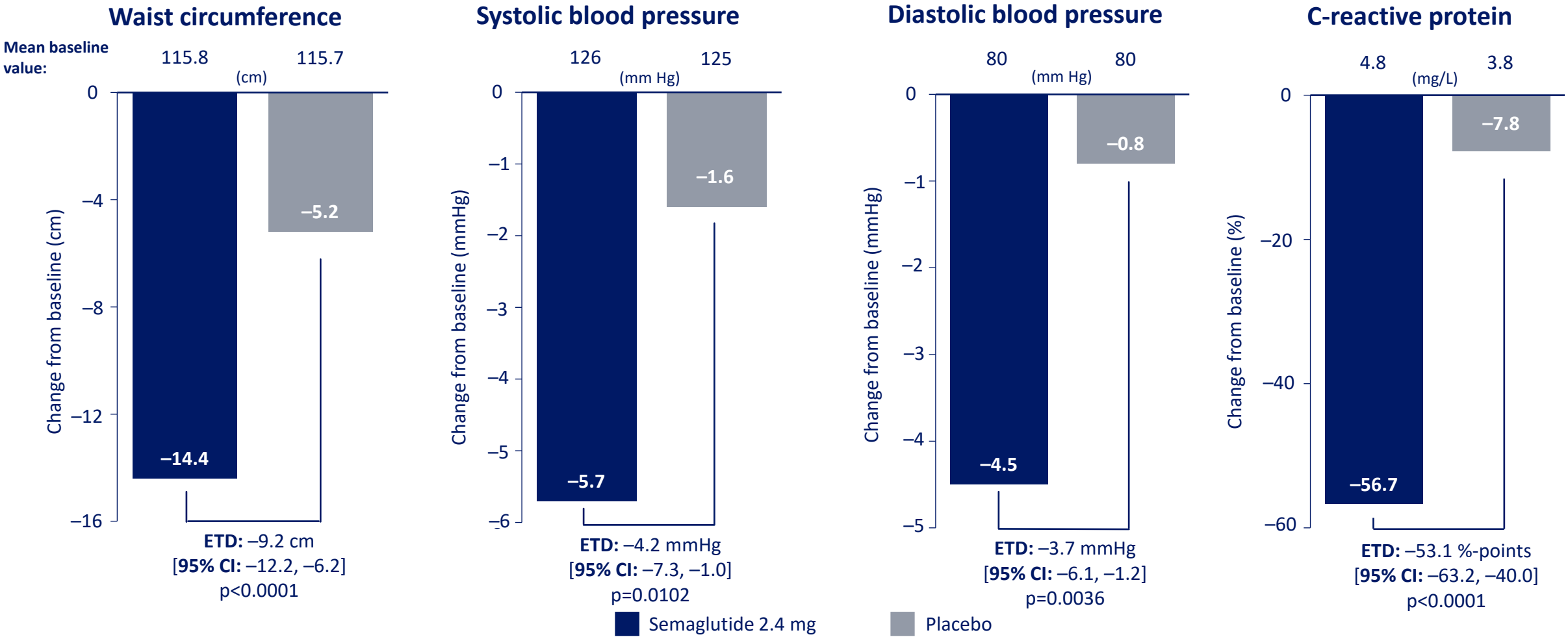


ETD: 2.94 %-points
95% CI: [1.40;4.49]

§ Observed data for the in-trial period; # Estimated data for the treatment policy estimand.
CI, confidence interval; DXA, dual energy x-ray absorptiometry; ETD, estimated treatment difference.
Wilding et al. presented at the Endocrine Society (ENDO) virtual meeting, March 20-23, 2021.

Cardiovascular risk factors

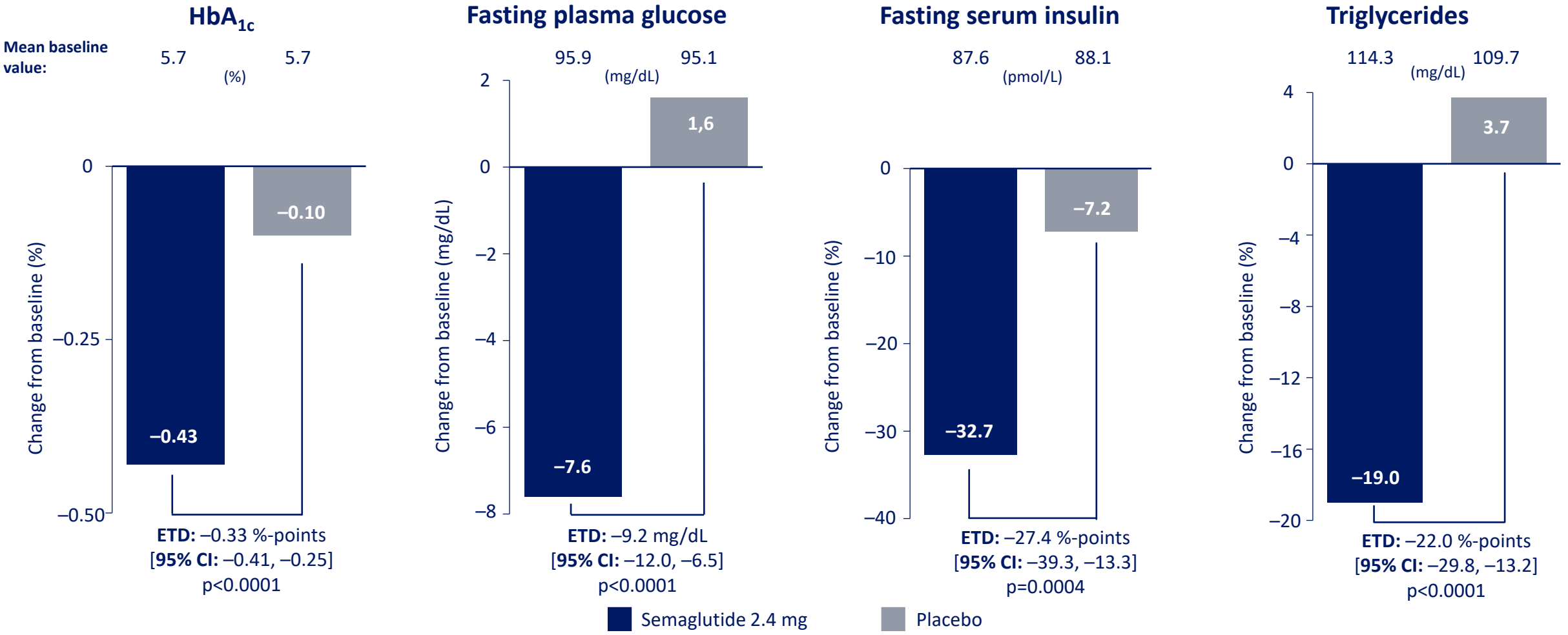
STEP 5



Change from baseline to week 104 based on the treatment policy estimand (assesses treatment effect regardless of treatment discontinuation or rescue intervention). CI, confidence interval; ETD, estimated treatment difference. Garvey et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021.

Metabolic risk factors

STEP 5



Change from baseline to week 104 based on the treatment policy estimand (assesses treatment effect regardless of treatment discontinuation or rescue intervention).
CI, confidence interval; ETD, estimated treatment difference. Garvey et al. Presented at the 39th Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1–5, 2021.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 21, 2022 VOL. 387 NO. 3

Tirzepatide Once Weekly for the Treatment of Obesity

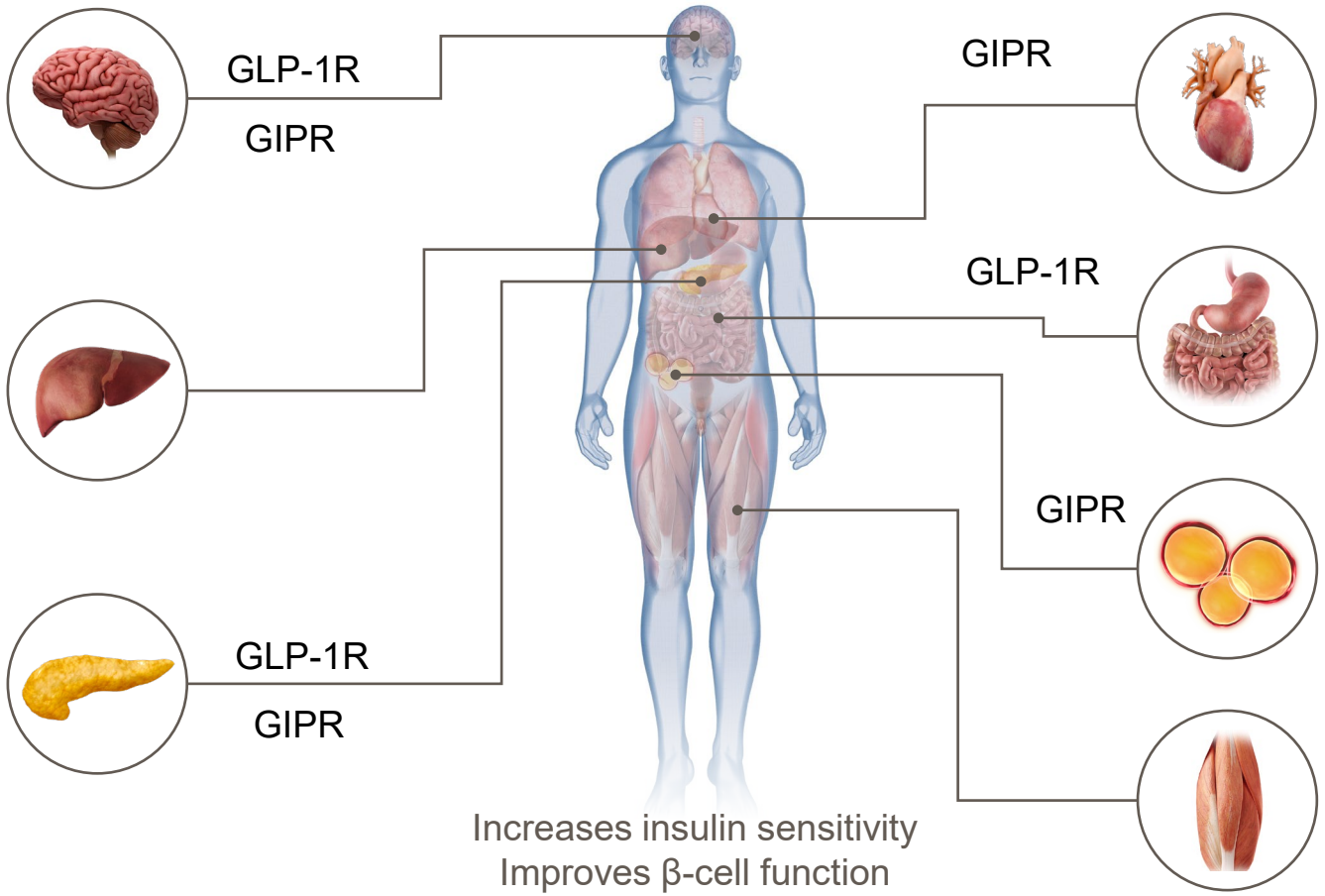
Ania M. Jastreboff, M.D., Ph.D., Louis J. Aronne, M.D., Nadia N. Ahmad, M.D., M.P.H., Sean Wharton, M.D., Pharm.D., Lisa Connery, M.D., Breno Alves, M.D., Arihiro Kiyosue, M.D., Ph.D., Shuyu Zhang, M.S., Bing Liu, Ph.D., Mathijs C. Bunck, M.D., Ph.D., and Adam Stefanski, M.D., Ph.D., for the SURMOUNT-1 Investigators*

Potential MOA of Tirzepatide

CNS
Appetite, feeding behavior, energy expenditure, and nausea

Liver (indirect)
Insulin sensitivity, lipid metabolism, and energy expenditure

Pancreas (islets)
Secretion of insulin and glucagon



Cardiovascular
Plasma lipids, inflammation, and endothelial function

GI tract (stomach)
Delayed gastric emptying

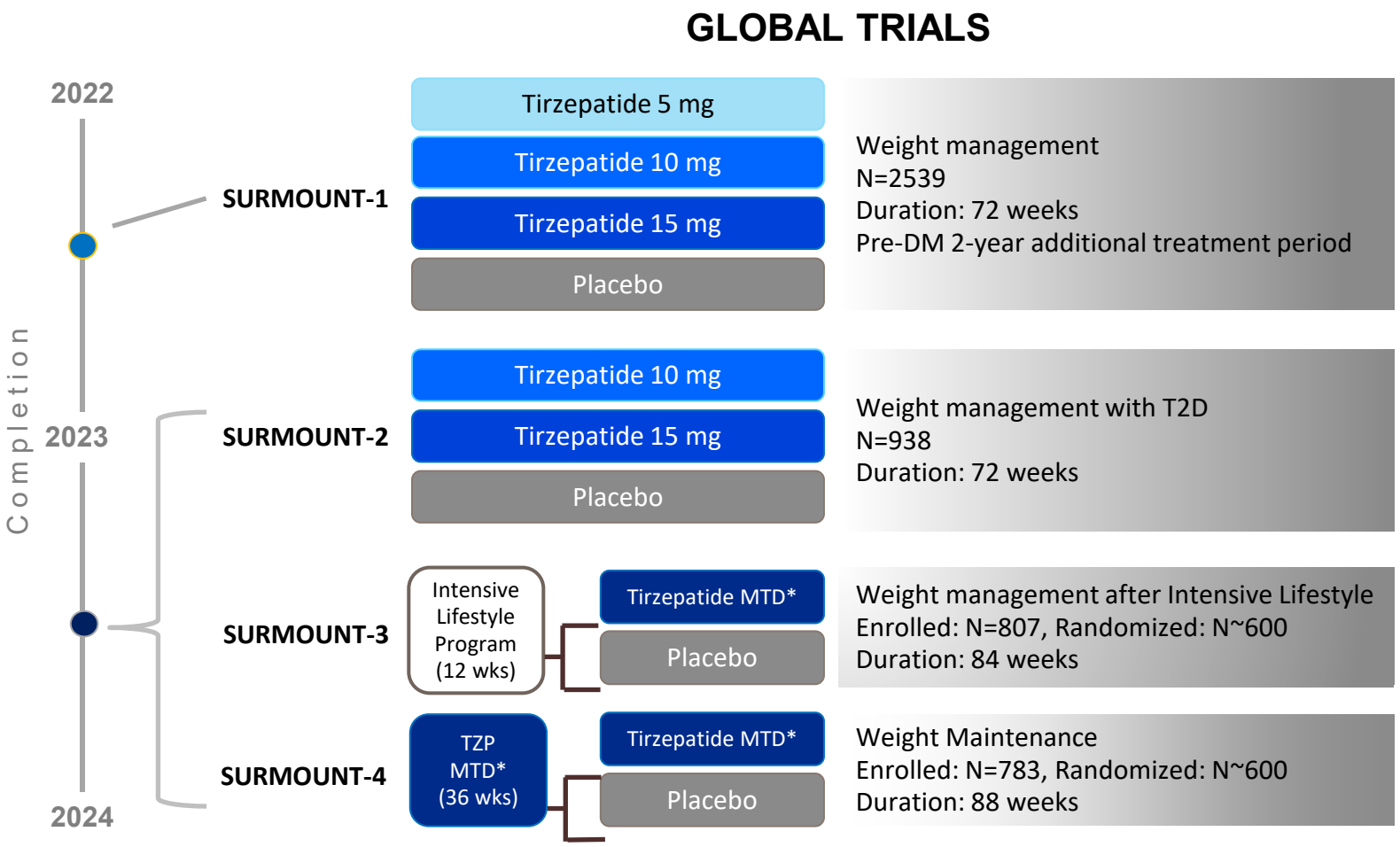
Adipose tissue
Lipid metabolism and insulin sensitivity

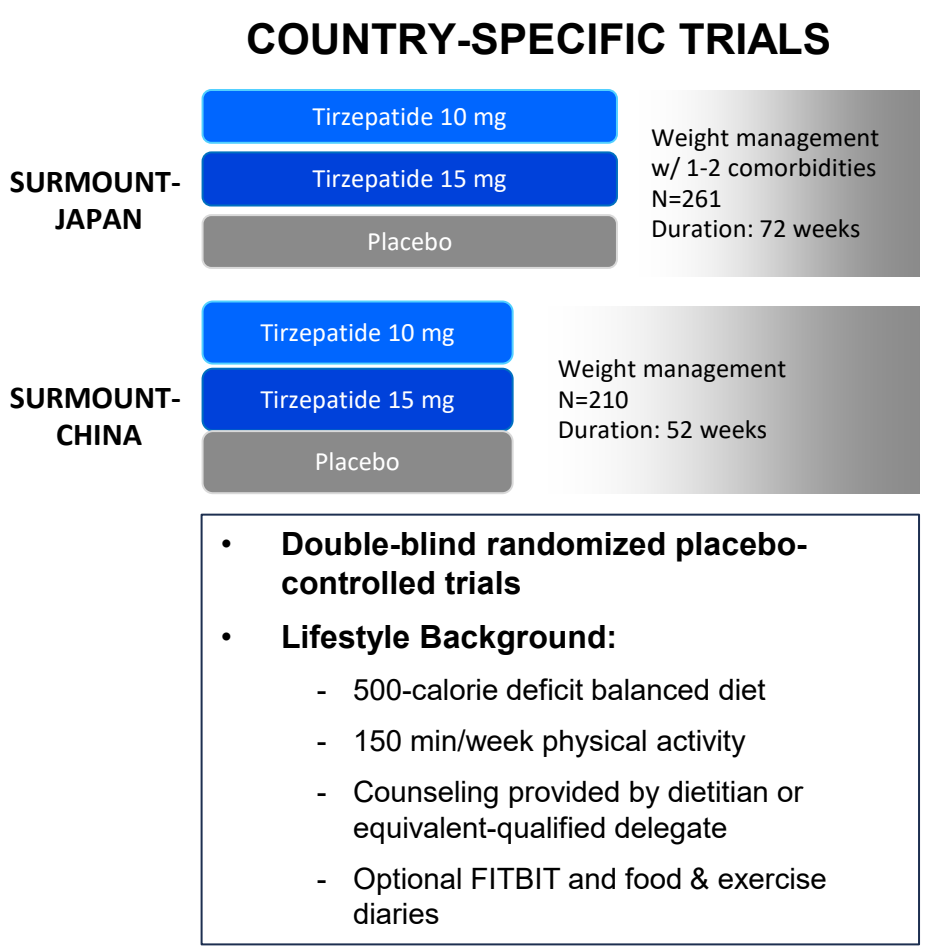
Skeletal muscle (indirect)
Insulin sensitivity and glucose disposal

Increases insulin sensitivity
Improves β-cell function
Reduces food intake
Increases energy expenditure
Improves metabolic flexibility and nutrient partitioning
Alters adverse event profile vs. GLP-1RA

CNS = central nervous system; GI = gastrointestinal; GIPR = glucose-dependent insulinotropic polypeptide receptor; GLP-1R = glucagon-like peptide-1 receptor; GLP-1RA = glucagon-like peptide-1 receptor agonist; MOA = mechanism of action.

SURMOUNT (Phase 3) Program Overview

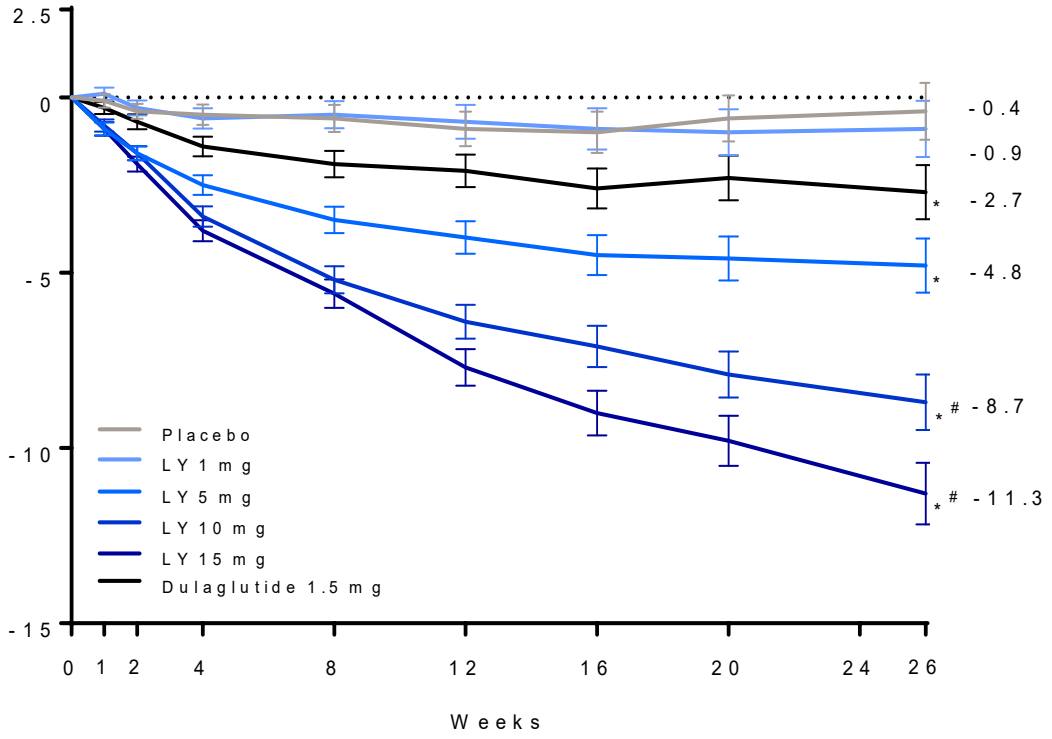




*MTD: maximal tolerated dose (10 mg or 15 mg)

Tirzepatide Phase 2 Study Secondary Endpoint: Body Weight 26-Week Change from Baseline

Weight Reduction from Mean Baseline of 92 kg

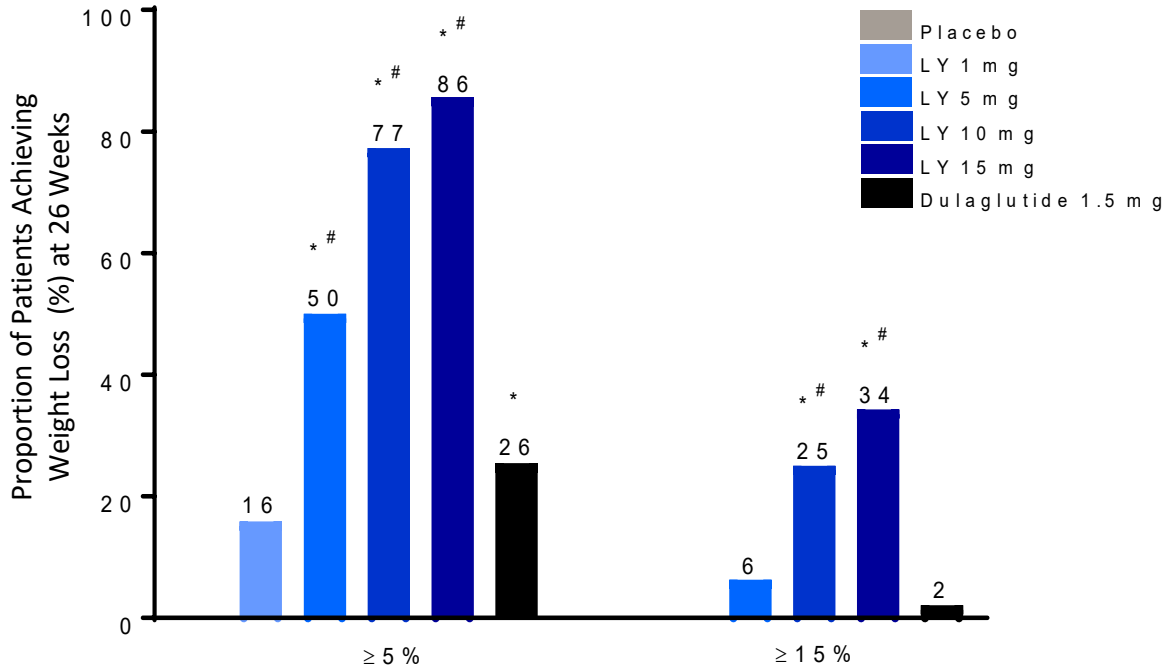


Observed significant and dose-related decreases in body weight (kg)

Data presented are LS mean ± SE. MMRM, on treatment analysis.
Trial Description: 26-week randomized trial; 1mg, 5mg, 10mg: 2 week titration, 15mg: 6 week titration, dulaglutide 1.5mg
Baseline Characteristics: Mean age 57, weight 91.5 kg, BMI 32.6, A1c 8.1%, 90% on metformin

Frías JP, et al. *Lancet* 2018; 17:2180-2193.

Weight Reduction (%)



34% of 15 mg dose patients achieve ≥15% body weight reduction

Data presented are from logistic regression, on treatment analysis.
*,#p<.05 vs placebo and vs. dulaglutide 1.5 mg, respectively

Top Line – Discontinuations and Safety

Discontinuations				
Disc. Due to AE	4.3%	7.1%	6.2%	2.6%
Overall Disc. Rate	14.3%	16.4%	15.1%	26.4%

Gastrointestinal Adverse Events				
TZP dose	***5mg***	***10mg***	***15mg***	***Pbo.***
Nausea	24.6%	33.3%	31.0%	9.5%
Diarrhea	18.7%	21.2%	23.0%	7.3%
Vomiting	8.3%	10.7%	12.2%	1.7%
Constipation	16.8%	17.1%	11.7%	5.8%

Eli Lilly and Company. 2022. Available at: Lilly's tirzepatide delivered up to 22.5% weight loss in adults with obesity or overweight in SURMOUNT-1 | Eli Lilly and Company. Accessed 29 April 2022

KEY POINTS

Il trattamento analoghi del GLP1 non può sicuramente sostituirsi ma può efficacemente affiancarsi nel grande obeso ad un trattamento chirurgico bariatrico

Valida alternativa alla chirurgia in pazienti in presenza di altri criteri di inelegibilità

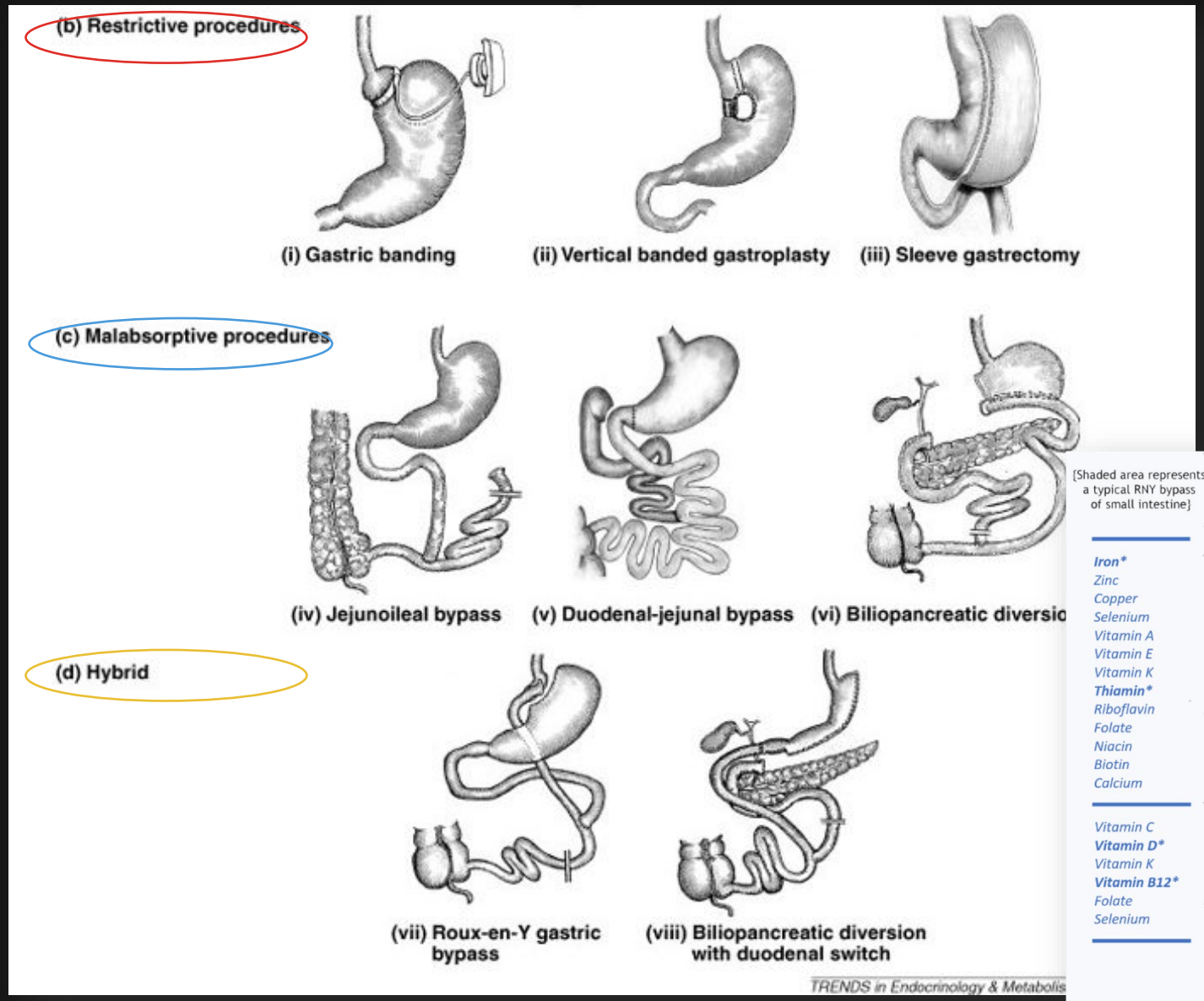
Stabilizzazione o calo ponderale in pazienti che necessitano di un lungo percorso preoperatorio

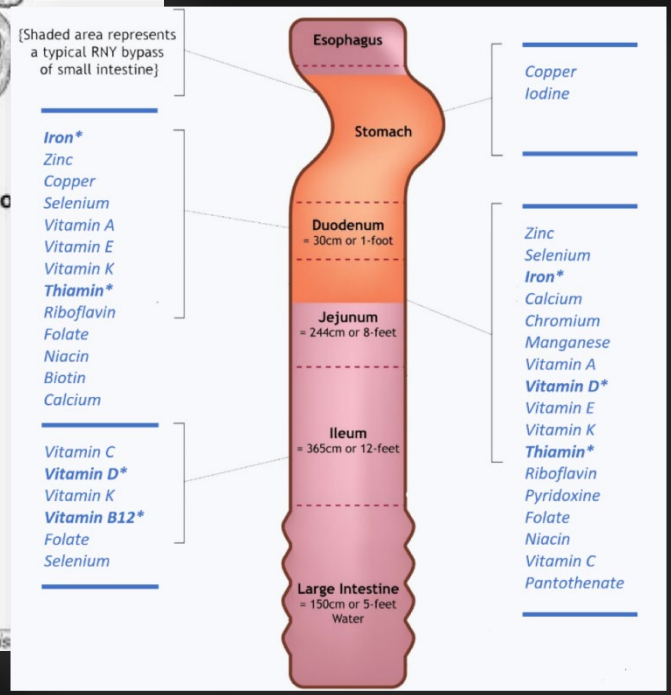
Utilizzo come trattamento di prima linea in paziento obesi con diabete di nuovo riscontro

Significativo effetto sul comportamento alimentare

Miglioramento dei parametri correlati alla patologia , effetti sulla progressione della malattia e sul rischio cardiovascolare

E poi ci fu l'intervento chirurgico..





ELSEVIER

Check for updates

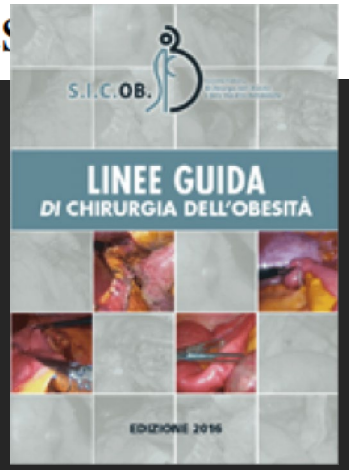
SURGERY FOR OBESITY AND RELATED DISEASES

Surgery for Obesity and Related Diseases 16 (2020) 175–247

Guidelines

Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures – 2019 update: cosponsored by American Association of Clinical Endocrinologists/American College of Endocrinology, The Obesity Society, American Society for Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists

Partendo dalla Good Clinical practice…



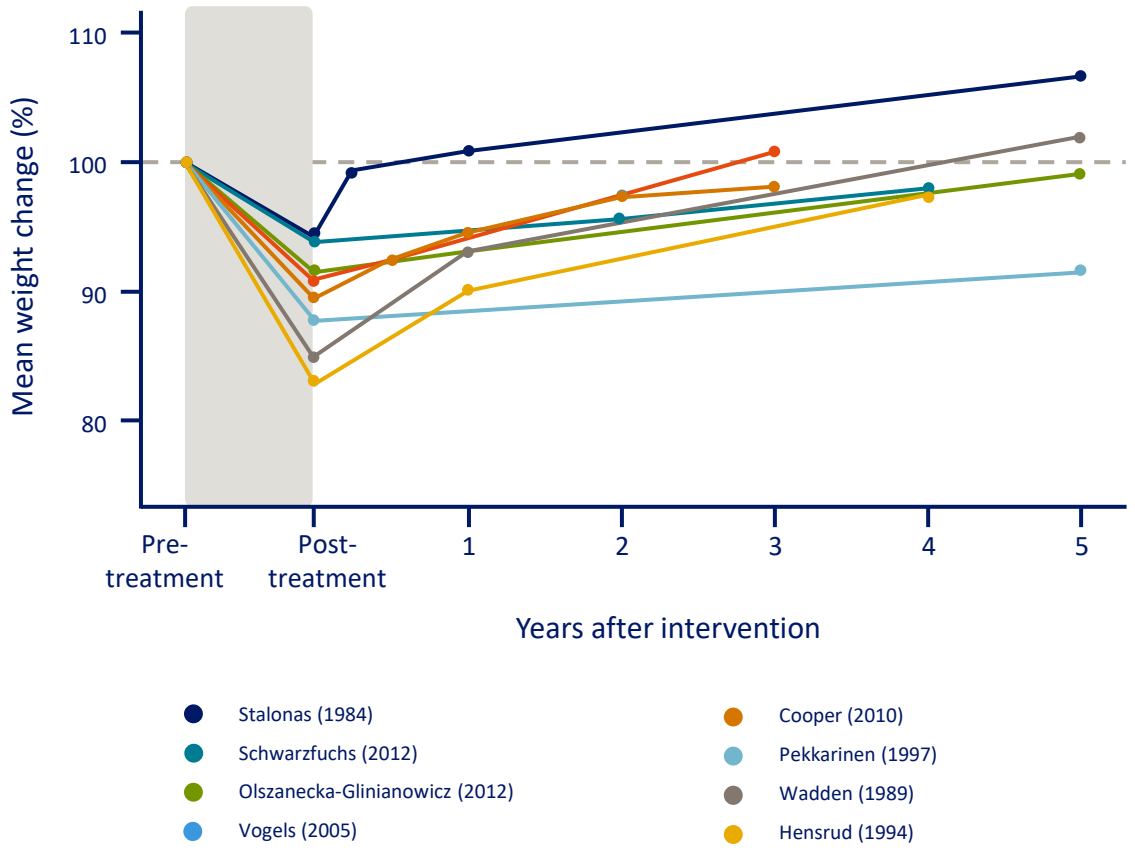
Recommended follow-up intervals are generally based on expert opinion . There are very few bariatric surgery studies reporting long-term results with sufficient follow-up of patients

Checklist item		LAGB	SG	RYGB	BPD/DS
Follow-up					
✓	Visits: initial, interval until stable, once stable (mo)	1, 1–2, 12	1, 3, 6, 12	1, 3, 6–12	1, 3, 6
✓	Monitor progress with weight loss and evidence of complications each visit	✓	✓	✓	✓
✓	SMA-21, CBC/plt with each visit (and iron at baseline and after as needed)	✓	✓	✓	✓
✓	Avoid nonsteroidal anti-inflammatory drugs	✓	✓	✓	✓
✓	Adjust postoperative medications	✓	✓	✓	✓
✓	Consider gout and gallstone prophylaxis in appropriate patients	✓	✓	✓	✓
✓	Need for antihypertensive therapy with each visit	✓	✓	✓	✓
✓	Lipid evaluation every 6–12 mo based on risk and therapy	✓	✓	✓	✓
✓	Monitor adherence with physical activity recommendations	✓	✓	✓	✓
✓	Evaluate need for support groups	✓	✓	✓	✓
✓	Bone density (DXA) at 2 yr	✓	✓	✓	✓
✓	24-hr urinary calcium excretion at 6 mo and then annually†	x	x	x	✓
✓	B_{12} (annually; MMA and HCy optional; then q 3–6 mo if supplemented)	✓	✓	✓	✓
✓	Folic acid (RBC folic acid optional), iron studies, 25-vitamin D, iPTH	x	x	✓	✓
✓	Vitamin A (initially and q 6–12 mo thereafter)	x	x	Optional	✓
✓	Copper, zinc, selenium evaluation with specific findings	x	x	✓	✓
✓	Thiamine evaluation with specific findings	✓	✓	✓	✓
✓	Consider eventual body contouring surgery	✓	✓	✓	✓
✓	Lifestyle medicine evaluation: healthy eating index; cardiovascular fitness; strength	✓	✓	✓	✓

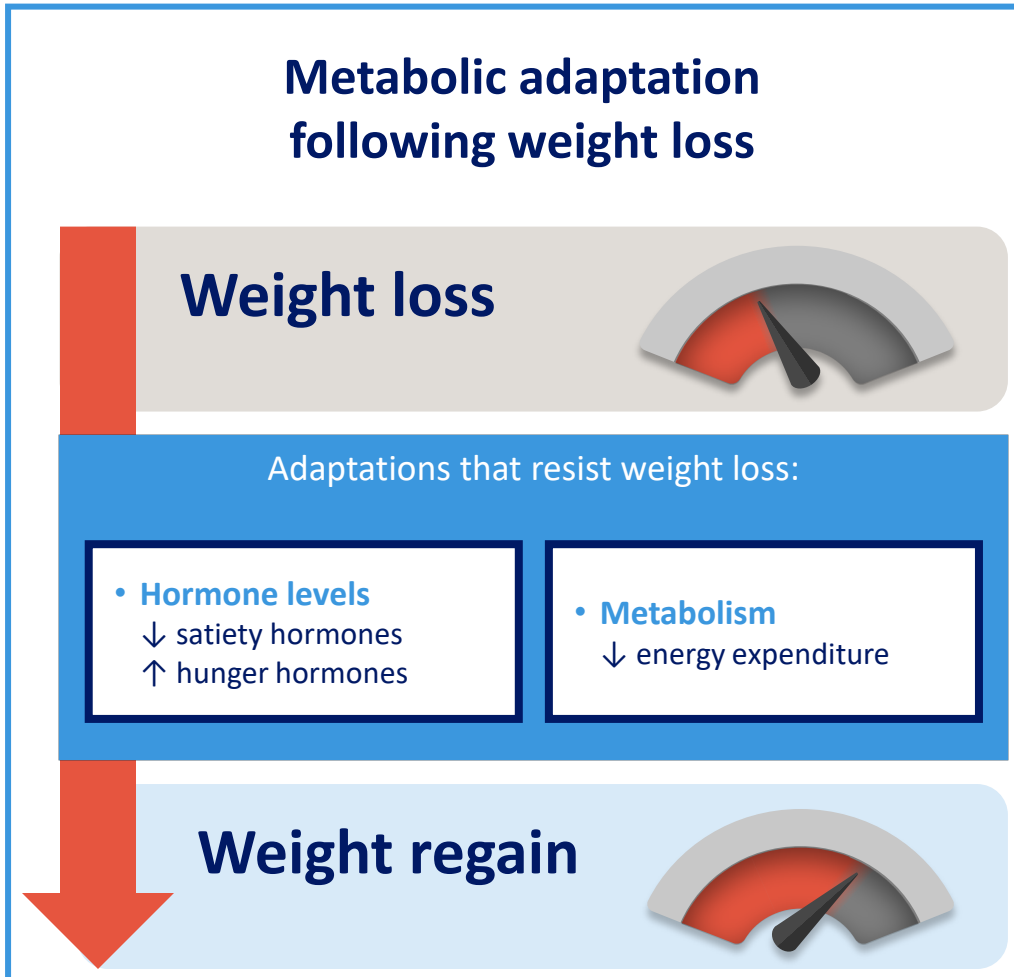
There are very few bariatric surgery studies reporting long-term results with sufficient follow-up of patients - only 29 of 7371 with at least 2-year follow-up …

Obesity is a relapsing disease

Maintenance of weight loss



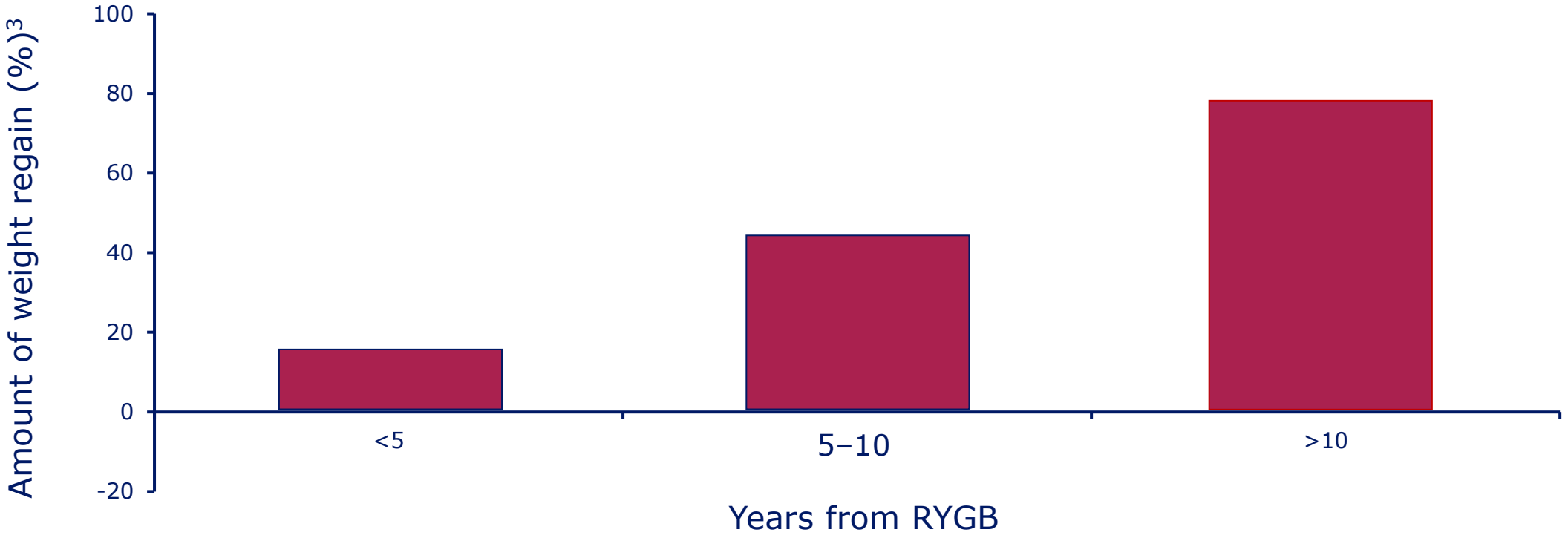
Metabolic adaptation following weight loss



Nordmo et al. Obes Rev 2019. doi: 10.1111/obr.12949. Fothergill E, Guo J, Howard L, et al. Obesity (Silver Spring). 2016;24:1612–1619; Sumithran P, Prendergast LA, Delbridge E, et al. N Engl J Med. 2011;365:1597–1604

Weight regain after bariatric surgery

- Significant WR (≥15%) occurs in **25–35%** of patients 2–5 years after surgery[1]
- However, there is no generally accepted definition for WR. Most are based on kg, BMI units or %EWL[2]



BMI, body mass index; EWL, excess weight loss; RYGB, Roux-en-Y gastric bypass; WR, weight regain

1. Cooper *et al. Obes Surg* 2015;25:1474–81; 2. Karmali *et al. Obes Surg* 2013;23:1922–33; 3. Jirapinyo *et al. BMJ Open Gastroenterol* 2017;4:e000153

Cause di Weight Regain

- Variazioni endocrino metaboliche
- Scarsa aderenza alla dieta e ai follow up
- Inattività fisica
- Disturbi dell'umore – Disturbi del comportamento alimentare
- Problematiche anatomiche/chirurgiche

Gastrointestinal Hormones in Weight Regain 2 Years After Roux-en-Y gastric bypass

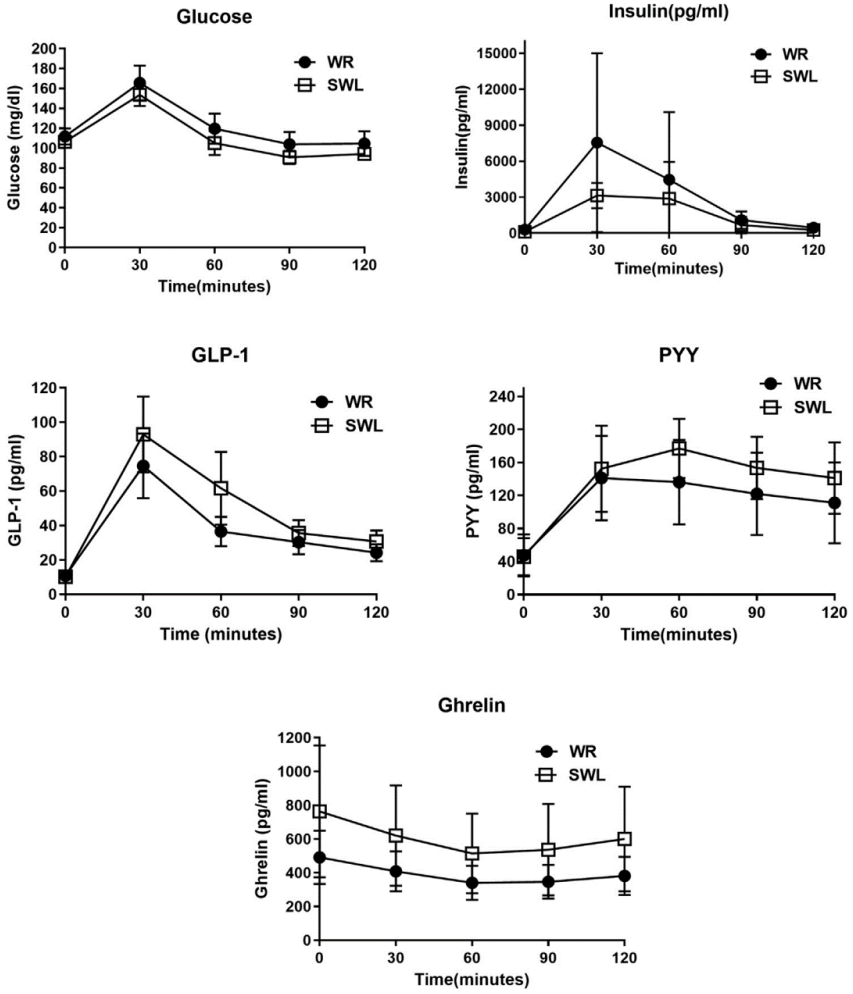


Table 3
Glucose, insulin, and gut hormonal response to meal stimulation

Variables	WR (n = 17)	SWL (n = 17)	*P* value
Glucose, mg/dL			
Fasting glucose	111.8 ± 15.5	106.4 ± 7.1	.199
Glucose $AUC_{0–120}$	14,919.7 ± 2940.0	13,486.8 ± 1609.5	.087
iGlucose $AUC_{0–120}$	1507.9 ± 1676.7	724.4 ± 978.2	.108
Insulin, pg/mL			
Fasting insulin	293.6 ± 109.3	113.2 ± 56.0	<.001
Insulin $AUC_{0–120}$	404,267.6 ± 309,978.2	206,852.6 ± 119,736.7	.020
iInsulin $AUC_{0–120}$	369,037.1 ± 300,262.1	193,264.4 ± 115,083.6	.031
Gut hormones			
GLP-1, pg/mL			
Fasting GLP-1	10.8 ± 5.8	10.0 ± 7.1	.708
GLP-1 $AUC_{0–120}$	4766.6 ± 1774.2	6314.6 ± 2407.2	.041
iGLP-1 $AUC_{0–120}$	3467.0 ± 1638.4	5115.3 ± 2157.9	.017
PYY, pg/mL			
Fasting PYY	47.6 ± 49.6	45.9 ± 43.7	.916
PYY $AUC_{0–120}$	14,357.6 ± 10,575.0	17,294.1 ± 8580.2	.381
iPYY $AUC_{0–120}$	8640.0 ± 7245.3	11,781.2 ± 5391.3	.161
Ghrelin, pg/mL			
Fasting ghrelin	491.3 ± 307.1	763.1 ± 759.8	.181
Ghrelin $AUC_{0–120}$	45,957.4 ± 26,076.1	70,586.5 ± 67,242.3	.169
iGhrelin $AUC_{0–120}$	−12,997.9 ± 12,197.4	−20,980.6 ± 24,608.5	.240
Insulin sensitivity index			
HOMA-IR	1.9 ± .7	.7 ± .4	<.001
Insulin sensitivity (Matsuda) index	5.4 ± 4.5	11.3 ± 5.2	.001

WR = weight regain; SWL = sustained weight loss; AUC = area under the curve; i = incremental; GLP-1 = glucagon like peptide-1; PYY = peptide YY; HOMA-IR = homeostatic model assessment of insulin resistance.
Data are presented as means ± standard deviation.

Shantavasinkul PC, Metabolic profiles, energy expenditures, and body compositions of the weight regain versus sustained weight loss patients who underwent Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2021 Dec

Luca Busetto[1] · Silvia Bettini[1] · Giulia Maria Pontesilli[1]

Scarsa aderenza alla dieta e inattività fisica

Con il passare del tempo, anche a causa delle alterazioni nei livelli di ormoni intestinali precedentemente citate, il paziente post-chirurgico tende ad aumentare l'intake calorico, spesso facendo scelte alimentari non aderenti alle indicazioni dietetiche fornite dagli specialisti: aumenta l'assunzione di cibi processati e/o ad alto contenuto calorico, di cibi fritti, di carboidrati raffinati, di bevande ricche di calorie e consuma un'insufficiente quantità di cibi a elevato contenuto di proteine o di fibre.

A questo squilibrio dietetico spesso si associa anche lo svolgimento di un'insufficiente quantità di esercizio fisico (generalmente considerata inferiore ai 150 minuti settimanali), legata alle varie 'barriere all'esercizio fisico'

Prevention and management	
Behavioral	Cognitive behavioral therapy, remote acceptance-based behavioral intervention, lifestyle counseling [87–90]
Dietary	Counseling with dietitian, structured dietary intervention [91–94]
Pharmacological	FDA approved: phentermine, phentermine–topiramate extended release, liraglutide, bupropion/naltrexone
	Off label: metformin, topiramate, zonisamide, bupropion [95–98]

Weight Regain and Insufficient Weight Loss After Bariatric Surgery: Definitions, Prevalence, Mechanisms, Predictors, Prevention and Management Strategies, and Knowledge Gaps—a Scoping Review

Walid El Ansari[1,2,3] · Wahiba Elhag[4]

Due to the complex etiology of WR and IWL, a multidisciplinary approach to treatment ensures effective long-term success

Managing severe obesity: understanding and improving treatment adherence in bariatric surgery

Megan M. Hood[1] · Joyce Corsica[1] · Lauren Bradley[1] · Rebecca Wilson[1] · Diana A. Chirinos[1] · Amanda Vivo[1]

J Behav Med
DOI 10.1007/s10865-016-9772-4

The self-management of health behaviors, such as regular attendance at pre- and post-operative medical appointments and following stringent dietary, exercise, and vitamin-use guidelines, is often assumed to be critical to achieving a positive outcome after bariatric surgery.

There is strong evidence that adherence to follow-up appointments is associated with greater weight loss.

Weight regain may lead to the reemergence of comorbid medical or psychological conditions

Patients may be more vulnerable to deviation from nutritional recommendations later because in the first 1–2 years after surgery, weight loss appears to occur at a similar rate regardless of adherence.

A number of studies suggest that preoperative binge eating and loss of control eating are associated with poorer weight loss after surgery

Sarwer et al. (2008) found that baseline depression, negative mood, caloric intake, and percent of calories from sweets were negatively associated with post-operative dietary adherence, whereas positive mood, self-esteem, cognitive restraint, and percent of calories from protein were positively associated with post-operative dietary adherence

Exercise is a strong predictor of weight loss, but is the most common domain of nonadherence.

Dieta ed esercizio fisico

In un campione di 2022 pazienti arruolati nello studio Longitudinal Assessment of Bariatric Surgery-2 (LABS-2), uno studio prospettico osservazionale condotto in 10 centri bariatrici statunitensi, tre variabili comportamentali spiegano la maggior parte della variabilità (16%) nella perdita di peso a 3 anni dall'intervento di bypass gastrico: l'esecuzione dell'automonitoraggio settimanale del peso, il fatto di continuare a mangiare anche quando ci si sente pieni e il fatto di mangiare continuamente durante il giorno (Mitchell JE et al)

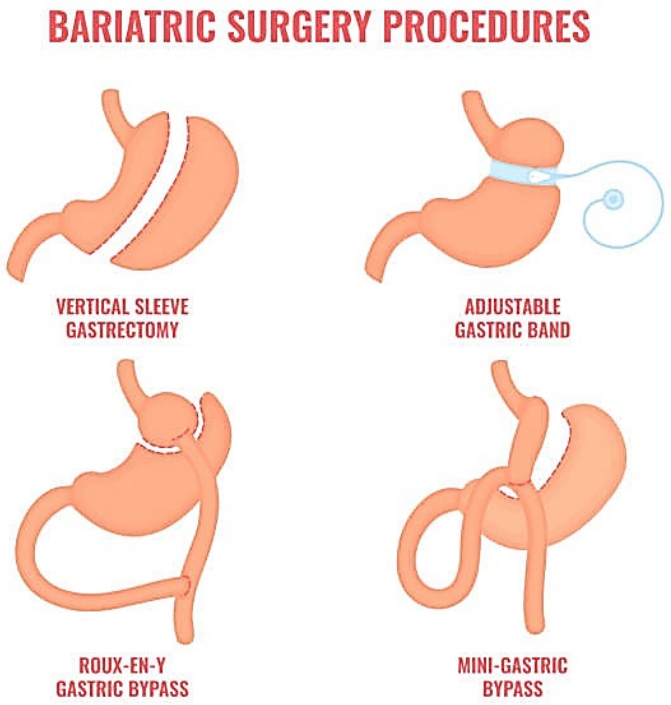
La partecipazione a programmi strutturati di intervento fisico dopo chirurgia era associato a un significativo miglioramento della fitness e della forza muscolare (Bellicha A et al)

The Role of Pharmacotherapy

Pre Bariatric Surgery

1. **Treat Metabolic Syndrome:**
   - ↑ EWL post-op [1]
   - ↓ Reduce hospital stay [1]
   - ↓ Post-op complications [2]
2. **Reduce Risk in Anesthesia**
3. **BMI > 65*** pre-surgical weight loss is mandatory to **reduce intra-abdominal volume** and **achieve operability** [3]
4. **Patients non-responsive to lifestyle intervention** [4]

* BMI > 55 main risk factor for unfavourable outcomes (SICOB guidelines 2016)



Post Bariatric Surgery

1. **Weight Regain** [5] (≥ 25 weight loss)
2. **Insufficient Weight Loss** [5] (< 50% EWL)
3. **Patients desiring further weight loss** [6]
1. **Patients with no indication for bariatric surgery** [7] (BMI < 40): endoscopic surgery

1. Hutcheon DA et al. J Am Coll Surg. 2018;226(4):514-524; 2. Cassie S et al. Surg Obes Relat Dis. 2011;7(6):760-7; 3. Stier et al. Diabetes 2015;64:A43; 4. Malone et al. Ann Pharmacother 2012;46:779–84; 5. Vinciguerra F, et al. 2021 Apr 1. doi: 10.23736/S2724-6507.21.03311-3; 6. Thakur U, et al. Obes Surg. 2021;31(1):84-92; 7. Badurdeen D, et al. Gastrointest Endosc. 2021 Jun;93(6):1316-1324.e1.

Liraglutide 3.0 mg for the management of insufficient weight loss or excessive weight regain post-bariatric surgery

Sean Wharton[1,2] | Jennifer L. Kuk[2] | Magdalena Luszczynski[1] | Elham Kamran[1] | Rebecca A. G. Christensen[1]

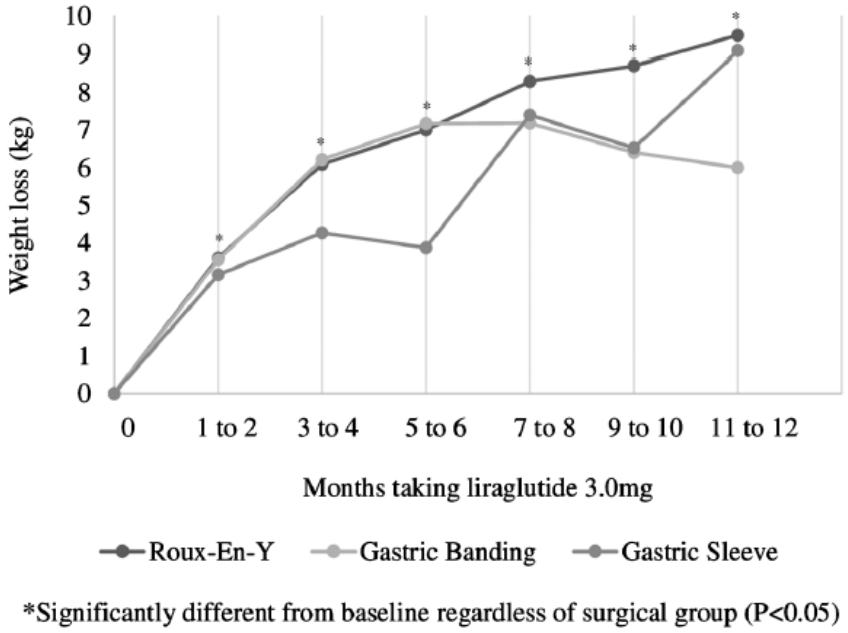
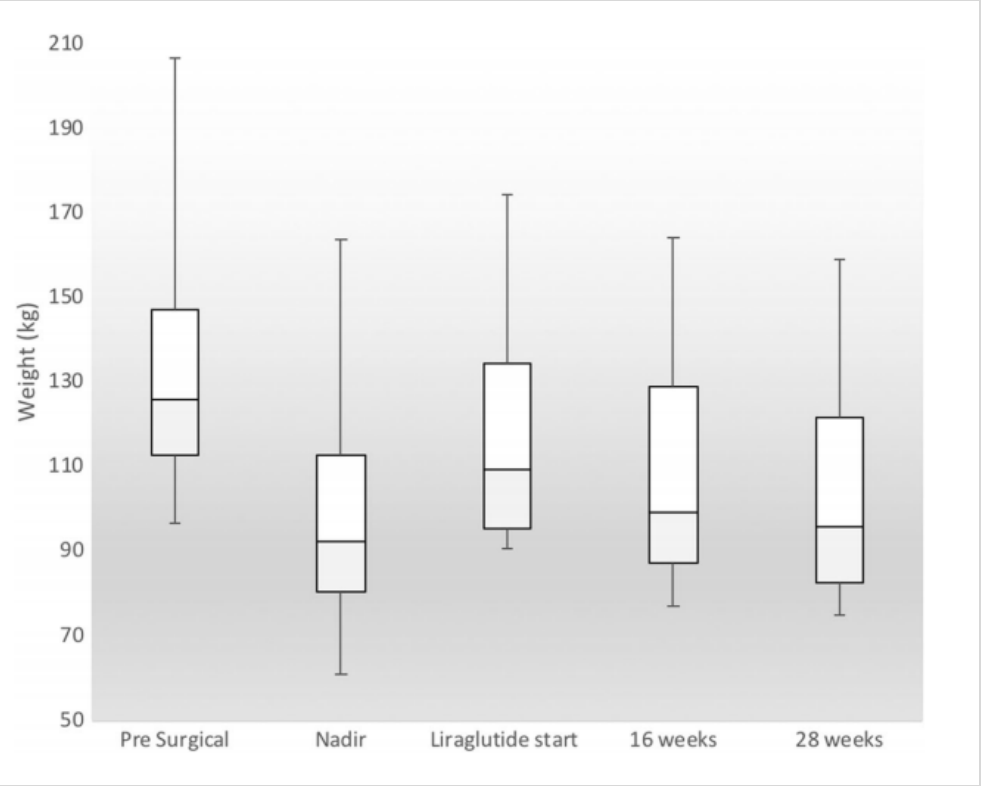


FIGURE 1 Weight loss while taking liraglutide 3.0 mg over time by type of bariatric surgery

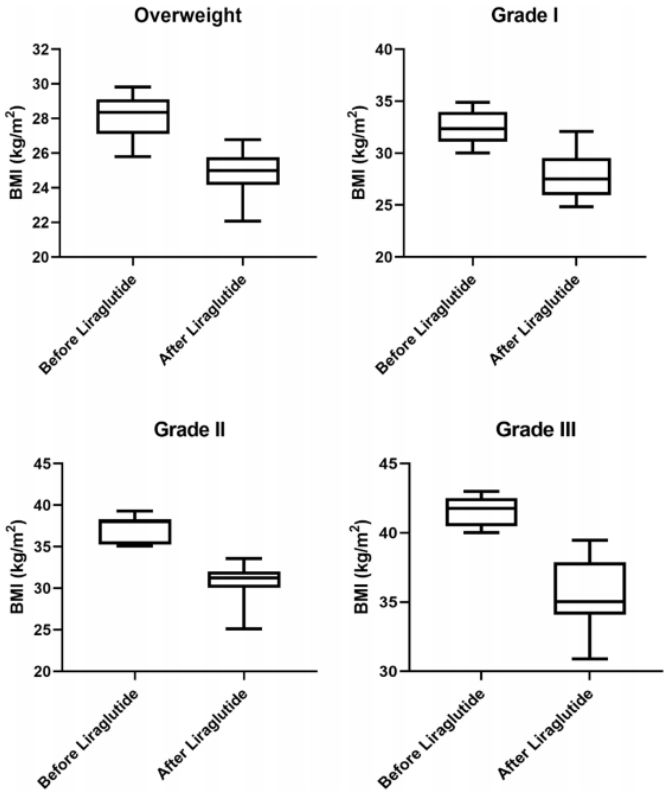
In summary, in our centre, we found that post-bariatric surgery patients with insufficient weight loss or excessive weight regain who use liraglutide 3.0 mg were able to achieve a statistically significant weight loss, regardless of the type of bariatric surgery they had undergone. In addition, post-bariatric surgery patients taking liraglutide 3.0 mg continue to lose weight at 1 year. Further, post-bariatric surgery patients taking liraglutide 3.0 mg have a similar side effect profile as what is observed in patients without bariatric surgery, with the exception being potentially more severe adverse events reported.

Efficacy of High-Dose Liraglutide as an Adjunct for Weight Loss in Patients with Prior Bariatric Surgery

Peter Rye[1] · Renuca Modi[2,3] · Sarah Cawsey[3,4] · Arya M. Sharma[3,4]



- We performed a retrospective chart review of 33 consecutive patients, aged 18–65, who received liraglutide for weight loss in the setting of any previous bariatric surgery.
- There is a growing body of data suggesting that pharmacotherapy, including liraglutide, is a useful adjunct to bariatric surgery in achieving further weight loss



Abstract

Purpose Bariatric surgery, as Roux-en-Y gastric bypass (RYGB), laparoscopic gastric banding (LGB), and laparoscopic sleeve gastrectomy (LSG), is considered the gold standard treatment to achieve long-term weight loss in severe obesity. In patients who fail to maintain the achieved weight, pharmacological treatment may be required. Here, we reported our real-life experience on the efficacy of liraglutide therapy in 62 patients who regained weight after bariatric surgery.

Methods We retrospectively evaluated 62 (60 F-2 M; mean age: 43.6 ± 9.9 years) patients received liraglutide for weight loss after bariatric surgery (17 RYGB, 22 LGB, and 23 LSG). Body mass index (BMI) before and after surgery was, respectively, of 45.4 ± 5.5 kg/m^2 and 29.5 ± 4.9 kg/m^2. Patients were followed up from 2016 until 2021. Liraglutide was administered after weight regain once-daily subcutaneously at starting dose of 0.6 mg and with weekly increases up to 3.0 mg. Treatments were administered when a weight regain of 10–15% occurred after reaching a minimum weight loss from bariatric surgery or if weight loss after bariatric surgery was unsatisfactory.

Results After a mean of 70.7 ± 43.7 months from any bariatric surgery, all patients started liraglutide therapy. At this time, mean BMI was 34.2 ± 4.8 kg/m^2 (mean increased BMI: 4.7 ± 2.8 kg/m^2). After a mean of 10.5 ± 4.4 months from the beginning of liraglutide, 9 patients achieved normal weight (BMI 24.1 ± 0.9 kg/m^2), and 28 were overweight (BMI 26.9 ± 1.6 kg/m^2). Twenty patients achieved grade I (BMI 32.1 ± 1.5 kg/m^2), 5 grade II (BMI 37.3 ± 2.0 kg/m^2) obesity, and none had grade III obesity (mean BMI change: − 5.1 ± 2.5 kg/m^2). The treatment was well tolerated, and no serious adverse events were recorded.

Conclusion These data confirm the efficacy and safety of liraglutide in patients who experienced weight regain after bariatric surgery. Considering the long-term follow-up, patients should be followed up regularly and the pharmacological treatment should be adapted to the weight fluctuations observed during the clinical history.

Efficacy of liraglutide 3.0 mg treatment on weight loss in patients with weight regain after bariatric surgery

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Emoglob.Glicata HbA1c [%]
Cambia Visualizzazione
semaglutide start
9,0
8,0
7,0
6,0
5,0
4,0
18/05/2021
16/06/2021
28/09/2021
25/10/2021
04/01/2022
04/04/2022
05/07/2022
20/10/2022
Peso [kg]
Cambia Visualizzazione
SG
160,0
140,0
120,0
100,0
80,0
60,0
40,0
20,0
0,0
18/05/2021
16/06/2021
28/09/2021
25/10/2021
04/01/2022
04/04/2022
05/07/2022
20/10/2022
BMI [Kg/m²]
Cambia Visualizzazione
60,0
55,0
50,0
45,0
40,0
35,0
30,0
25,0
20,0
18/05/2021
16/06/2021
28/09/2021
25/10/2021
04/01/2022
04/04/2022
05/07/2022
20/10/2022

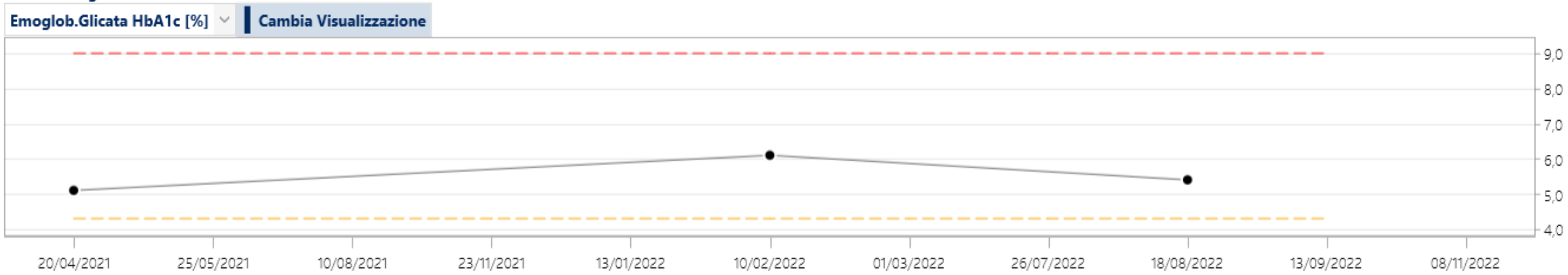
CASO CLINICO 2 M.P.

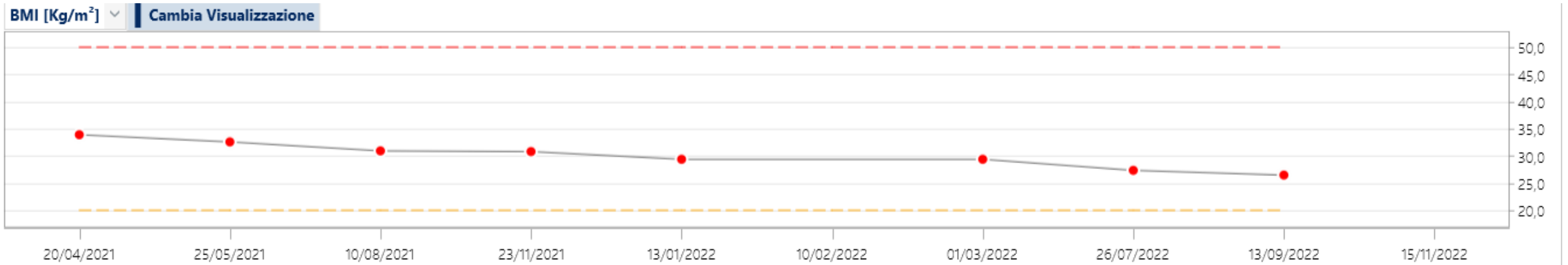
Paziente donna, di anni 61, diabetica dal 2017, fratello affetto da DM2

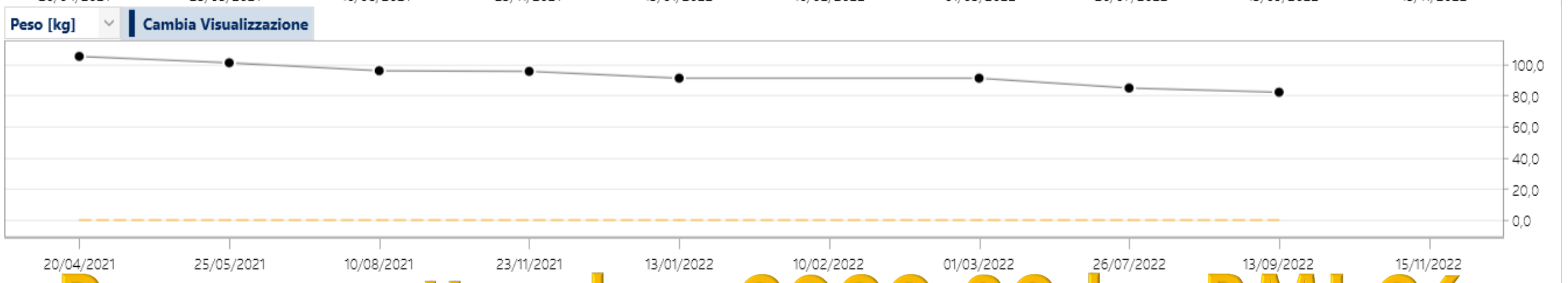
Seguita dai nostri ambulatori dal 2011, peso in prima valutazione 176 kg, ipotiroidismo in trattamento sostitutivo, sindrome ansioso depressiva. La paziente non è indirizzata al trattamento chirurgico ed afferisce con scarsa continuità ai nostri ambulatori seguendo un percorso dietoterapico. Nel 2017 rivalutata in prima visita Diabetologica per riscontro di DM di nuova insorgenza, HBa1c% pari a 6.8%.

La paziente in considerazione della diagnosi di DM rivaluta l'opportunità chirurgica e viene reindirizzata al centro multidisciplinare. A Gennaio 2018 la paziente viene sottoposta ad intervento di SG , in 2 anni raggiunge un peso al nadir di 90 kg mantenuto costante fino al periodo Covid.

Rivalutiamo la paziente ad aprile 2021 dove assistiamo ad una tendenza al weight regain (peso 105 kg). Si introduce semaglutide 0,5 fino a novembre 2021 e a segure titolato ad1mg OW







Peso a settembre 2022 82 kg BMI 26

TAKE HOME MESSAGES

La chirurgia bariatrica/metabolica è ad oggi la strategia più efficace per il trattamento dell'obesità complicata soprattutto se associata a patologia diabetica

Il paziente affetto da obesità è un paziente complesso sul profilo clinico e di conseguenza terapeutico con alto rischio di recidiva

La varietà dei quadri clinici rende perennemente necessario un approccio multimodale

Le strategie farmacologiche di supporto presenti e future mostrano un grado elevato di sicurezza efficacia e tollerabilità in tutte le fasi della storia clinica

Nei pazienti affetti da DM e obesità patologica è consigliabile effettuare delle scelte terapeutiche che consentano una terapia metabolica con impatto sul peso corporeo

In tutti le fasi del percorso si dimostra indispensabile il riconoscimento e il trattamento precoce e il follow up di tipo multidisciplinare

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