Belgium Menopause Society Symposium

Should our patients be treated with obesity medication ?

Saturday 23 Novembre 2024

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DECLARATION OF INTERESTS

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Laurent Crenier

- Honorariums for participations to advisory boards and / or speaker bureau for Abbott, Astra-Zeneca, Boehringer-Ingelheim, Dexcom, Eli Lilly, Medtronic, Menarini, LifeScan, Novo-Nordisk, Roche, Sanofi.

- Coverage of participation fees for scientific conferences by Eli Lilly, Novo-Nordisk, Sanofi.

Natural Incretins

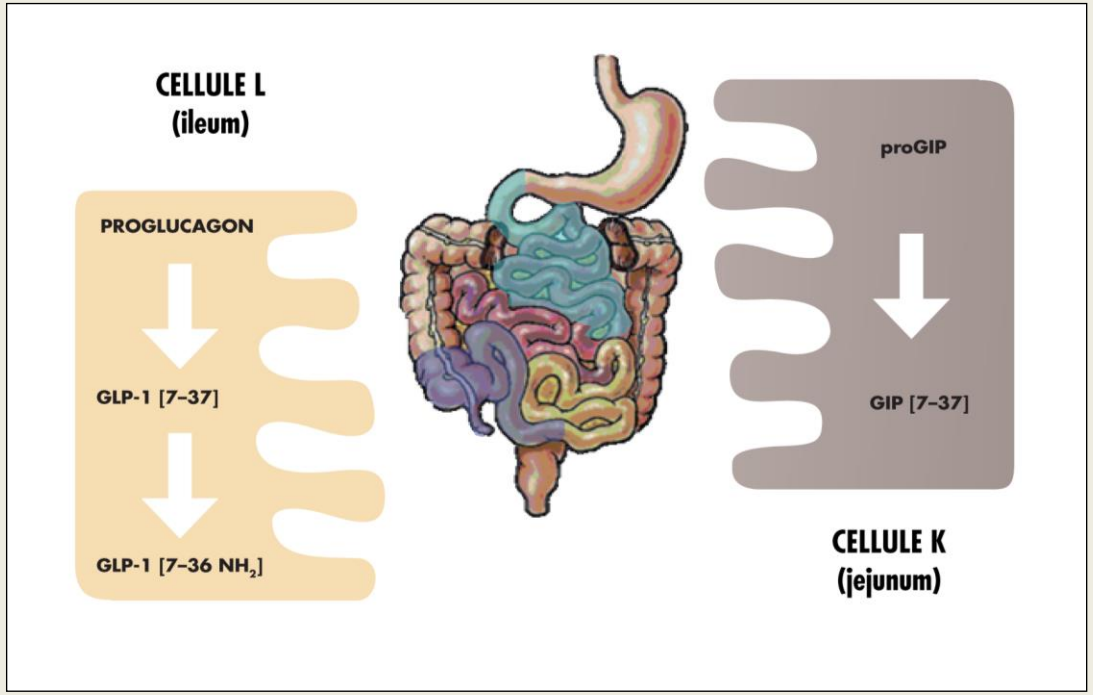
Intestinal hormones, secreted in response to food intake

GLP-1: Glucagon-Like peptide-1

- 31 amino acids Peptide (cleavage of pro-glucagon)
- Secreted by L cells (distal ileum & colonic mucosa)

GIP : Glucose-dependent insulinotropic polypeptide

- Previously called Gastric Inhibitory Peptide
- Peptide of 42 amino acids
- Secreted by K cells (duodenum & small intestine)



Enzymatic cleavage by DPP-4

→ **GLP-1 $t_{1/2}$ = 1.5–2.1 minutes**
GIP $t_{1/2}$ = 5–7 minutes

"Main" effect of incretin hormones :
gluco-dependant stimulation of insulin secretion

Glucacon-like peptide 1 Receptors agonists (GLP-1RA)

Incretinomimetics as Anti-Obesity Medication (AOM)

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First of its class : “Byetta”

- Exendin-4: Extracted from the saliva of the Gila Monster
- Exenatide: Synthetic Exendin-4 GLP-1 agonist

  (53% homology with GLP-1)
- Half-life: 2.4 hours
- Administered via s.c injection, 2 times per day
- Short duration of action

Reimbursed in Belgium since 1/1/2008 (Af)
Withdrawn from the market

Glucacon-like peptide 1 Receptors agonists (GLP-1RA)

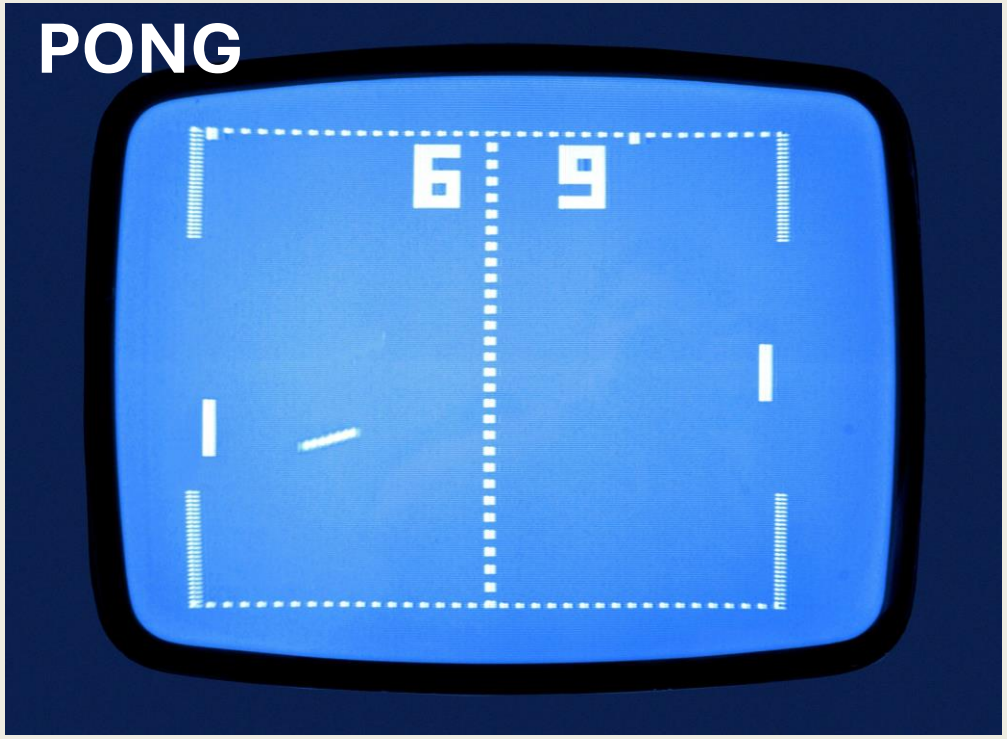
Incretinomimetics as Anti-Obesity Medications

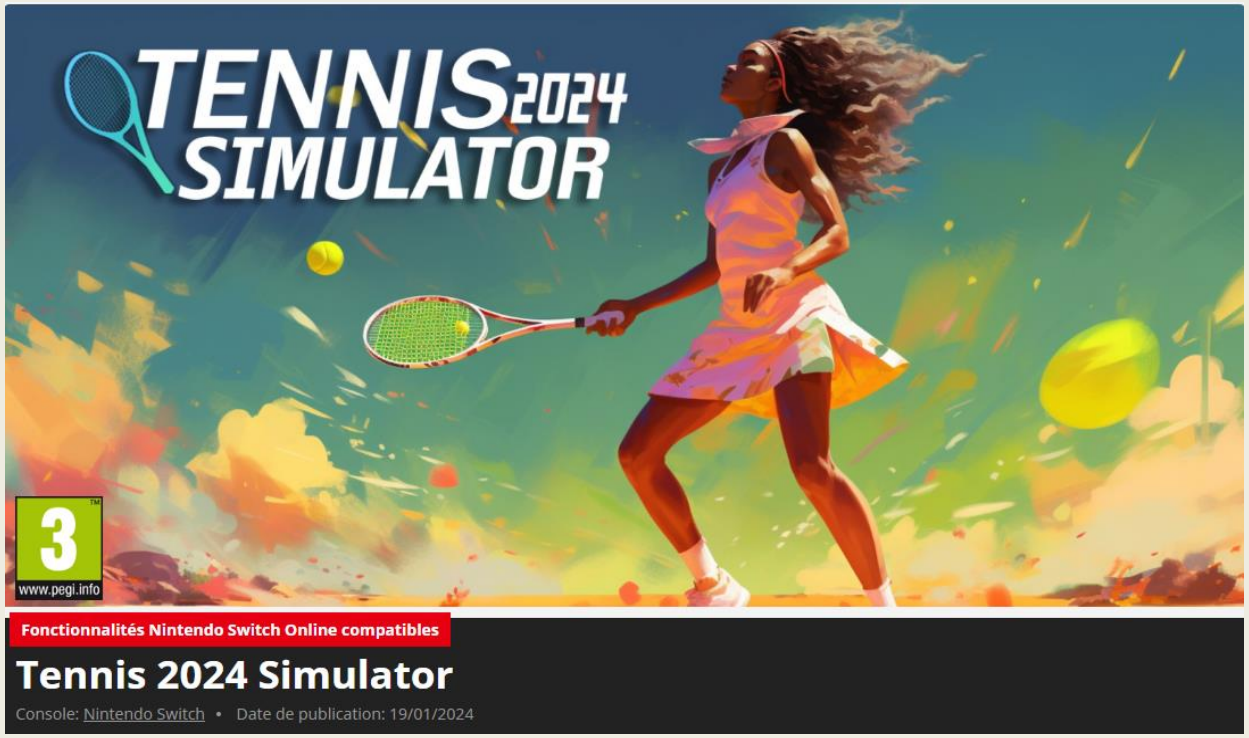
« Old » GLP-1 RA

Exenatide, lixisenatide, liraglutide

New generation of GLP-1 / dual GLP-1/ GIP RA

Dulaglutide, Semaglutide, Tirzepatide





Long acting GLP-1 Receptor Analogues (weekly injection)

- Human GLP-1 Analogues
- Resistant to DPP4 cleavage
- Prolonged half-life (several days)
  - Dulaglutide + Immunoglobulin Fc fragment
  - Semaglutide + fatty acid

- Rybelsus : oral semaglutide !
  - Semaglutide + Na salcaprozate (SNAC).

Oral semaglutide

GLP-1 / GIP Dual Receptors agonist

Tirzepatide

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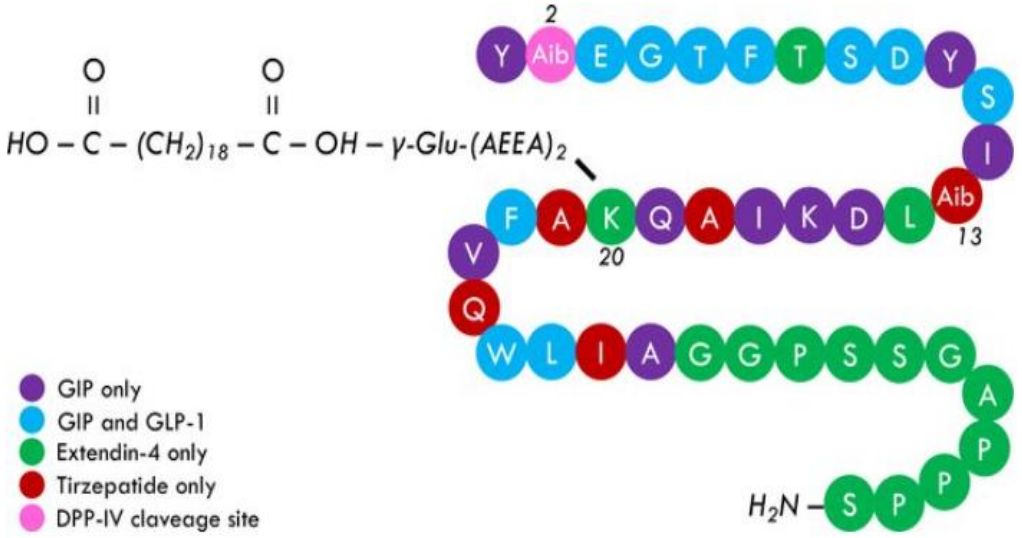
Tirzepatide : Long acting Dual GLP-1 / GIP Receptor agonist (weekly injection)

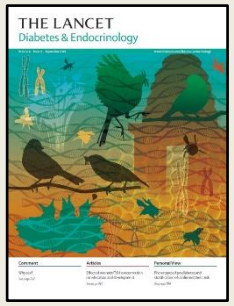
Tirzepatide : Dual GLP-1 / GIP Receptor agonist

Alpha aminobutyric acid



Glucacon-like peptide 1 Receptors analogues (GLP-1RA)

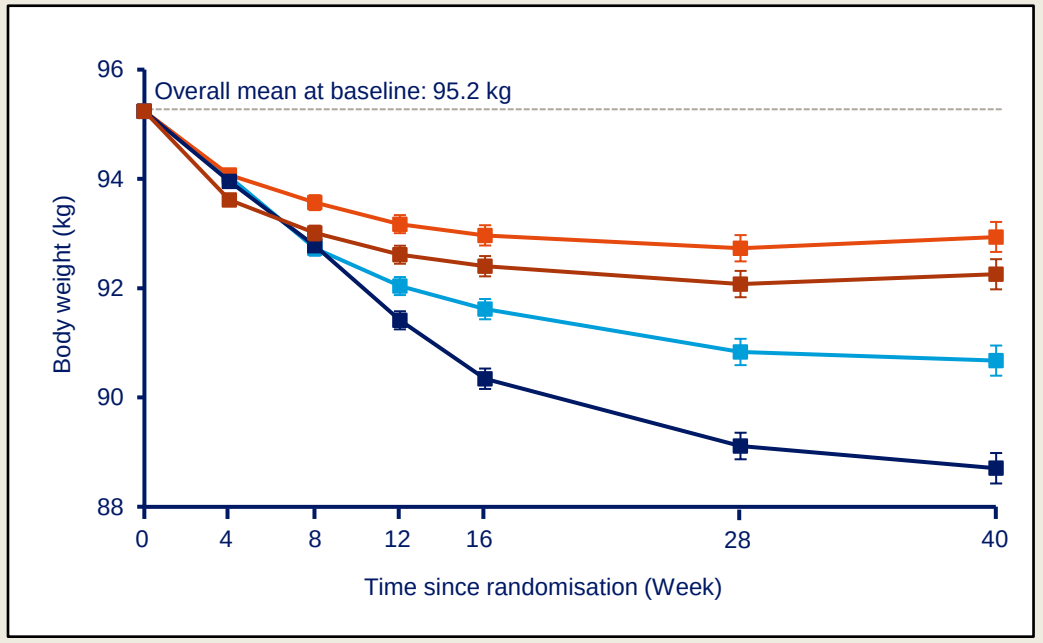
Semaglutide & Dulaglutide Weight Loss in patients with type 2 diabetes

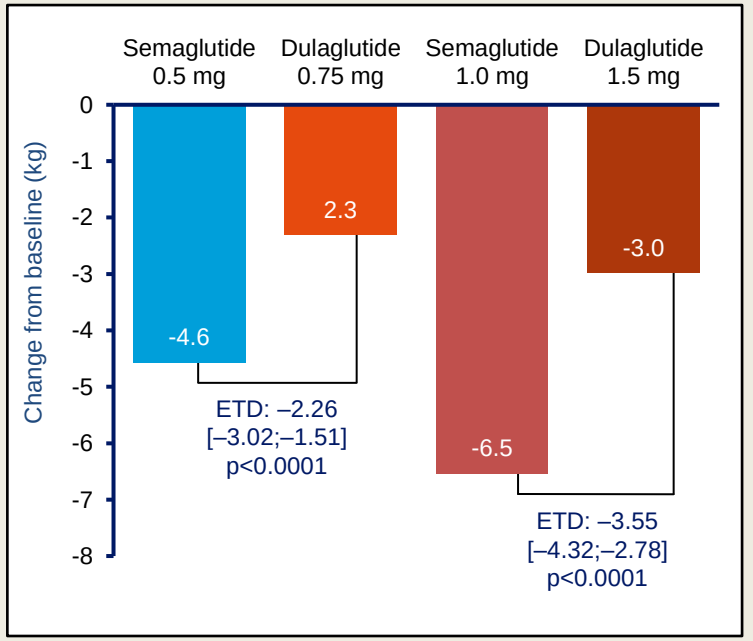


Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomized, open-label, phase 3b trial.

Pratley RE et al. *Lancet Diabetes Endocrinol* 2018;6:275–286.

Evolution du poids (en kg) après 40 semaines





Semaglutide 0.5 mg — Dulaglutide 0.75 mg — Semaglutide 1.0 mg — Dulaglutide 1.5 mg

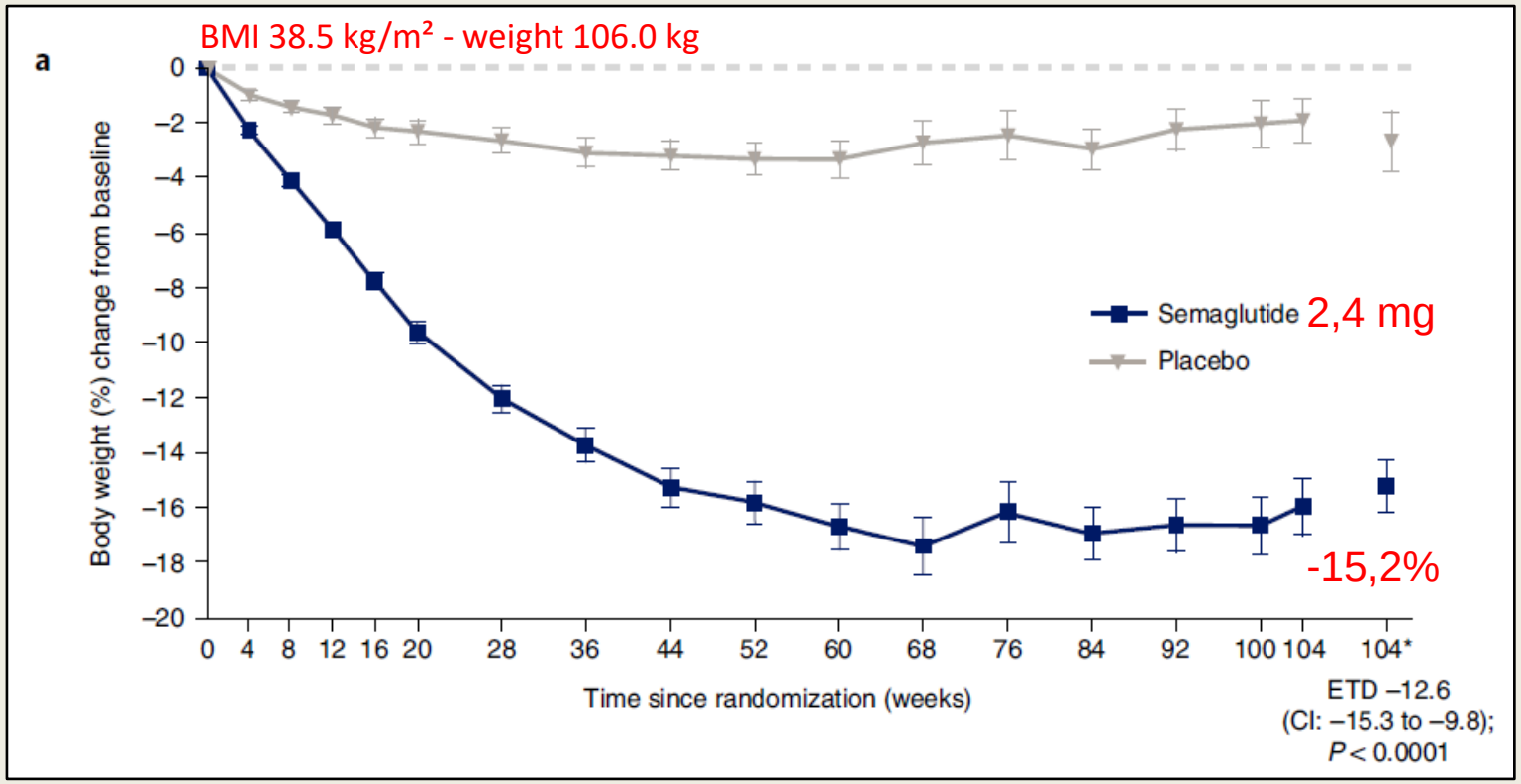
Values are estimated means with associated ETDs and 95% confidence intervals from a mixed model for repeated measurements analysis using data from all randomised patients exposed to at least one dose of trial product (full analysis set) using data obtained while on treatment and prior to onset of rescue medication. Dashed line indicates the overall mean value at baseline. ETD, estimated treatment difference.

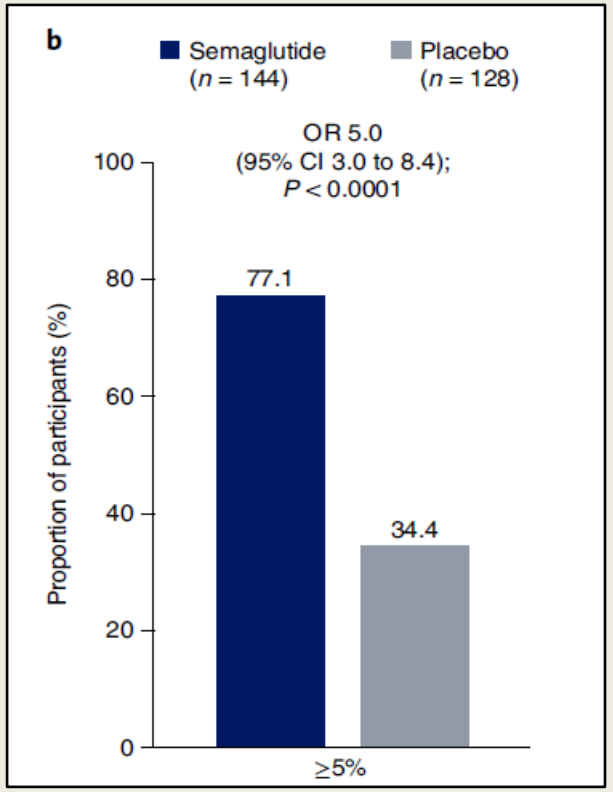
Glucacon-like peptide 1 Receptors analogues (GLP-1RA)

Semaglutide Weight Loss in obese patients

Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial (Wegovy)

Garvey WT et al. *Nat Med* 2022 Oct;28(10):2083-2091





Glucacon-like peptide 1 Receptors analogues (GLP-1RA)

Semaglutide Weight Loss in obese patients

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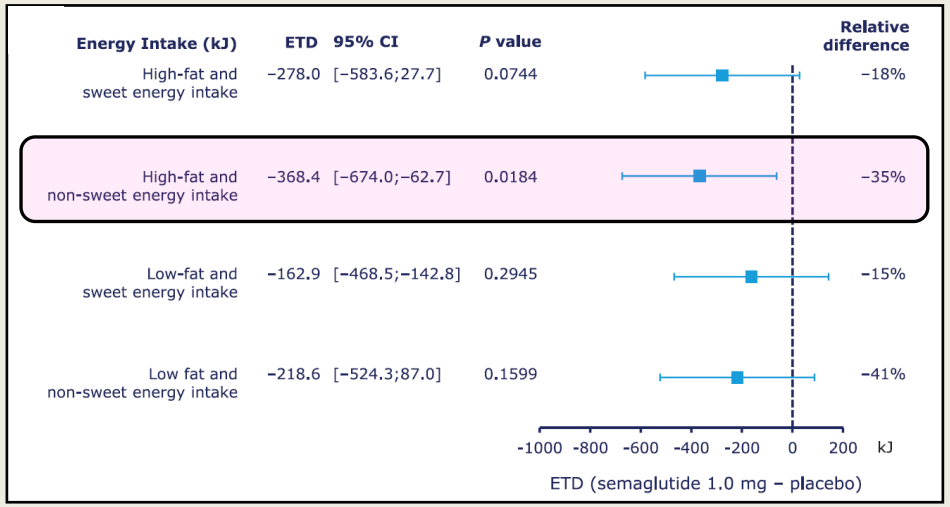
Semaglutide during 12 weeks in obese patients

Semaglutide reduces the preference for high caloric, high fat foods.

Energy intake of food categories in the ad libitum evening snack box



Food preference Leeds Food Preference Task

Ratings	Treatment difference, Semaglutide – placebo [95% CI]	*P* value
Explicit liking, High-fat and non-sweet (mm)	−13.9 [−22.5; −5.4]	0.0016
Explicit liking, High-fat and sweet (mm)	−3.9 [−12.5; 4.7]	0.3703
Explicit liking, Low-fat and non-sweet (mm)	−8.2 [−16.7; 0.4]	0.0612
Explicit liking, Low-fat and sweet (mm)	−3.5 [−12.1; 5.0]	0.4192
Implicit wanting, High-fat and non-sweet (no unit)	−15.8 [−29.1; −2.5]	0.0203
Implicit wanting, High-fat and sweet (no unit)	0.8 [−12.5; 14.1]	0.9063
Implicit wanting, Low-fat and non-sweet (no unit)	1.1 [−12.3; 14.4]	0.8766
Implicit wanting, Low-fat and sweet (no unit)	13.9 [0.6; 27.3]	0.0401

SPC Ozempic®: Semaglutide reduces body weight and body fat mass through lowered energy intake, involving an overall reduced appetite. In addition, semaglutide reduces the preference for high fat foods.

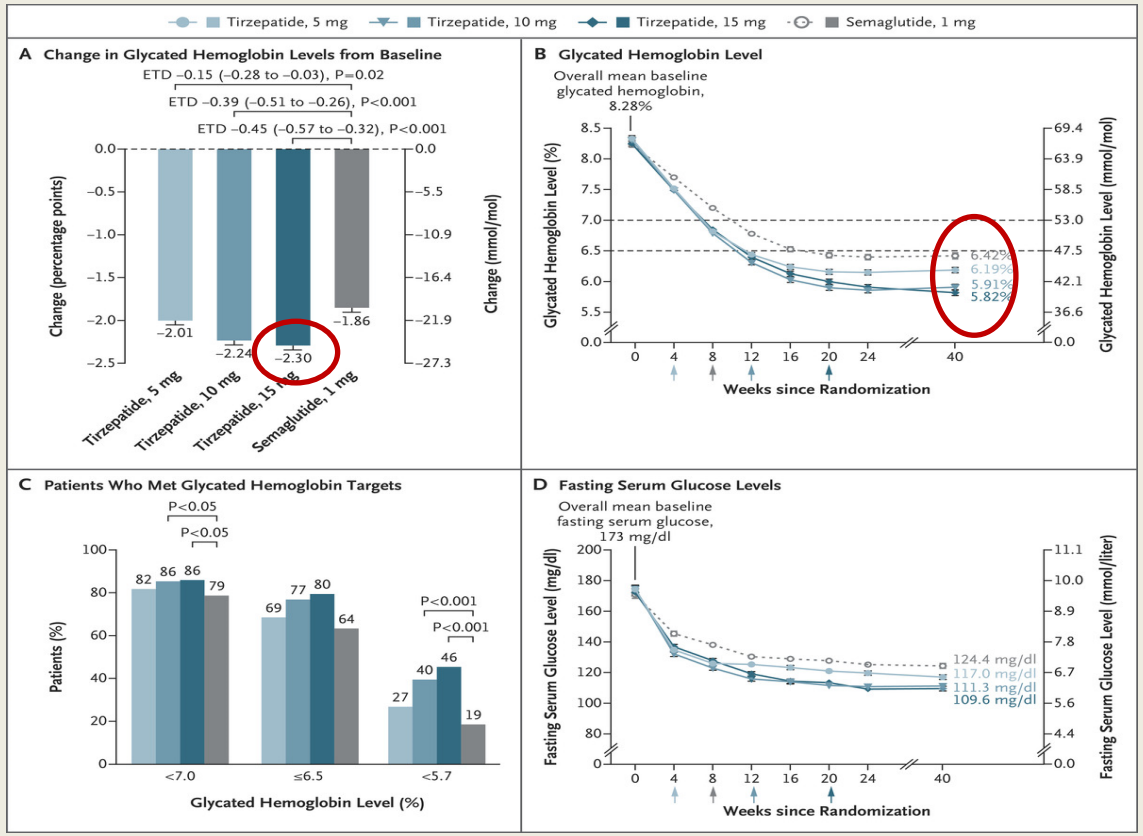
Blundell J et al. *Diabetes Obes Metab* 2017;19:1242–51.

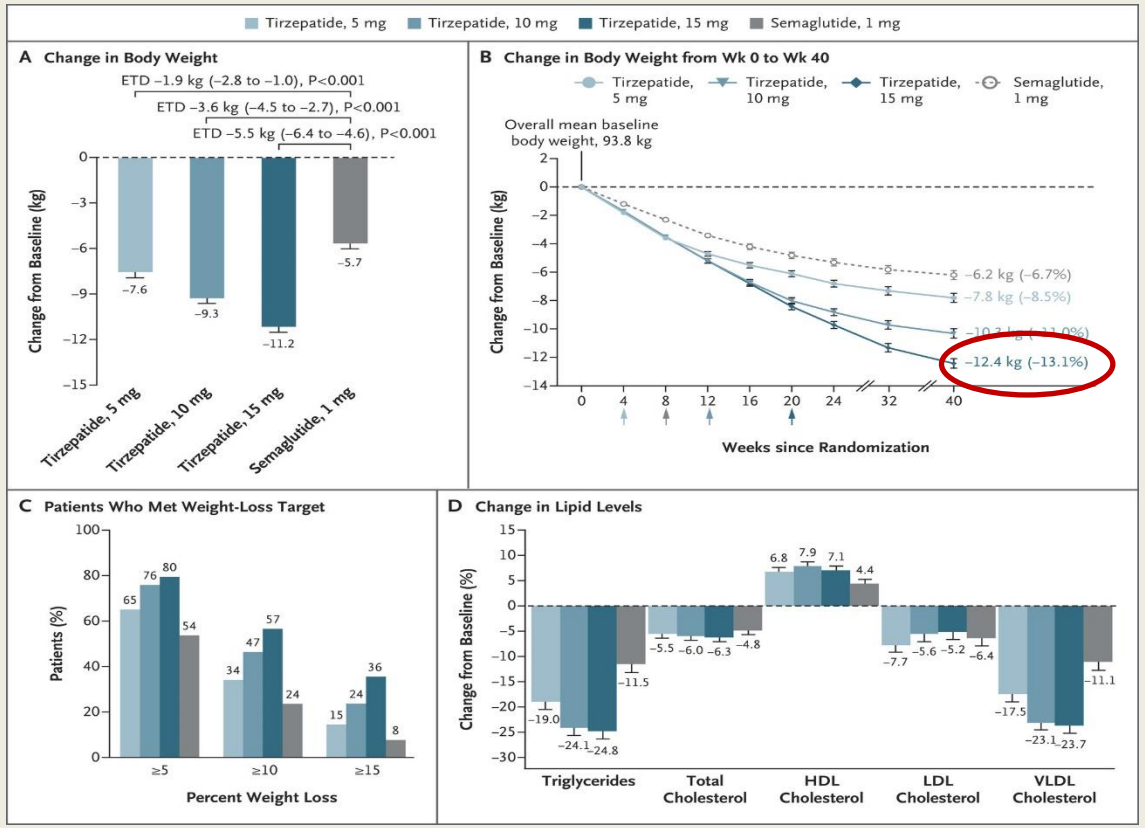
GLP-1 / GIP Dual Receptors agonist Tirzepatide

Tirzepatide in People with Type 2 Diabetes

Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes (SURPASS-2 Study)

JP Frías et al. *N Engl J Med* 2021;385:503-515.



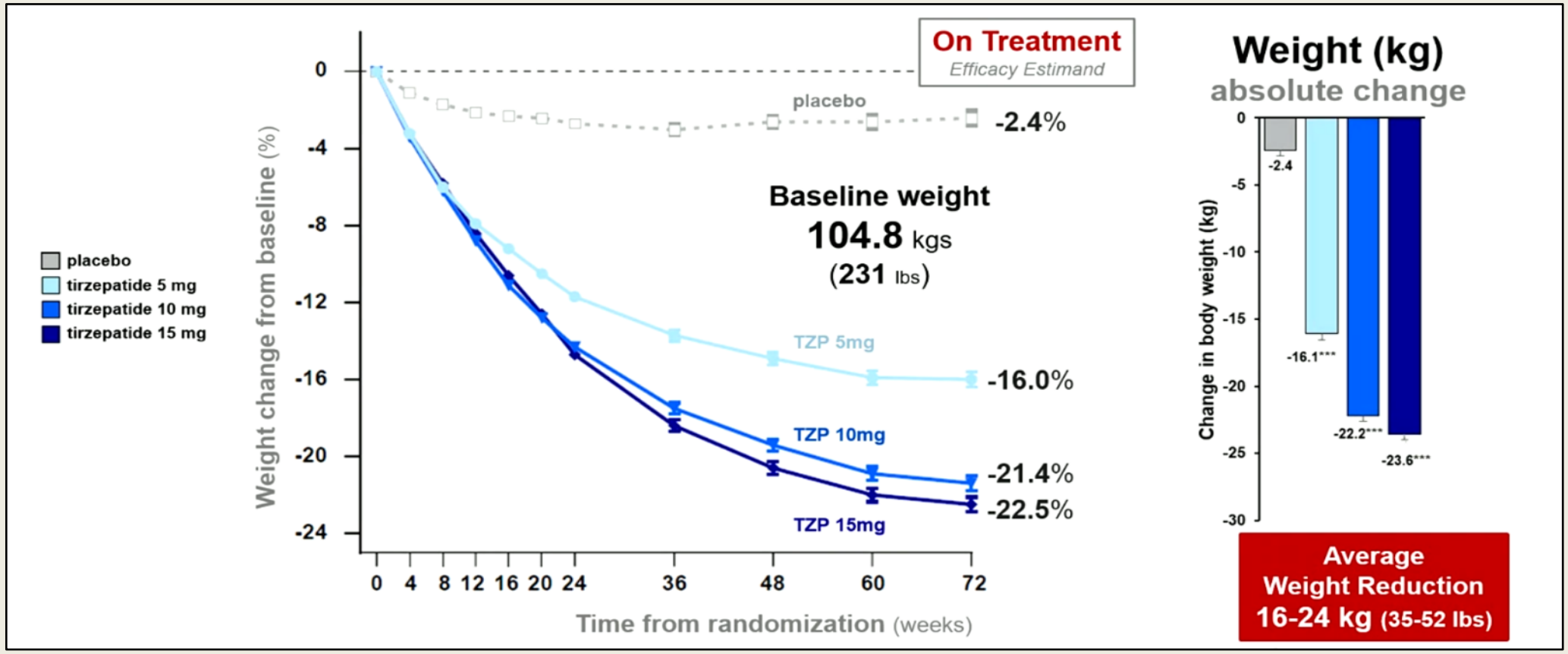


GLP-1 / GIP Dual Receptors agonist Tirzepatide

Tirzepatide Weight Loss in obese patients

Tirzepatide Once Weekly for the Treatment of Obesity (SURMOUNT-1 Study)

AM Jastreboff et al. *N Engl J Med* 2022;387:205-216.



Following these studies, The EMEA has granted Semaglutide & Tirzepatide the indications for :

- The treatment of Diabetes
- The Treatment of Obesity (BMI of 30 kg/m^2 or more)
- The treatment of Overweight (BMI > 27 kg/m^2) with weight-related health problems such as diabetes, abnormally high levels of fat in the blood, high blood pressure or obstructive sleep apnoea

Cardiometabolic Health after menopause

Multiple challenges !

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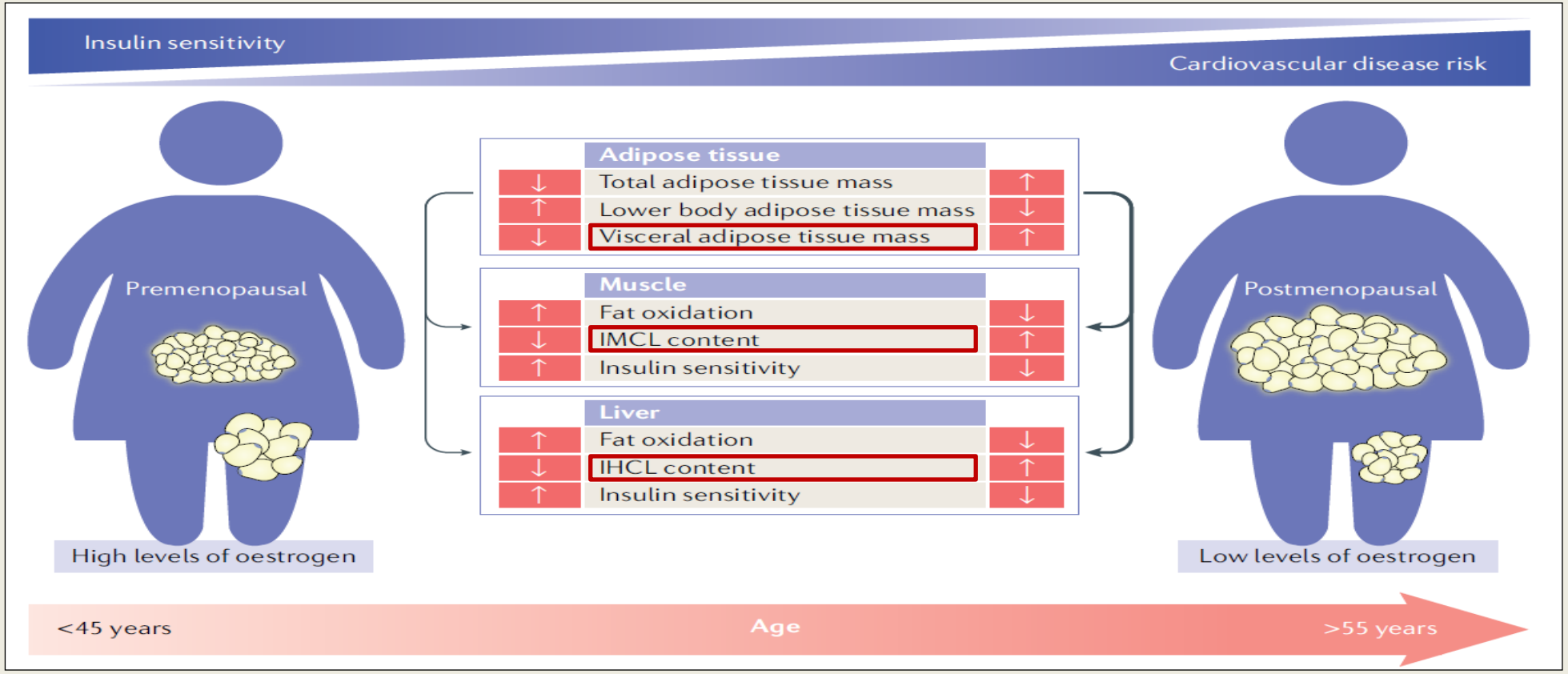
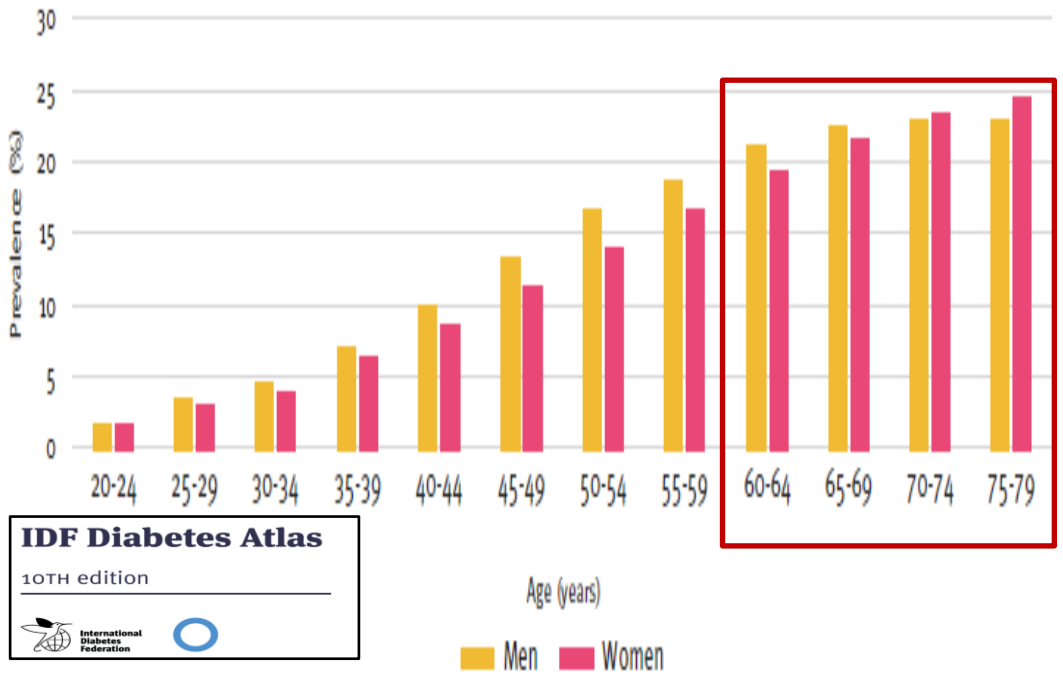
Menopause induces insulin resistance and increases cardiometabolic disease risk in women



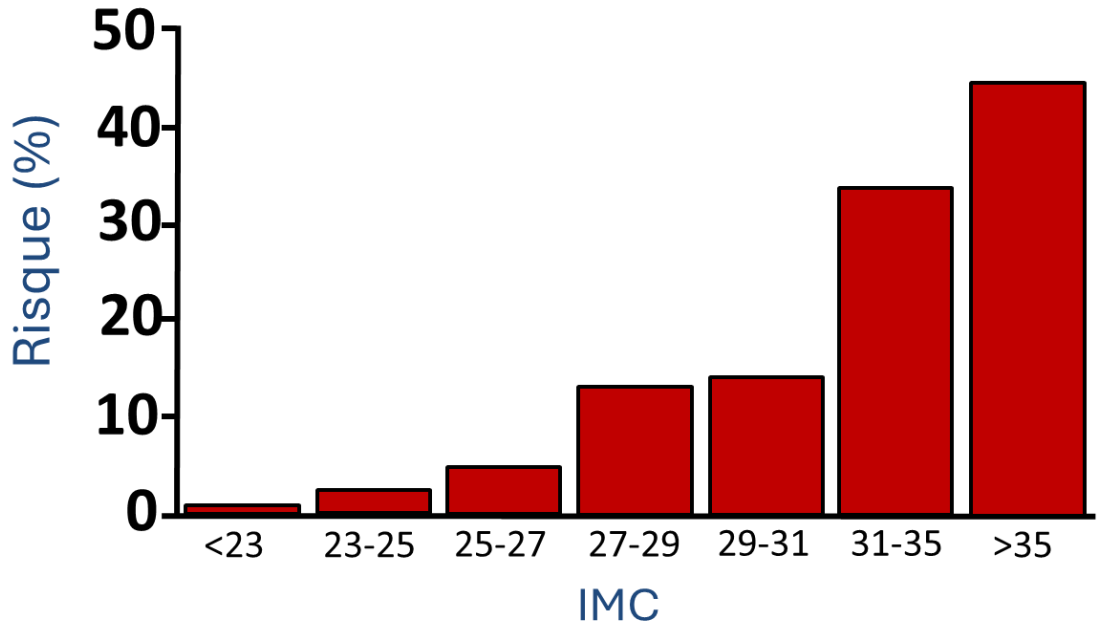
Goossens et al. *Nat Rev Endocrinol* 17, 47–66 (2021)

Diabetes : influence of Age and BMI

Prevalence of diabetes in function of age (2021)



Risque de developing diabetes in function of BMI



Chan et al. *Diabetes Care* 1994;17: 961-969

Cardiometabolic Health after menopause

Multiple challenges !

Menopause and Heart Disease

Association of menopausal characteristics and risk of coronary heart disease: a pan-European case–cohort analysis

From the EPIC-CVD Study

Table 2. Hazard ratio (HR) and 95% confidence intervals (CIs) for the association between menopausal status and any first CHD event

	Post-menopausal vs pre-menopausal		
Model	HR (95% CI)	*p*-value	PE% (95% CI)[a]
Age-adjusted model	1.23 (1.08–1.40)	0.002	/
Confounder-adjusted model[b]	1.13 (0.98–1.30)	0.09	40.5 (30.4–54.6)
Confounder- and intermediate-adjusted model[c]	1.08 (0.93–1.26)	0.29	60.7 (54.4–80.6)

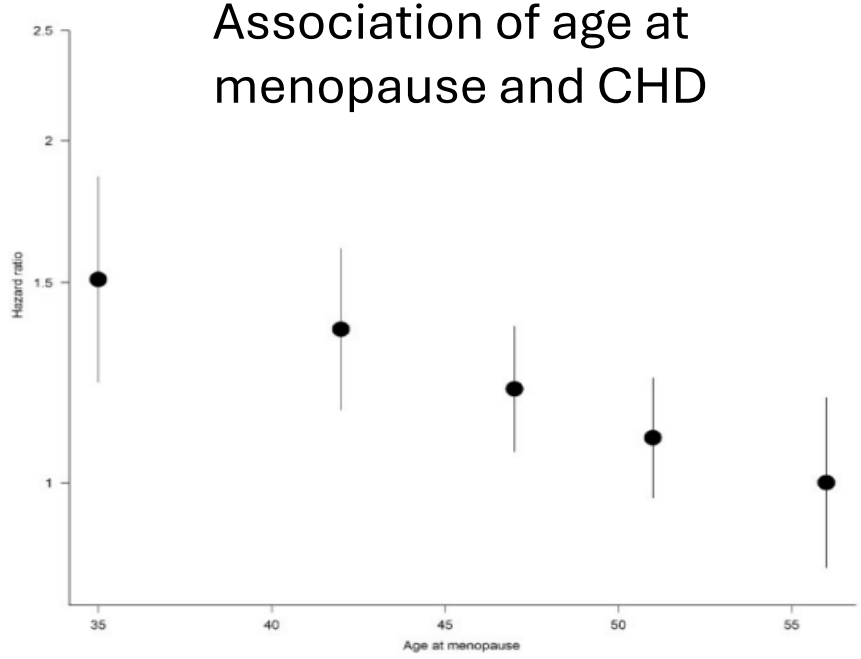
N (*N* of events): post-menopausal 9916 (4074), pre-menopausal 5486 (679).

[a]PE, proportion explained.

[b]Adjusted for baseline age, smoking status, BMI, HbA1c, education level, physical activity, full-term pregnancy, age at menarche and ever hormone use.

[c]Additionally adjusted for high-sensitivity C-reactive protein, total cholesterol, HDL-cholesterol, triglycerides and high blood pressure.

Association of age at menopause and CHD



Veerle Dam et al. *International Journal of Epidemiology*, 2019, Vol. 48, No. 4

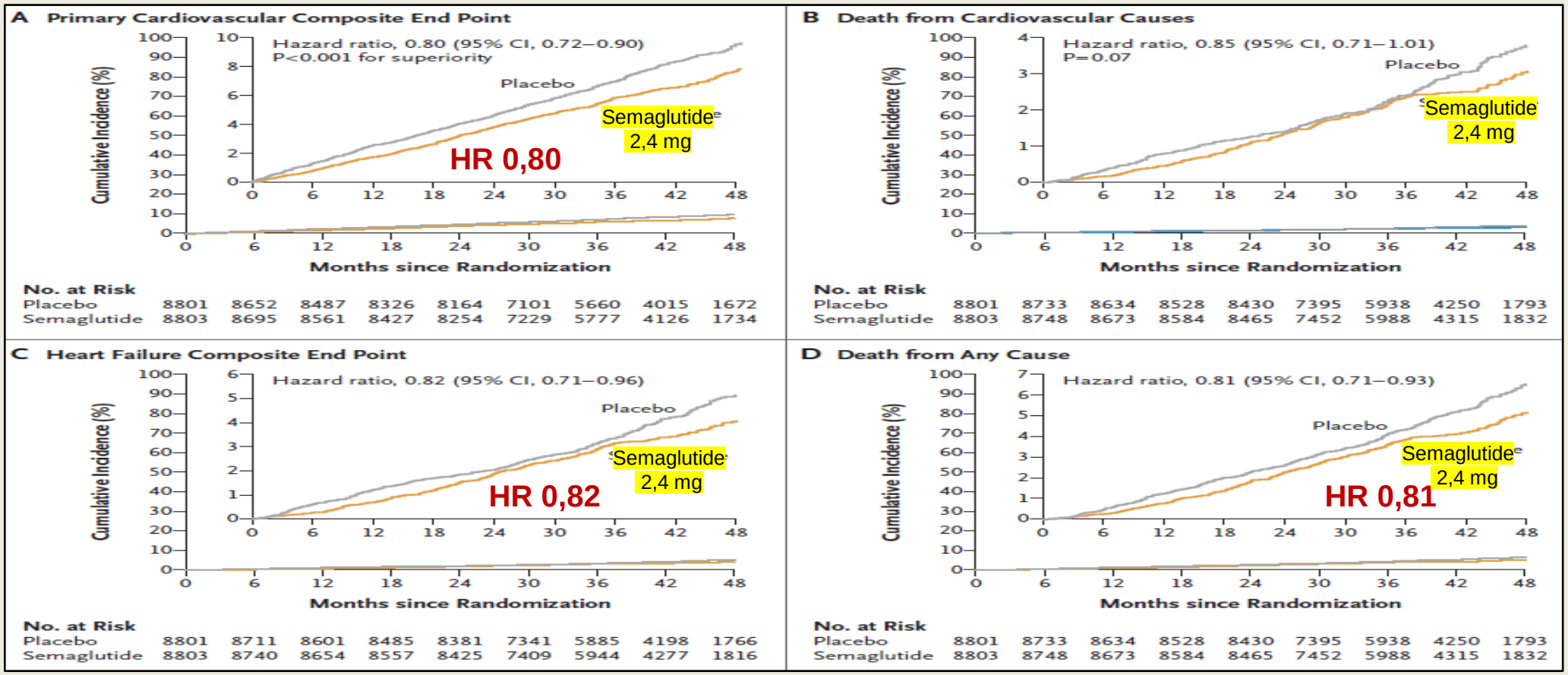
Glucacon-like peptide 1 Receptors analogues (GLP-1RA)

Cardiovascular Outcome Trials (CVOTs)

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes (STEP-1 Study)

Michael Lincoff et al. *N Engl J Med* 2023;389:2221-32.

BMI > 27 kg/m² + CVD



Glucacon-like peptide 1 Receptors analogues (GLP-1RA)
as Anti-Obesity Medication after menopause

Weight loss response to semaglutide in postmenopausal women with and without hormone therapy use

Maria D. Hurtado et el. *Menopause* 2024; Vol. 31, No. 4, pp. 266-274

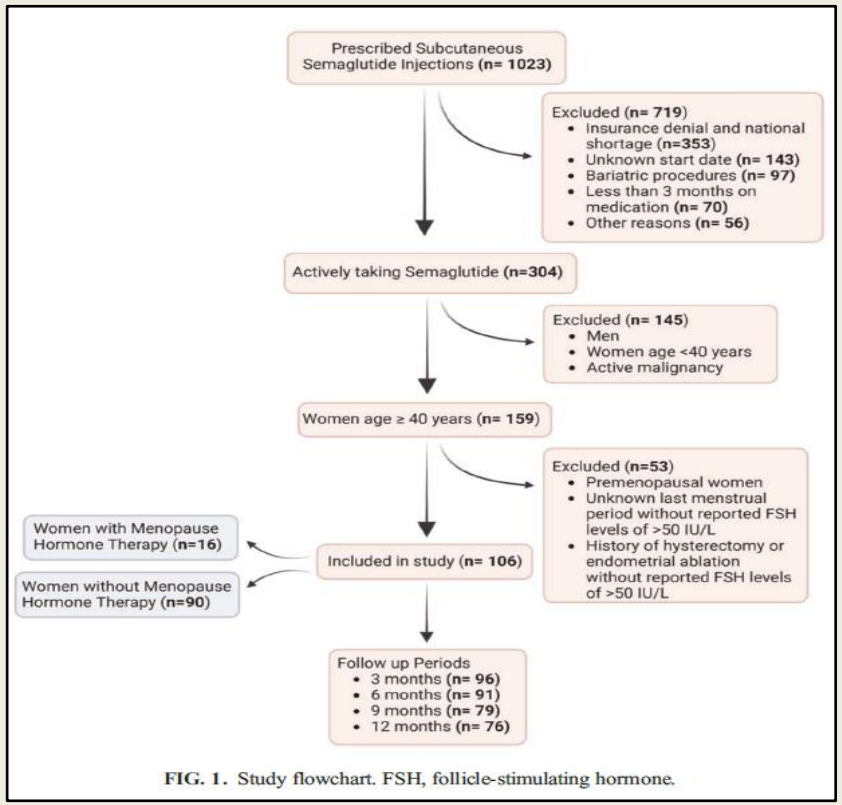
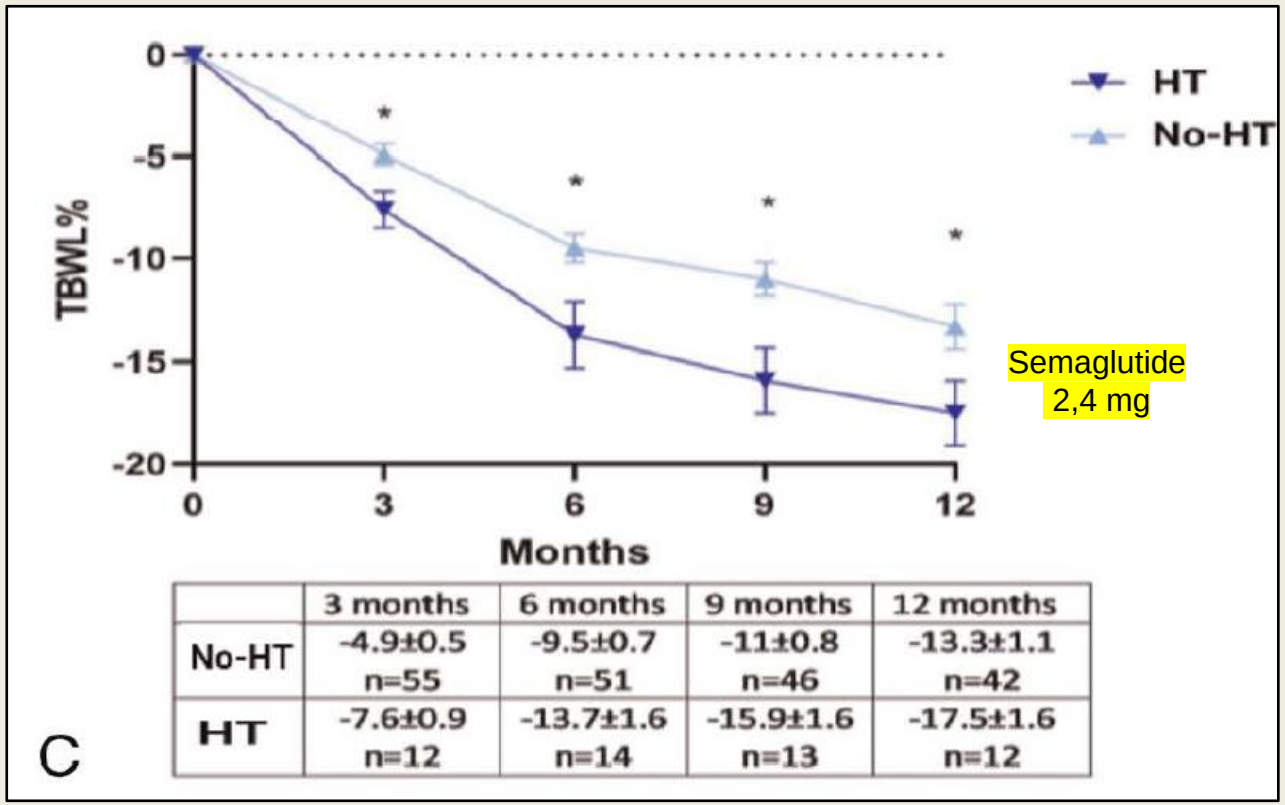


FIG. 1. Study flowchart. FSH, follicle-stimulating hormone.



	3 months	6 months	9 months	12 months
No-HT	-4.9±0.5 n=55	-9.5±0.7 n=51	-11±0.8 n=46	-13.3±1.1 n=42
HT	-7.6±0.9 n=12	-13.7±1.6 n=14	-15.9±1.6 n=13	-17.5±1.6 n=12

Menopause : risks of muscle loss & sarcopenic obesity

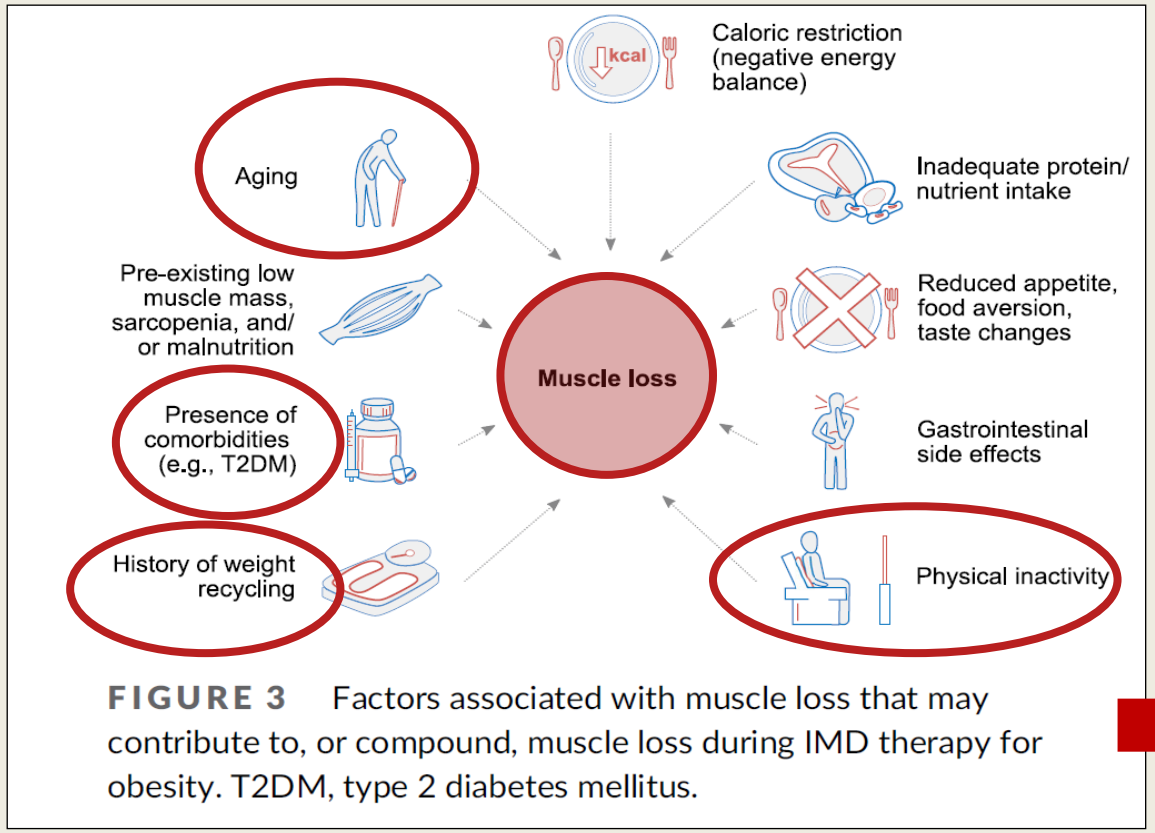
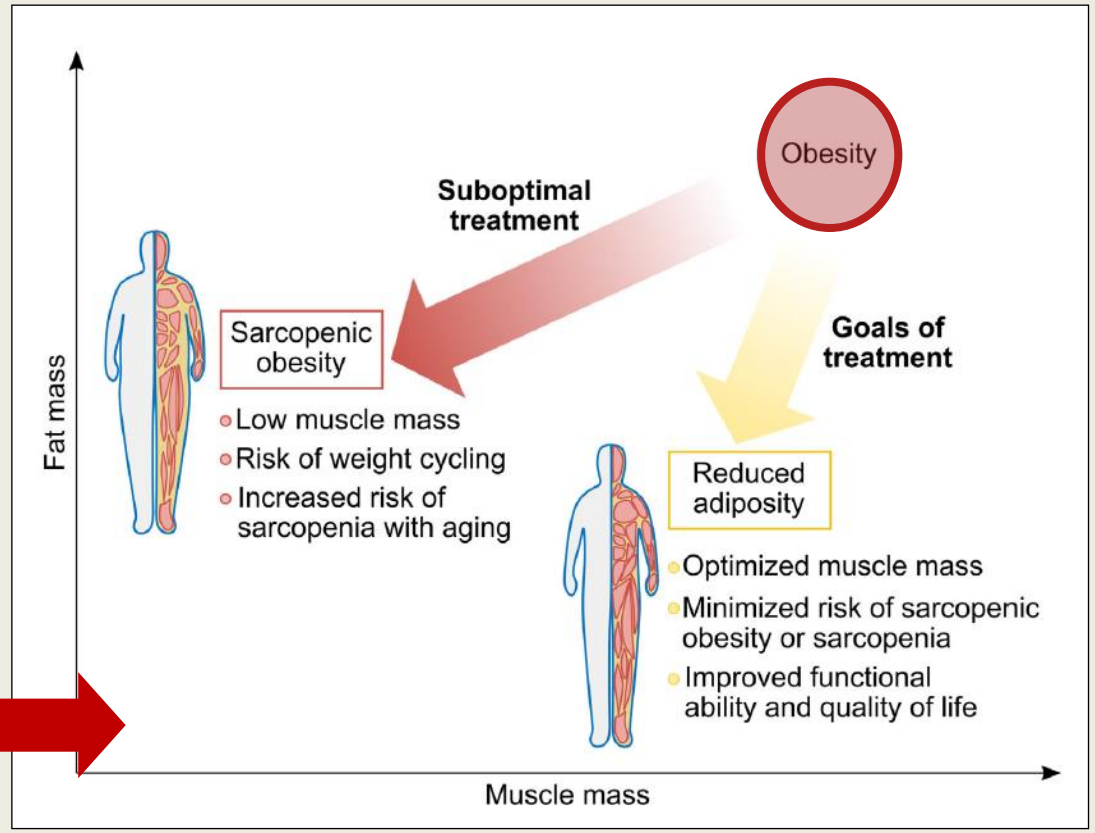


FIGURE 3 Factors associated with muscle loss that may contribute to, or compound, muscle loss during IMD therapy for obesity. T2DM, type 2 diabetes mellitus.



Mechanick JI et al. *Obesity Reviews*. 2024;e13841

Risks of muscle loss after GPL-1 RA induced weight loss

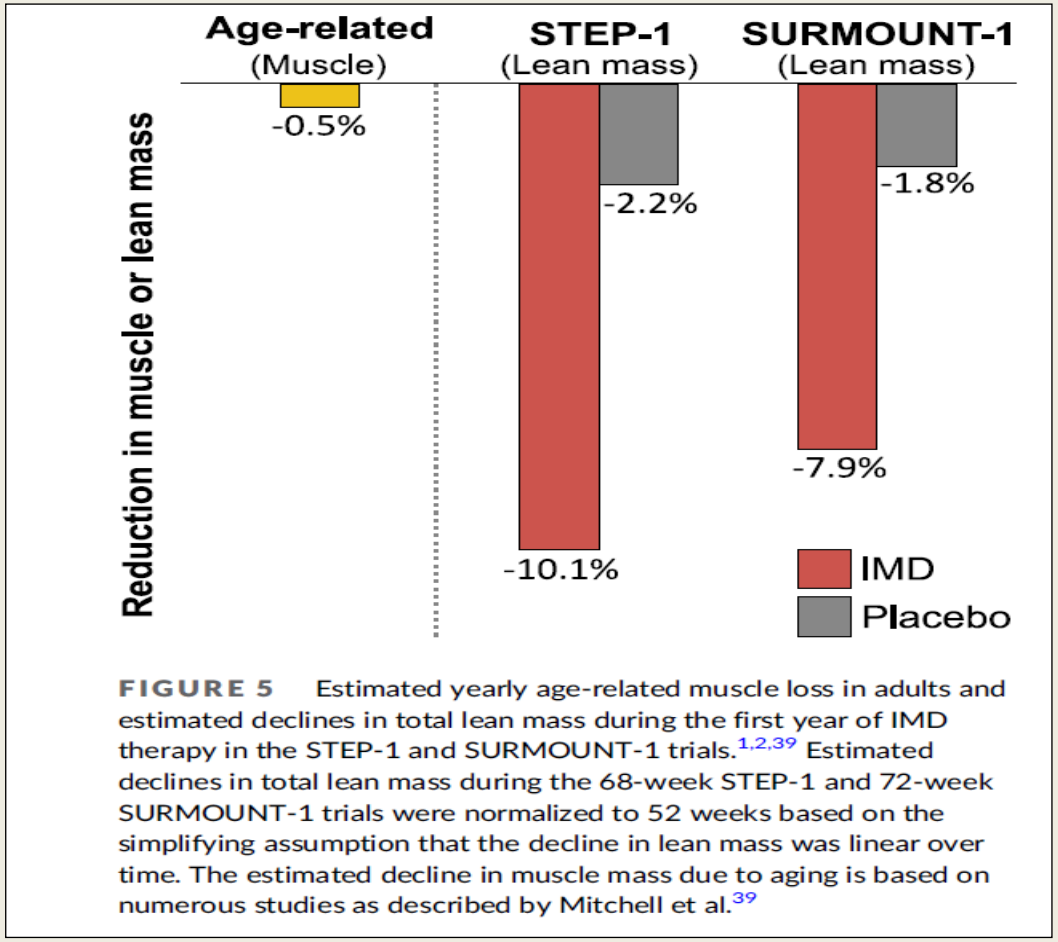
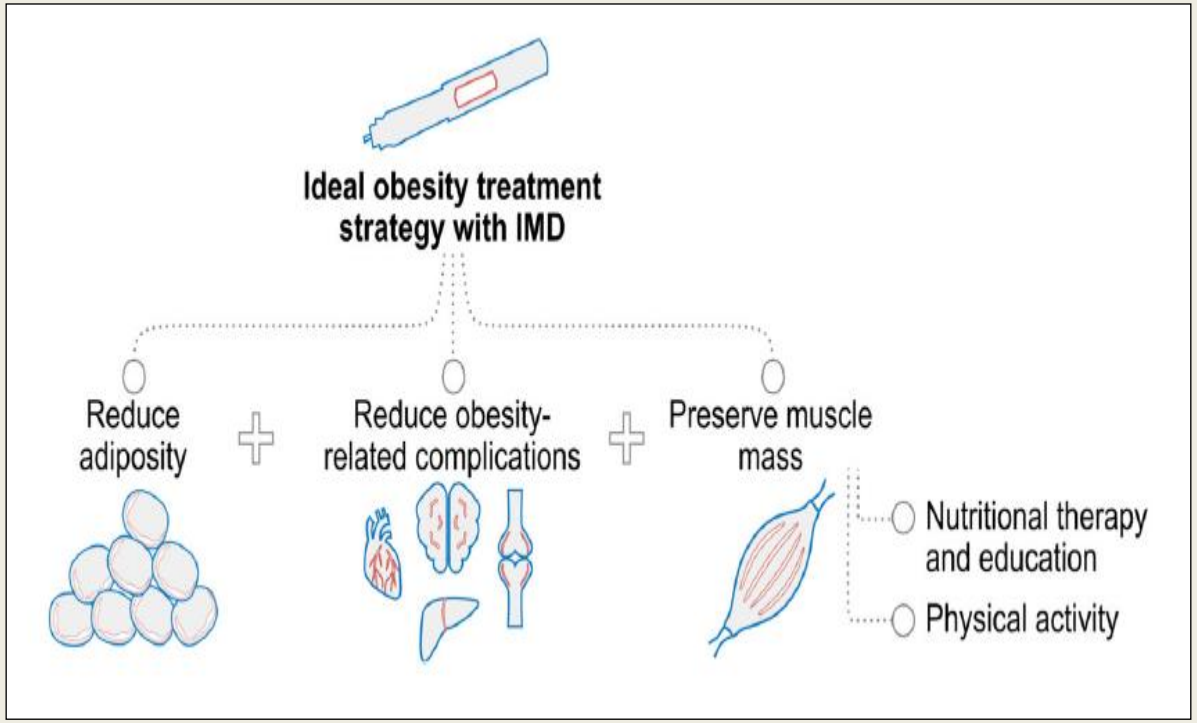


FIGURE 5 Estimated yearly age-related muscle loss in adults and estimated declines in total lean mass during the first year of IMD therapy in the STEP-1 and SURMOUNT-1 trials.[1,2,39] Estimated declines in total lean mass during the 68-week STEP-1 and 72-week SURMOUNT-1 trials were normalized to 52 weeks based on the simplifying assumption that the decline in lean mass was linear over time. The estimated decline in muscle mass due to aging is based on numerous studies as described by Mitchell et al.[39]

- Those declines may be consistent with declines in lean mass expected in people experiencing large weight reductions.
- Available evidence suggests that GLP-1 RA therapy has beneficial effects on muscle structure and function in animal models and humans.
- It is unclear whether those effects are sufficient to counteract the loss of muscle mass.
- There is evidence that exercise has beneficial effects when added to GLP-1 RA therapy

Mechanick JI et al. *Obesity Reviews*. 2024;e13841

Risks of muscle loss after GPL-1 RA induced weight loss



- Protein intake should be monitored
- Recommended Dietary Allowance for protein in healthy people is 0.8 g/kg body weight/day.
- Higher amounts have been recommended for healthy people older than 65 years (1.2–1.5 g/kg body weight).

Mechanick JI et al. *Obesity Reviews*. 2024;e13841

Glucacon-like peptide 1 Receptors analogues (GLP-1RA)
as Anti-Obesity Medication after menopause

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Medicine

The effects of exenatide and insulin glargine treatments on bone turnover markers and bone mineral density in postmenopausal patients with type 2 diabetes mellitus

Akyay et al. • *Medicine* (2023) 102:39

Table 3

Impact of exenatide versus insulin glargine treatment on DXA parameters.

Variables	Exenatide group (N = 15)	Glargine group (N = 15)	*P* value
Lumbar L1–L4 T-score-$_{pre}$	0.06 ± 1.25	−0.32 ± 1.10	.303
Lumbar L1–L4 T-score-$_{post}$	−0.05 ± 1.32	−0.16 ± 1.06	.803
P value	.614	.235	
Lumbar L1–L4 BMD-$_{pre}$ (g/cm2)	0.19 ± 0.14	1.11 ± 0.15	.188
Lumbar L1-L4 BMD-$_{post}$ (g/cm2)	1.17 ± 0.14	1.13 ± 0.15	.521
P value	.482	.255	
Change from baseline (%)	−0.24 (−5.4 to 7.1)	0.0 (−5.3 to 7.3)	.14
Femur neck T-score-$_{pre}$	−0.13 ± 1.27	−0.03 ± 1.21	.865
Femur neck T- score-$_{post}$	−0.01 ± 1.11	0.47 ± 1.57	.397
P value	.340	.389	
Femur neck BMD-$_{pre}$ (g/cm2)	1.02 ± 0.17	0.99 ± 0.18	.721
Femur neck BMD-$_{post}$ (g/cm2)	1.04 ± 0.14	1.11 ± 0.21	.357
P value	.348	.406	
Change from baseline (%)	0.8 (−4.4 to 14.2)	−0.06 (−5.6 to 72)	.61
Femur Total T- score-$_{pre}$	0.51 ± 1.26	0.28 ± 1.19	.698
Femur Total T- score-$_{post}$	0.62 ± 1.34	0.89 ± 1.46	.549
P value	.598	.452	
Femur total BMD-$_{pre}$ (g/cm2)	1.08 ± 0.15	1.05 ± 0.16	.801
Femur total BMD-$_{post}$(g/cm2)	1.09 ± 0.16	1.15 ± 0.18	.393
P value	.582	.472	
Change from baseline (%)	0.000 (−3.1 to 5.33)	0.004 (−6.2 to 49.5)	.68

Data was given as mean ± Standard Deviation or median (min-max) depending on the distribution.
BMD = bone mineral density, DXA = dual-energy X-ray absorptiometry.

- This study showed that despite significant weight loss with exenatide treatment, BMD did not decrease;
- Further evaluation is required with patients with a larger number of patients and longer follow-ups.

Glucacon-like peptide 1 Receptors analogues (GLP-1RA)
as Anti-Obesity Medication after menopause

Pharmacotherapy treatment algorithm proposal for menopausal women living with obesity

- "We believe GLP-1 receptor agonists should be the gold standard if patients meet the indication for the initiation of treatment (BMI≥ 27 kg/m^2 plus one obesity-associated comorbidity or BMI≥ 30 kg/m^2), and as part of an individualized plan this should include behavioral therapy aimed at gaining health."

- Stopping rule: treatment with anti-obesity medication should be discontinued after 12 weeks if patients have been unable to lose at least 5% of their initial body weight)

- It should be maintained until individualized goals are achieved in order to later assess and consider long-term continuation.

Santiago Palacios, et al. *Climateric* (17 Jul 2024): Management of obesity in menopause

Glucacon-like peptide 1 Receptors analogues (GLP-1RA)

Incretinomimetics as Anti-Obesity Medications

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- GLP-1 Receptor Analogues are only reimbursed (Af) for people with Type 2 Diabetes and BMI > 30 kg/m^2
- GLP-1 Receptor Analogues are not reimbursed for treating Obesity (cost ± 110€ / month)
- Dual agonist Tirzepatide is not reimbursed at all (cost ± 232€ / month for 2,5 mg & 5 mg dosages)

Take-home messages

- GLP-1 RA are very effective to induce weight loss in obese patients (w / w.o. diabetes)
- GLP-1 RA could more effective to induce weight loss in postmenopausal women taking HT
- Semaglutide showed a CV protective effect in overweight and obese patients at very high risk (with established CVD)
- It is not clear if muscle loss should be a concern, but physical activity individualized nutrition education is advised (caution : sarcopenic obesity !)
- GLP-1 RA will be “game changers” in the management of diabetes and obesity !

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Thank you !