ANALOGUES GLP-1 ET OBÉSITÉ

TÉLÉMEETING DU MERCREDI 11 JANVIER 2023

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DEFINITION

- Pathologie **chronique** et hétérogène caractérisée par une augmentation des dépôts de graisse (ICD-10 code 66)
- Pathologie **multifactorielle** liée à d'environnements obésogènes, facteurs psycho-sociaux et variantes génétiques
- Perturbation de la **santé physique, mentale et socio-économique**

Yumuk V et al. Obes Facts 2015

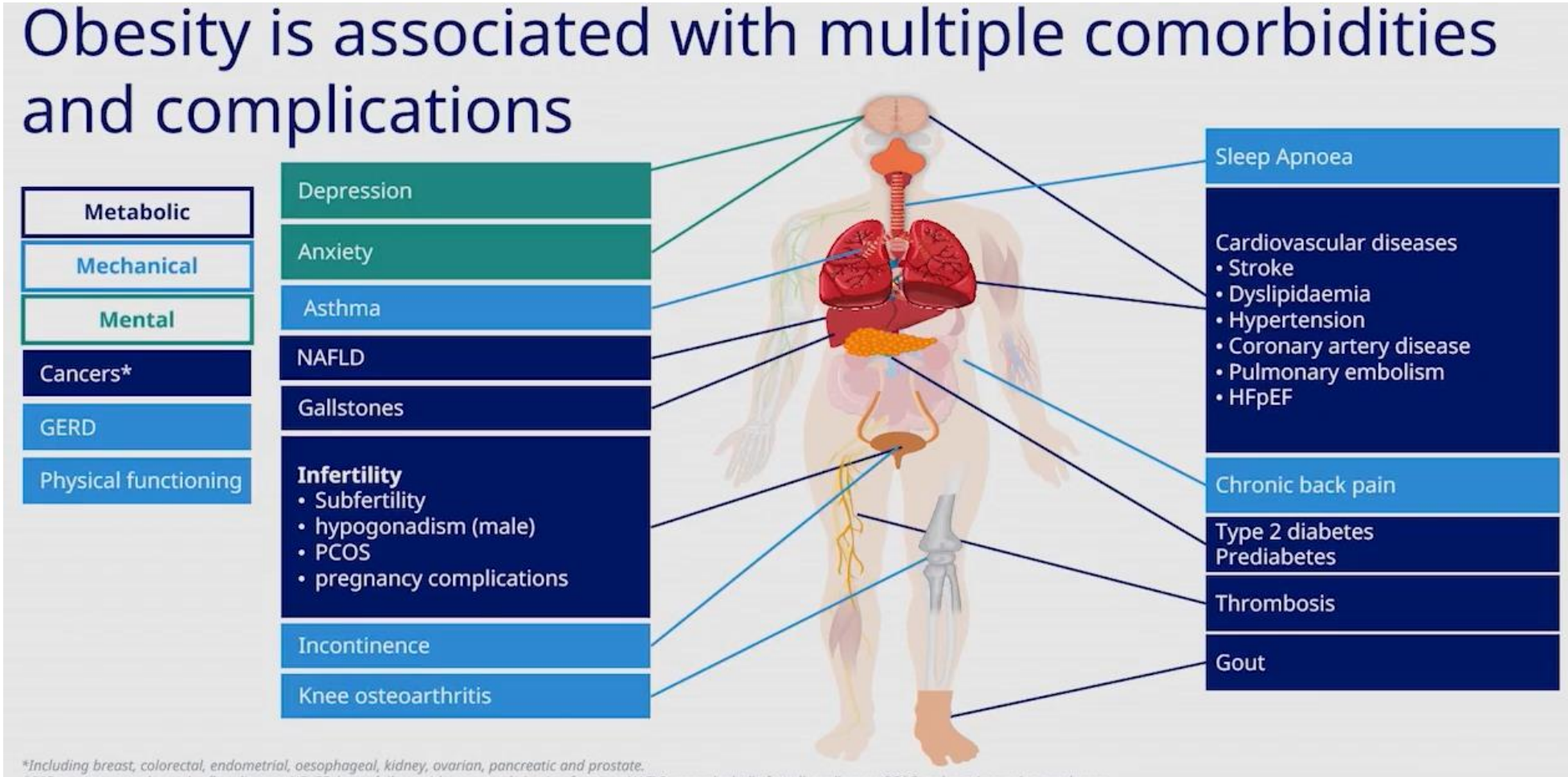
EPIDEMIOLOGY

- Environ **13% de la population adulte mondiale** (11% H et 15% F) en condition d'obésité en 2016
- En Suisse 12% de la population adulte (11% H et 9% F)
- Prévalence triplée au niveau mondial entre 1975 et 2016
- Coût important pour la santé

Yumuk V et al. Obes Facts 2015

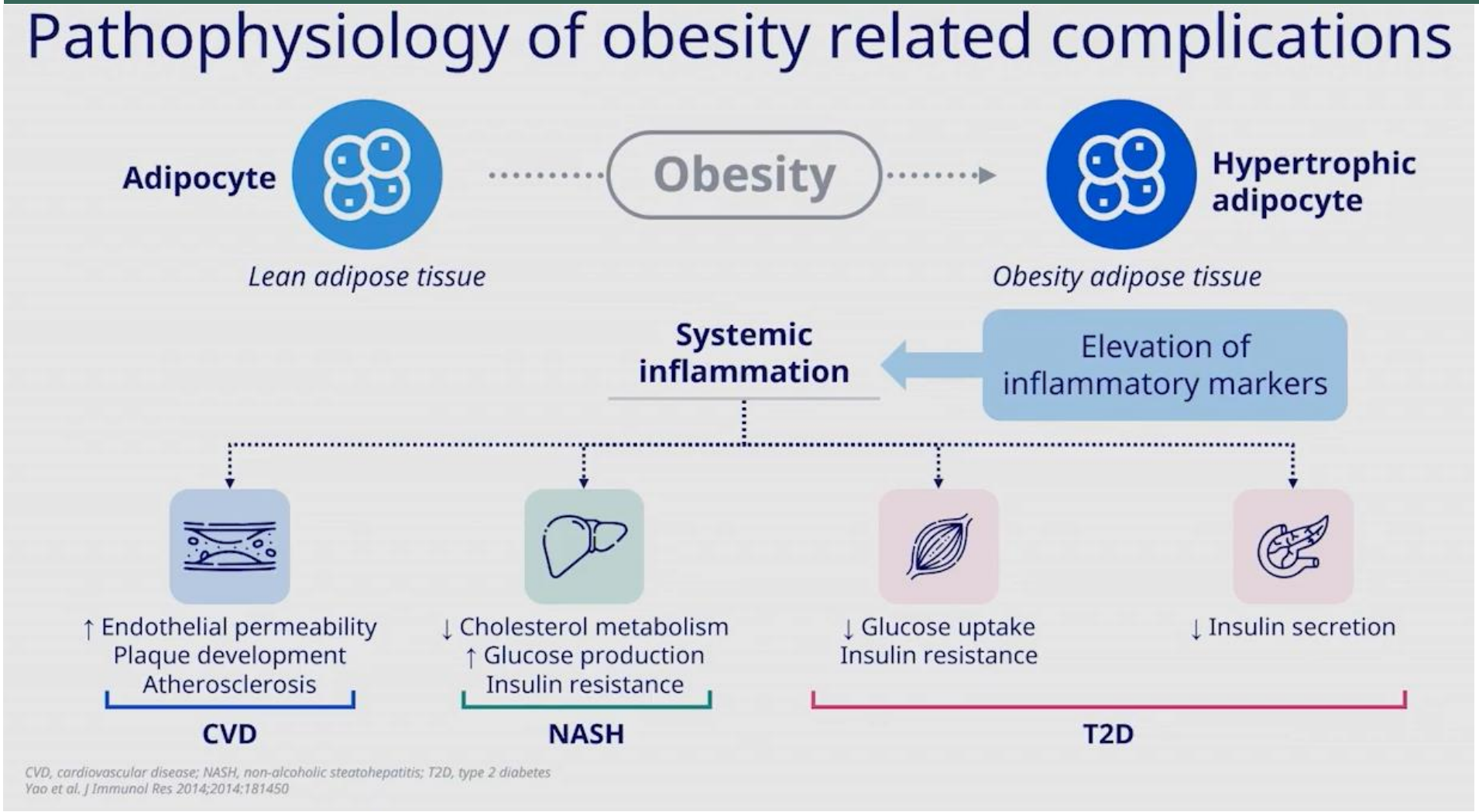
COMPLICATIONS

Obesity is associated with multiple comorbidities and complications

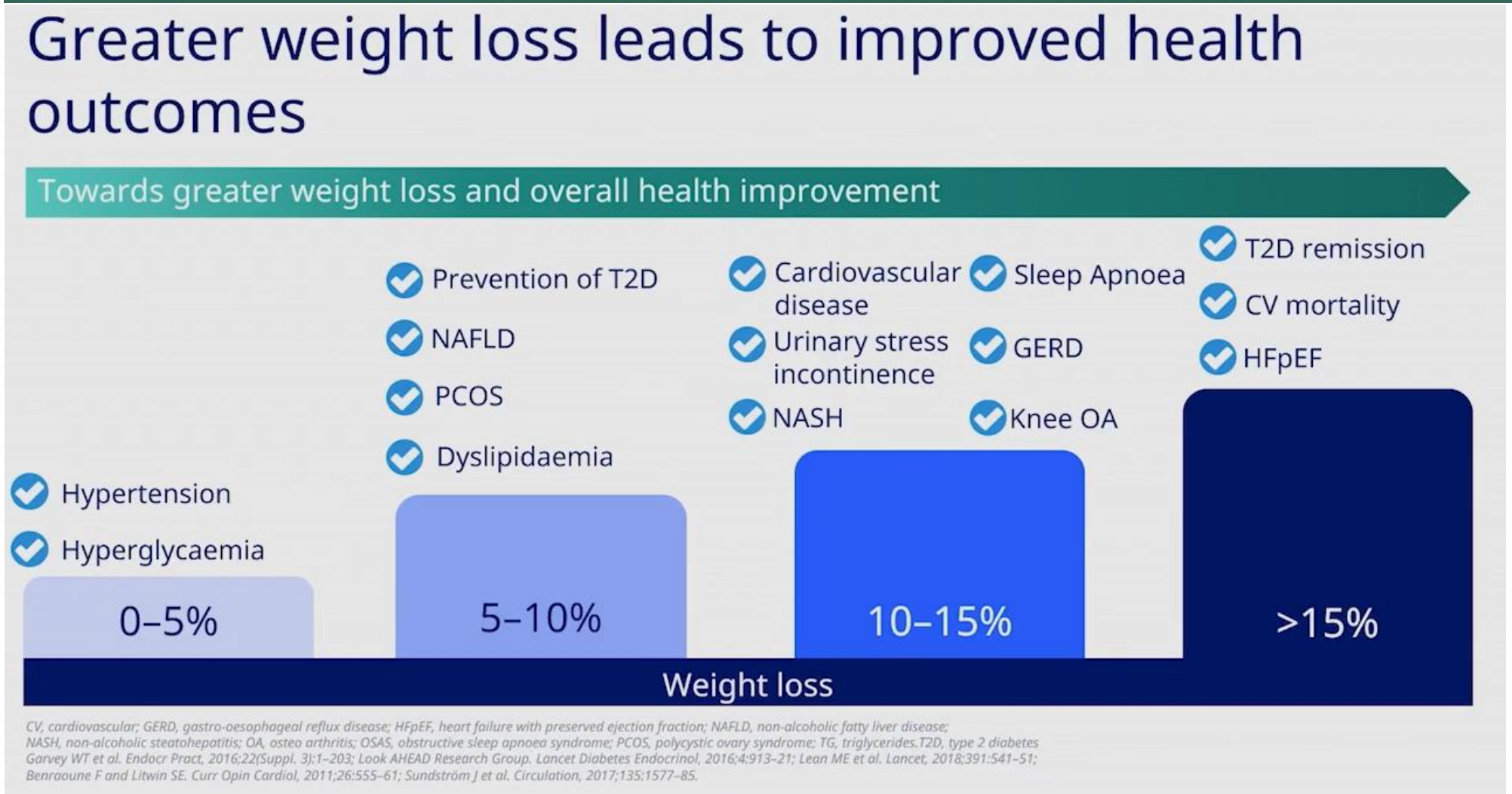


*Including breast, colorectal, endometrial, oesophageal, kidney, ovarian, pancreatic and prostate.
GERD, gastro-oesophageal reflux disease; HFpEF, heart failure with preserved ejection fraction; NAFLD, non-alcoholic fatty liver disease; PCOS, polycystic ovarian syndrome
Sharma AM. Obes Rev 2010;11:808–9; Guh DP et al. BMC Public Health 2009;9:88; Luppino FS et al. Arch Gen Psychiatry 2010;67:220–9; Simon GE et al. Arch Gen Psychiatry 2006;63:824–30; Church TS et al. Gastroenterology 2006;130:2023–30; Li C et al. Prev Med 2010;51:18–23; Hosler AS. Prev Chronic Dis 2009;6:A48.

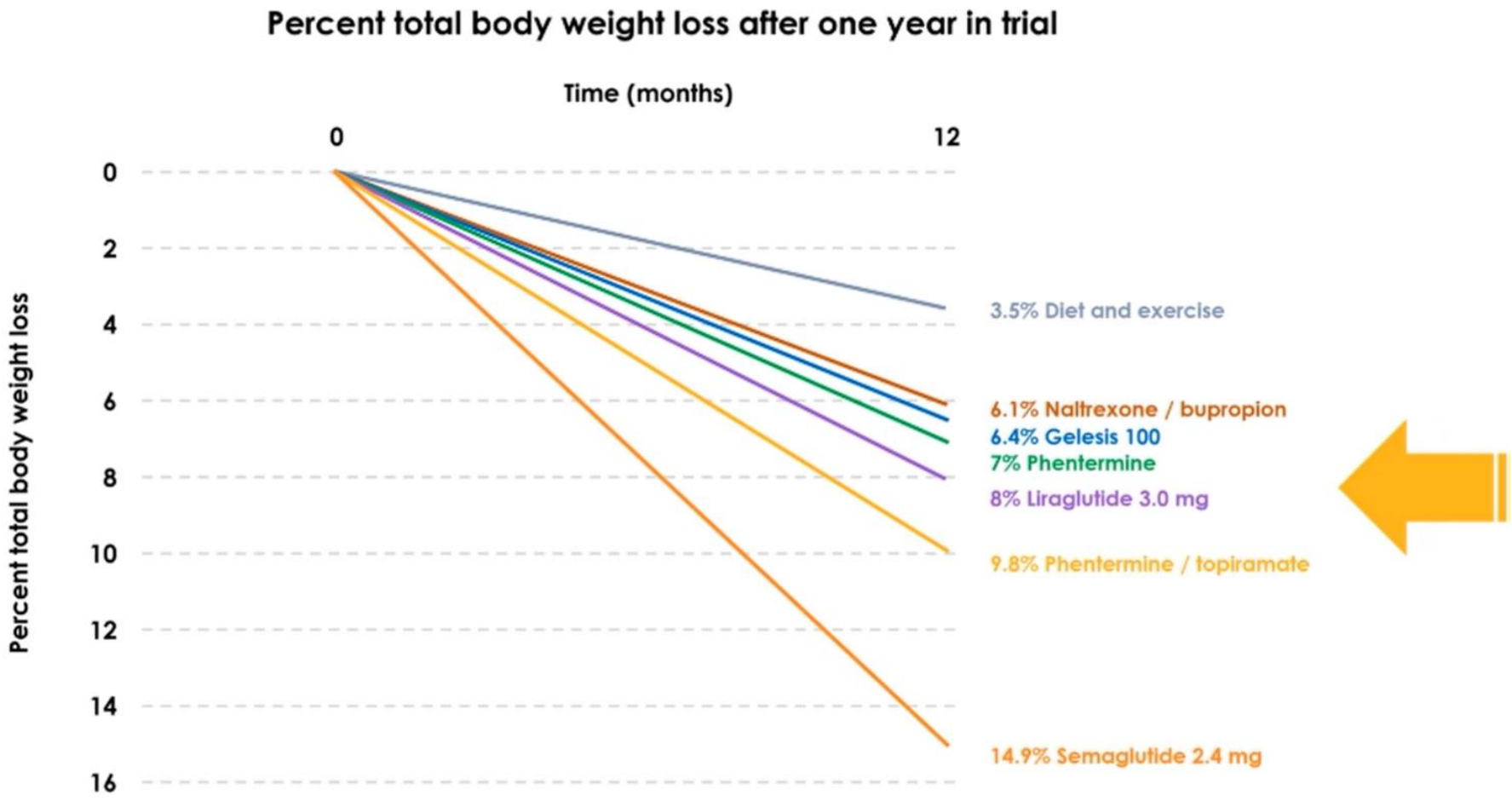
COMPLICATIONS



HOW MUCH WEIGHT SHOULD I LOOSE?



HOW TO GET THERE



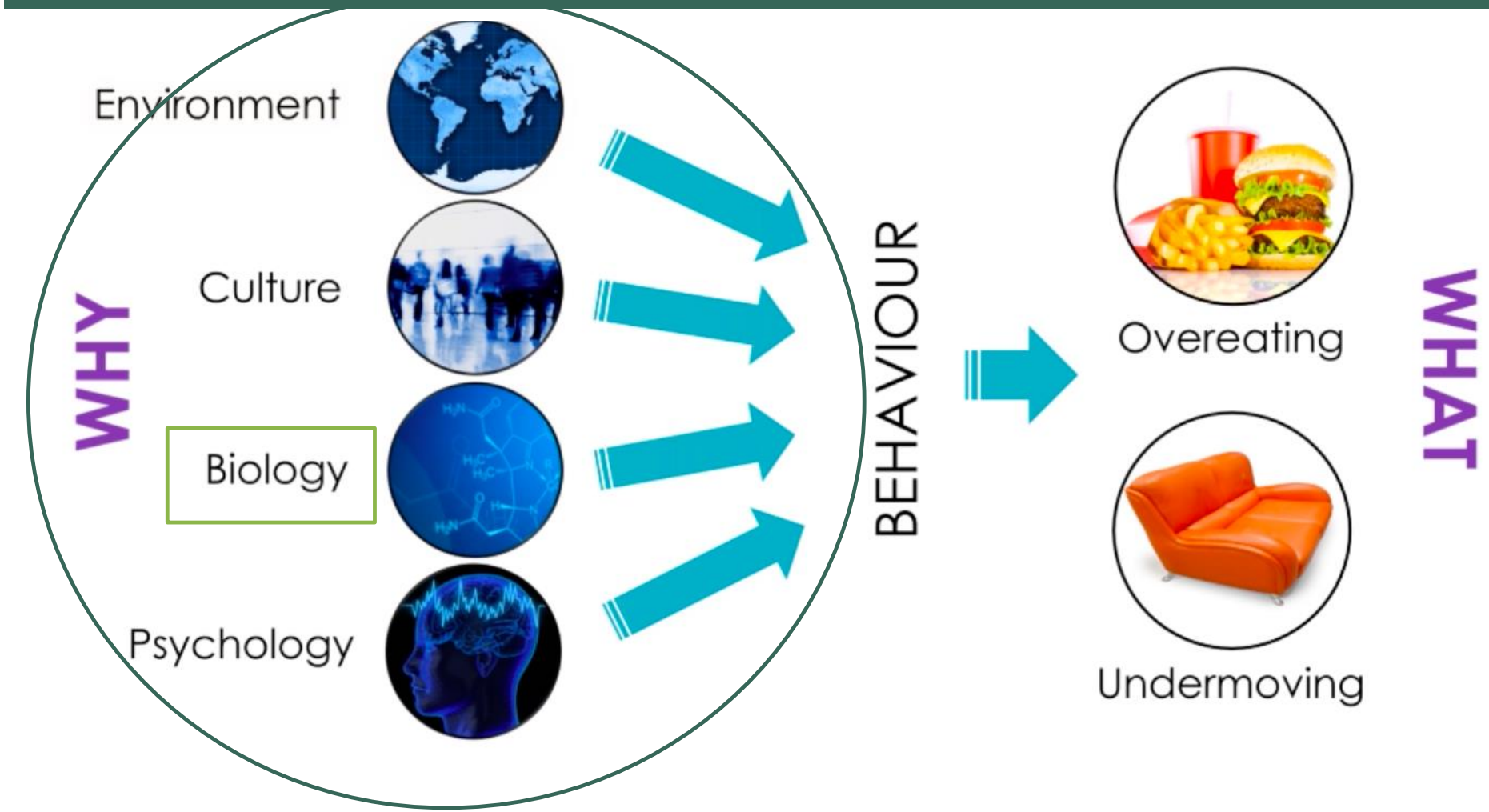
SCOPE E-Learning

LES ANALOGUES GLP-1

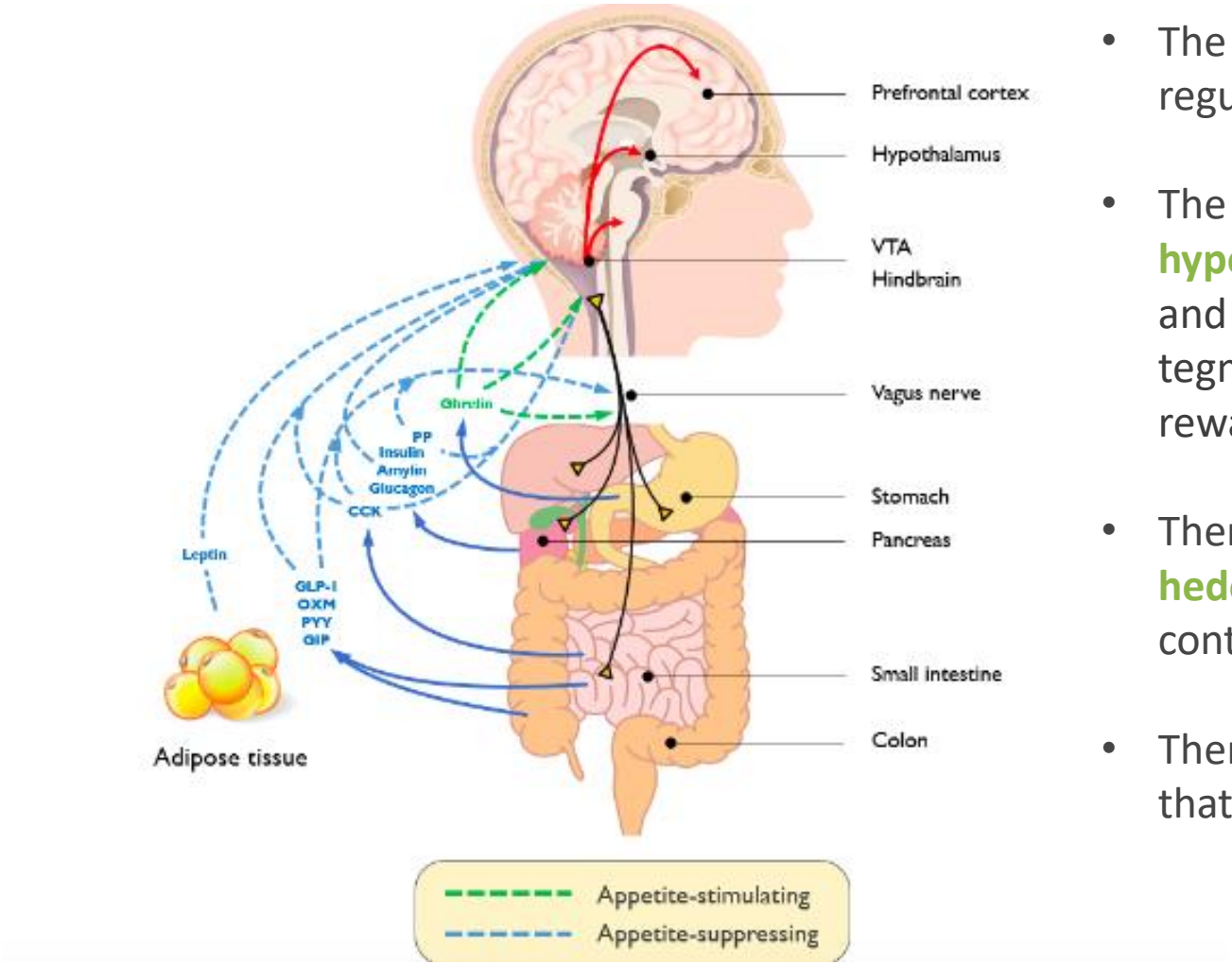
ENERGY IN – ENERGY OUT

Se focaliser sur des conseils de diminution des apports et augmentation des dépenses serait comme regarder que la point de l'iceberg 'obésité'

NOT ROCKET SCIENCE BUT FAR MORE COMPLICATED

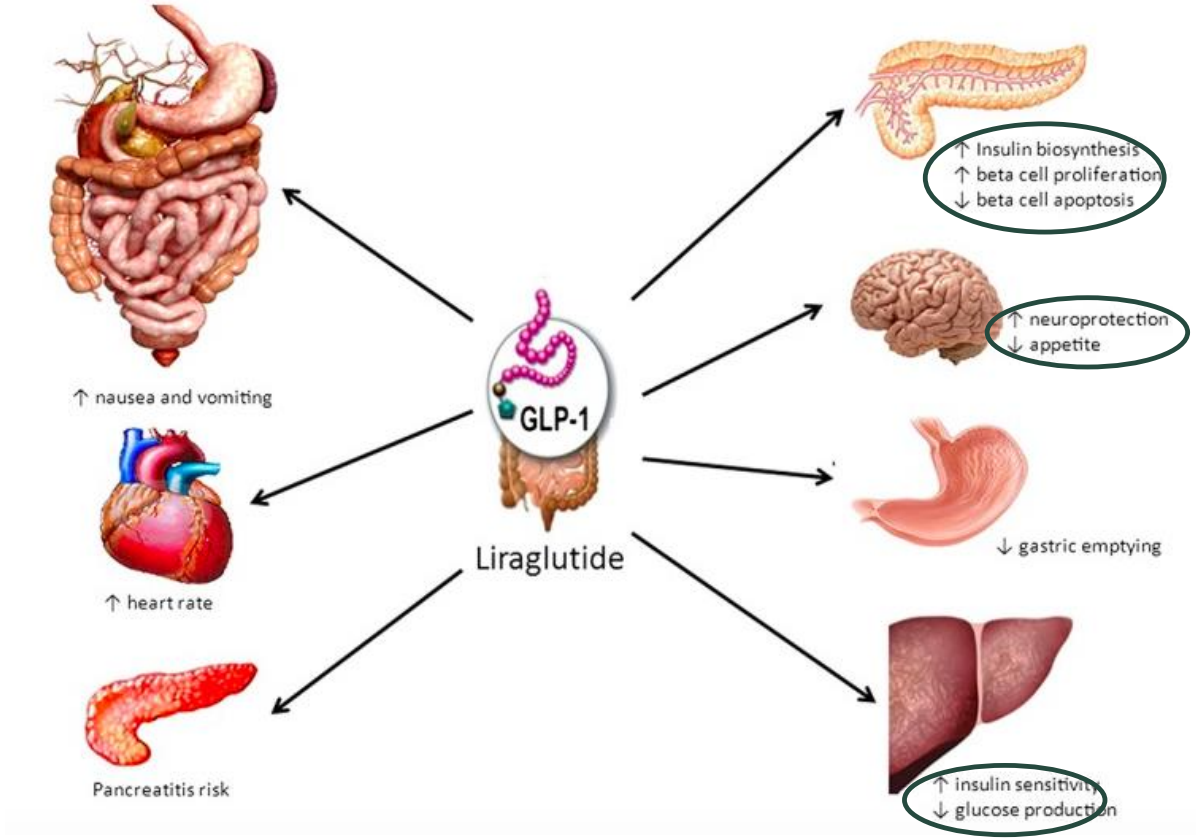


APPETITE REGULATION SYSTEM



- The brain integrates signals from peripheral tissues to regulate appetite.
- The major appetite control centre is the **arcuate the hypothalamus**, where we find two pathways (anorexigenic and orexigenic pathways). The area postrema and the ventral tegmental areas in the brain also play a role in appetite and reward centre brain activity.
- There also appear to be **additional pathways that affect hedonic eating** or cravings in addition to these appetite control pathways.
- There are **hormones and neuropeptides from the periphery** that send messages back to the central nervous system.

GLP-1 & GLP-1 RA



Liraglutide

Liraglutide is an injectable long-acting GLP-1R agonist designed to resist rapid metabolism by dipeptidyl peptidase-IV. While glucose-induced insulin release is stimulated, the glucagon response is reduced and appetite suppressed with additional effects on gastric emptying [100]. It has already successfully been introduced in type 2 diabetic patients (1.2–1.8 mg) once daily. After approval by the FDA and EMA, the drug (in a dosage of 3 mg once daily) was launched for obesity treatment in the USA in November 2014 and in Europe in March 2015. The product licence requires 5% weight loss after 12 weeks of treatment. If a patient does not reach this target, the drug should be discontinued [71–74, 101–104]. The efficacy and safety of the drug were assessed in the following RCTs: SCALE-Maintenance [105], SCALE-Obesity [106] and LEADER [107–109]. Liraglutide is generally well tolerated. Nausea and vomiting are the main, usually transient, side-effects, but they may actively contribute to weight loss [110].

EASO

GLP-1 RA & OBESITY: MECHANISMS OF ACTION

1. Ralentissement de la vidange gastrique
2. Stimulation de la satiété
3. Reduction de faim et appétit
4. Reduction des envies et des cravings alimentaires (sucres)

GLP-1 RA & PRECAUTIONS

- **Contrindiqués :** grossesse, hypersensibilité
- **A éviter :** gastroparésie, MICI, eGFR < 30 ml/min/1.73m2
- **Discutés en littérature :** hyperplasie cellules C thyroïdiennes (MEN, k médullaire), lithiase vésiculaire, pancréatites
- **Side effects :** nausées, ballonnements, vomissements, altérations du transit, pyrosis, tachycardie

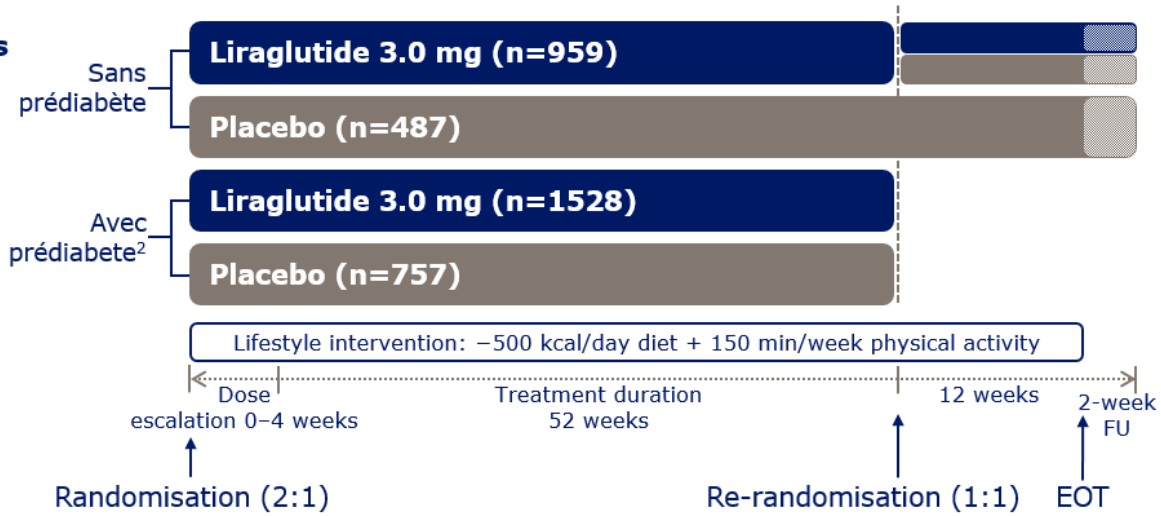
LIRAGLUTIDE : STUDIES. SCALE OBESITY

Design de l'étude : SCALE Obésité et Prédiabète

Liraglutide 3,0 mg dans la gestion du poids (56 semaines)[1]

3731 participants

- ≥18 ans
- Poids stable
- BMI ≥30 kg/m² ou ≥27 kg/m² + comorbidités



Information sur l'étude

- Juin 2011 à mars 2013
- Étude randomisée, contrôlée, en double aveugle
- 191 sites dans 27 pays
- Durée: 56 semaines (avec prédiabète), 68 semaines (sans prédiabète)

Objectif de l'étude

- Efficacité et innocuité du Liraglutide 3,0 mg, en association au D&E, chez les participants souffrant d'obésité ou de surpoids et de comorbidités, sans diabète

Critères principaux

- 3 co-primaire: changement, perte de 5% ou 10% de poids
- Secondaire: changements par rapport à la valeur initiale de l'IMC, du TT, des variables de contrôle glycémique, des facteurs de risque cardiométaboliques et de la QVSH

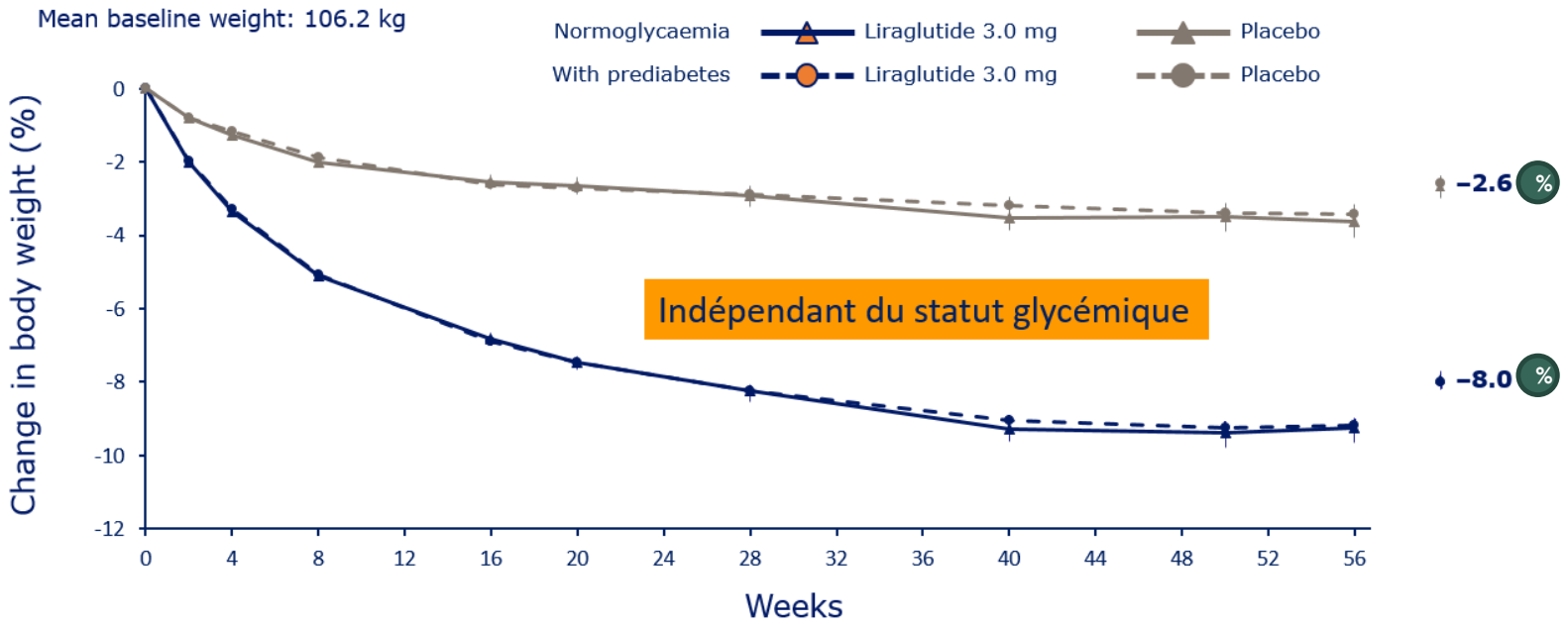
BMI, Body Mass Index; BW, body weight; D&E, diet and exercise; EOT, end of treatment; FU, follow-up; HRQoL, health-related quality of life; WC, waist circumference.

N Engl J Med 2015;373:11–22. 2. ADA. *Diabetes Care* 2010;33(Suppl. 1):S11–61.

LIRAGLUTIDE : STUDIES. SCALE OBESITY

Changement moyen du poids corporel

Par statut de prédiabète: 0 à 56 semaines



Pi-Sunyer X et al. N Engl J Med 2015;373:11-22.

LIRAGLUTIDE : STUDIES. SCALE MAINTENANCE

ORIGINAL ARTICLE

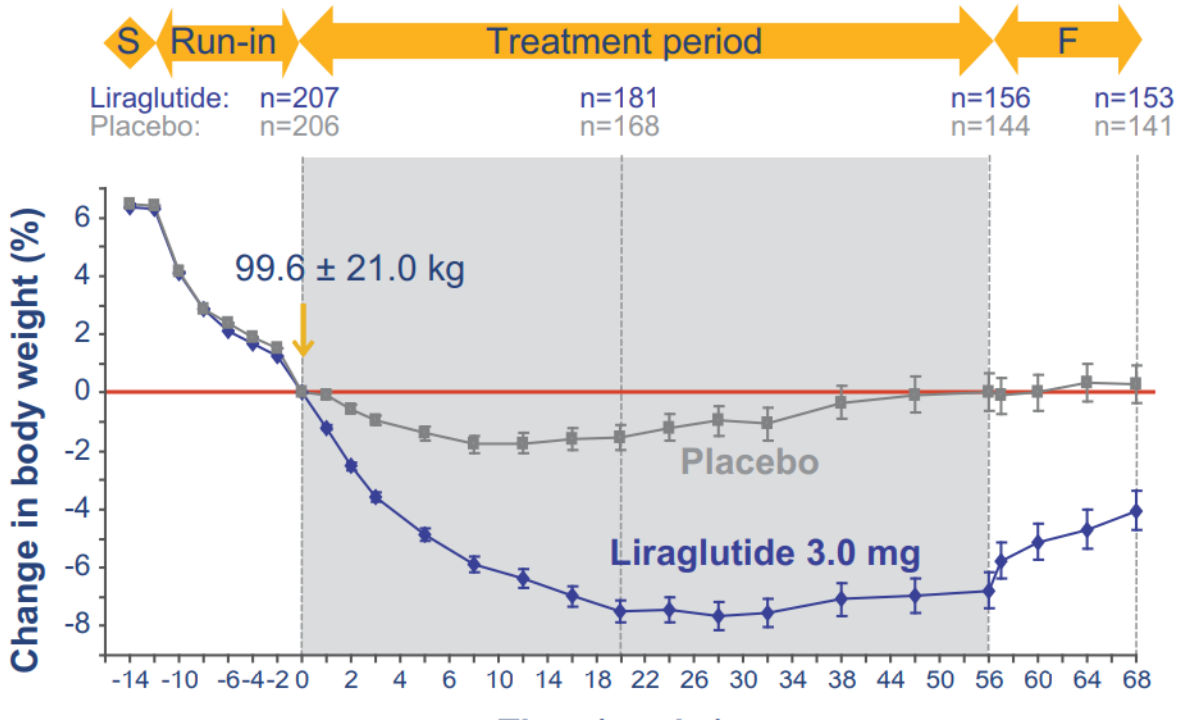
Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: The SCALE Maintenance randomized study

This article has been corrected since online publication and an erratum is also printed in this issue

TA Wadden[1], P Hollander[2], S Klein[3], K Niswender[4], V Woo[5], PM Hale[6] and L Aronne[7] on behalf of the NN8022-1923 Investigators[8]

OBJECTIVE: Liraglutide, a once-daily human glucagon-like peptide-1 analog, induced clinically meaningful weight loss in a phase 2 study in obese individuals without diabetes. The present randomized phase 3 trial assessed the efficacy of liraglutide in maintaining weight loss achieved with a low-calorie diet (LCD).
METHODS: Obese/overweight participants (⩾18 years, body mass index ⩾30 kg m^{-2} or ⩾27 kg m^{-2} with comorbidities) who lost ⩾5% of initial weight during a LCD run-in were randomly assigned to liraglutide 3.0 mg per day or placebo (subcutaneous administration) for 56 weeks. Diet and exercise counseling were provided throughout the trial. Co-primary end points were percentage weight change from randomization, the proportion of participants that maintained the initial ⩾5% weight loss, and the proportion that lost ⩾5% of randomization weight (intention-to-treat analysis). ClinicalTrials.gov identifier: NCT00781937.
RESULTS: Participants ($n=422$) lost a mean 6.0% (s.d. 0.9) of screening weight during run-in. From randomization to week 56, weight decreased an additional mean 6.2% (s.d. 7.3) with liraglutide and 0.2% (s.d. 7.0) with placebo (estimated difference −6.1% (95% class intervals −7.5 to −4.6), $P<0.0001$). More participants receiving liraglutide (81.4%) maintained the ⩾5% run-in weight loss, compared with those receiving placebo (48.9%) (estimated odds ratio 4.8 (3.0; 7.7), $P<0.0001$), and 50.5% versus 21.8% of participants lost ⩾5% of randomization weight (estimated odds ratio 3.9 (2.4; 6.1), $P<0.0001$). Liraglutide produced small but statistically significant improvements in several cardiometabolic risk factors compared with placebo. Gastrointestinal (GI) disorders were reported more frequently with liraglutide than placebo, but most events were transient, and mild or moderate in severity.
CONCLUSION: Liraglutide, with diet and exercise, maintained weight loss achieved by caloric restriction and induced further weight loss over 56 weeks. Improvements in some cardiovascular disease-risk factors were also observed. Liraglutide, prescribed as 3.0 mg per day, holds promise for improving the maintenance of lost weight.

International Journal of Obesity (2013) **37,** 1443–1451; doi:10.1038/ijo.2013.120



LIRAGLUTIDE: STUDIES AMONGST ADOLESCENTS

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

Safety and Efficacy of Glucagon-Like Peptide-1 Receptor Agonists in Children and Adolescents with Obesity: A Meta-Analysis

Paul M. Ryan, MB, BCh, BAO, PhD[1], Sean Seltzer, MB, BCh, BAO, MSc[2], Nathaniel E. Hayward, MB, BCh, BAO, MSc[3], David Avelar Rodriguez, MD[4], Ryan T. Sless, MB, BCh, BAO, MSc[5], and Colin P. Hawkes, MD, PhD[1,6,7]

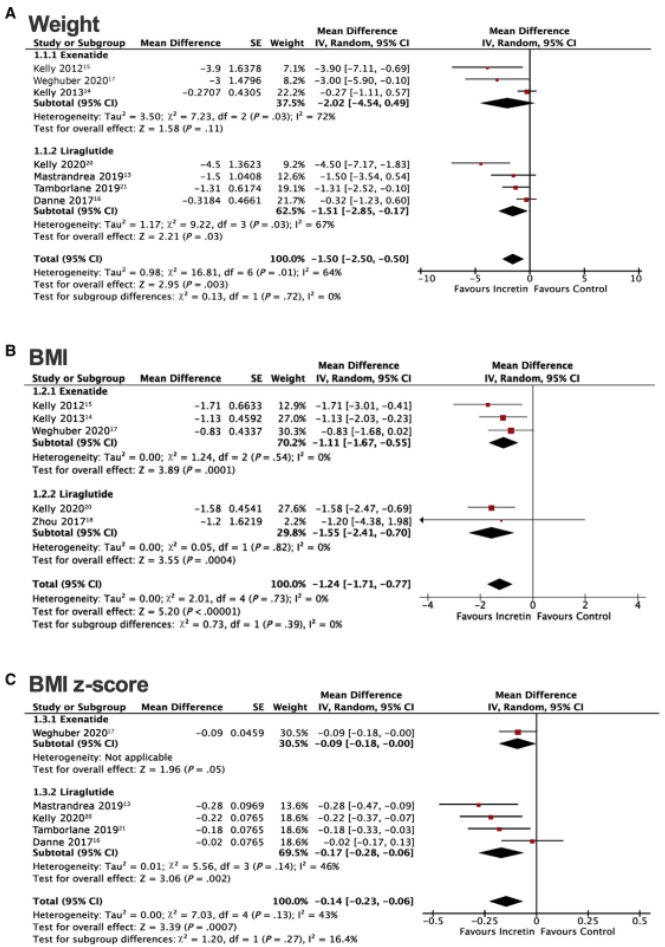
Objectives To determine the weight, body mass index (BMI), cardiometabolic, and gastrointestinal effects of glucagon-like peptide-1 (GLP-1) receptor agonists in children with obesity.

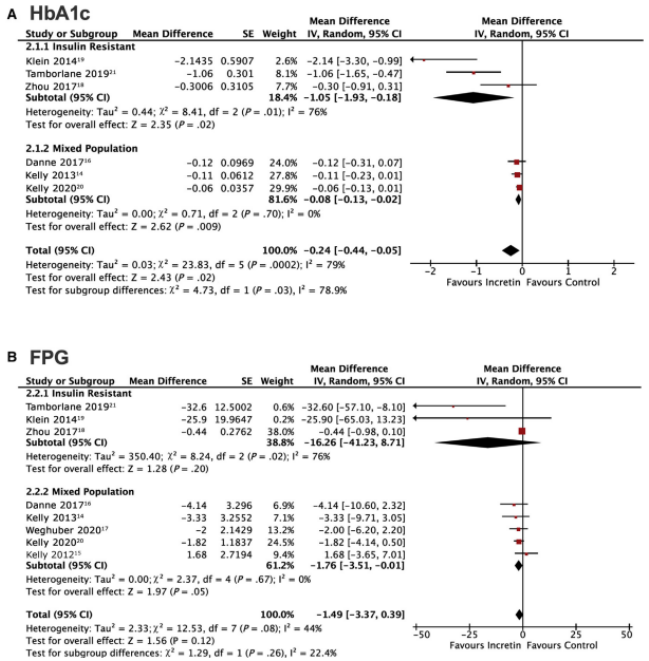
Study design Web of Science, PubMed/MEDLINE, and Scopus databases from 01/01/1994-01/01/2021 for randomized control trials examining the weight, BMI, cardiometabolic, or gastrointestinal effects of GLP-1 receptor agonists in children and adolescents with obesity. Data were extracted by 2 independent surveyors and a random effects model was applied to meta-analyze generic inverse variance outcomes. Primary outcomes were related to weight and cardiometabolic profile, and secondary outcomes of interest were gastrointestinal-related treatment-emergent adverse events.

Results Nine studies involving 574 participants were identified, of which 3 involved exenatide and 6 involved liraglutide. GLP-1 receptor agonists use caused a modest reduction in body weight (mean difference [MD] -1.50 [-2.50,-0.50] kg, I^2 64%), BMI (MD -1.24 [-1.71,-0.77] kg/m^2, I^2 0%), and BMI z score (MD -0.14 [-0.23,-0.06], I^2 43%). Glycemic control was improved in children with proven insulin resistance (glycated hemoglobin A1c MD -1.05 [-1.93,-0.18] %, I^2 76%). Although no lipid profile improvements were noted, a modest decrease in systolic blood pressure was detected (MD -2.30 [-4.11,-0.49] mm Hg; I^2 0%). Finally, analysis of gastrointestinal-related treatment-emergent adverse events revealed an increased risk of nausea (risk ratio 2.11 [1.44, 3.09]; I^2 0%), without significant increases in other gastrointestinal symptoms.

Conclusions This meta-analysis indicates that GLP-1 receptor agonists are safe and effective in modestly reducing weight, BMI, glycated hemoglobin A1c, and systolic blood pressure in children and adolescents with obesity in a clinical setting, albeit with increased rates of nausea. *(J Pediatr 2021;236:137-47)*.

PROSPERO ID CRD42020195869.





SEMAGLUTIDE: STUDIES. STEP 1

RESEARCH SUMMARY

Once-Weekly Semaglutide in Adults with Overweight or Obesity

Wilding JPH. et al. DOI: 10.1056/NEJMoa2032183

CLINICAL PROBLEM

Clinical guidelines suggest pharmacologic intervention in addition to diet and exercise to promote weight loss among adults with BMI ≥30 (or ≥27 in those with coexisting conditions). Barriers to medication use include limited efficacy, adverse effects, and cost. Subcutaneous semaglutide, a glucagon-like peptide-1 analogue FDA-approved to treat type 2 diabetes in adults, has been accompanied by weight loss in previous clinical trials.

CLINICAL TRIAL

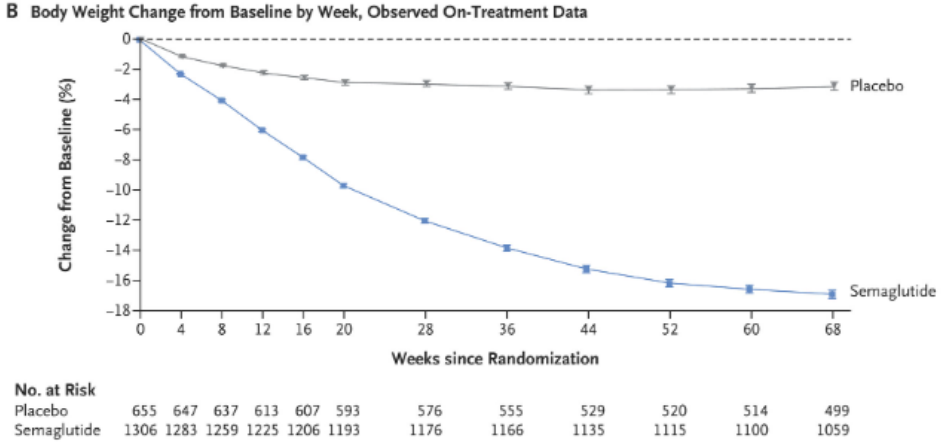
A phase 3, double-blind, randomized, controlled trial comparing semaglutide with placebo, plus lifestyle changes, in overweight or obese adults without diabetes.

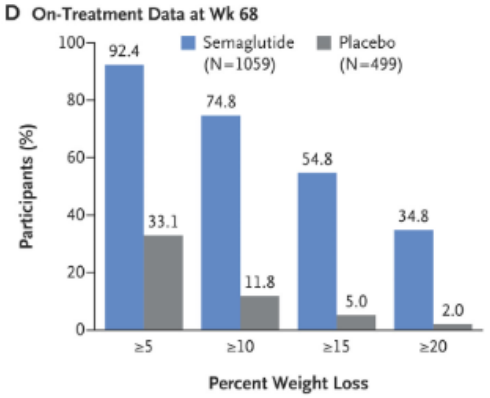
1961 participants were assigned to receive 2.4 mg of subcutaneous semaglutide (with gradual increase to the 2.4 mg dose) or placebo weekly for 68 weeks; both groups received a counseling intervention involving diet and exercise. Coprimary end points were percentage change in body weight and weight reduction ≥5%.

RESULTS

Efficacy:
By week 68, mean weight declined more with semaglutide than with placebo (14.9% vs. 2.4%; estimated difference, −12.4 percentage points; 95% CI, −13.4 to −11.5). In addition, more participants in the semaglutide group than in the placebo group had weight loss of ≥5% (86.4% vs. 31.5%).

Safety:
Adverse events, mainly gastrointestinal, were most often mild to moderate but led to treatment discontinuation in 7.0% of the semaglutide group and 3.1% of the placebo group. Serious adverse events, primarily gastrointestinal and hepatobiliary events, were reported more often with semaglutide.





SEMAGLUTIDE: STUDIES. STEP 4

Design, Setting, and Participants Randomized, double-blind, 68-week phase 3a withdrawal study conducted at 73 sites in 10 countries from June 2018 to March 2020 in adults with body mass index of at least 30 (or ≥27 with ≥1 weight-related comorbidity) and without diabetes.

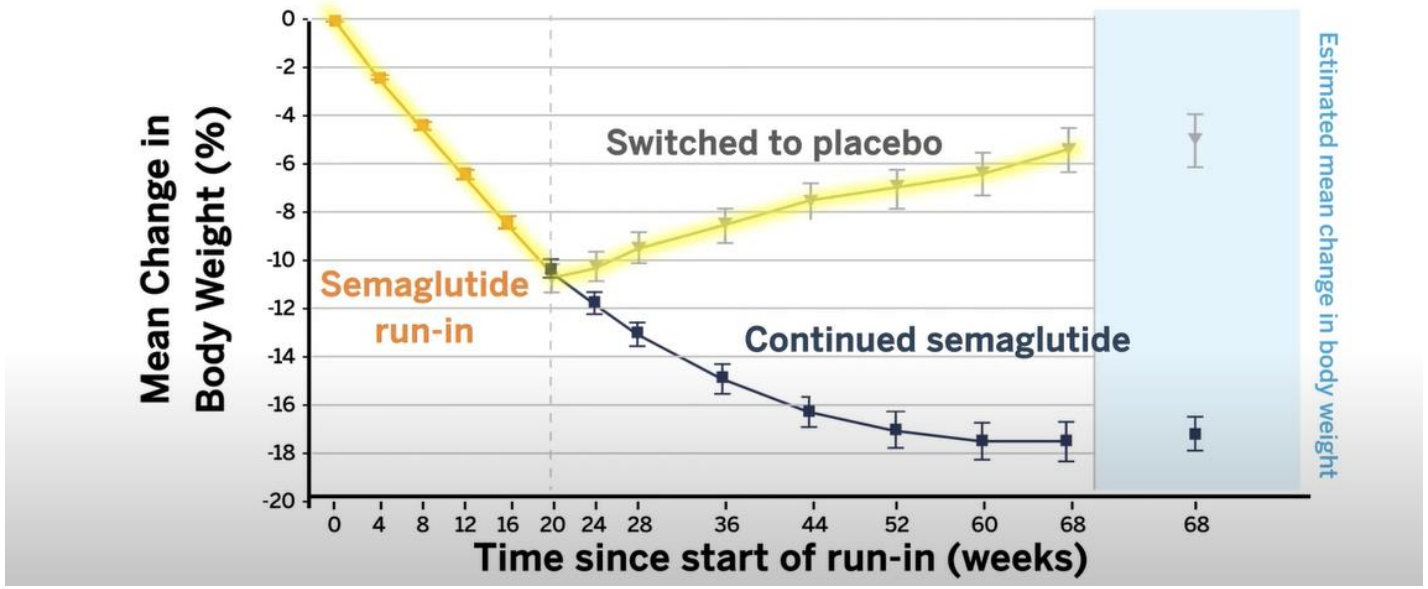
Interventions A total of 902 participants received once-weekly subcutaneous semaglutide during run-in. After 20 weeks (16 weeks of dose escalation; 4 weeks of maintenance dose), 803 participants (89.0%) who reached the 2.4-mg/wk semaglutide maintenance dose were randomized (2:1) to 48 weeks of continued subcutaneous semaglutide (n=535) or switched to placebo (n=268), plus lifestyle intervention in both groups.

Main Outcomes and Measures The primary end point was percent change in body weight from week 20 to week 68; confirmatory secondary end points were changes in waist circumference, systolic blood pressure, and physical functioning (assessed using the Short Form 36 Version 2 Health Survey, Acute Version [SF-36]).

Results Among 803 study participants who completed the 20-week run-in period (with a mean weight loss of 10.6%) and were randomized (mean age, 46 [SD, 12] years; 634 [79%] women; mean body weight, 107.2 kg [SD, 22.7 kg]), 787 participants (98.0%) completed the trial and 741 (92.3%) completed treatment. With continued semaglutide, mean body weight change from week 20 to week 68 was −7.9% vs +6.9% with the switch to placebo (difference, −14.8 [95% CI, −16.0 to −13.5] percentage points; $P<.001$). Waist circumference (−9.7 cm [95% CI, −10.9 to −8.5 cm]), systolic blood pressure (−3.9 mm Hg [95% CI, −5.8 to −2.0 mm Hg]), and SF-36 physical functioning score (2.5 [95% CI, 1.6-3.3]) also improved with continued subcutaneous semaglutide vs placebo (all $P<.001$). Gastrointestinal events were reported in 49.1% of participants who continued subcutaneous semaglutide vs 26.1% with placebo; similar proportions discontinued treatment because of adverse events with continued semaglutide (2.4%) and placebo (2.2%).

Conclusions and Relevance Among adults with overweight or obesity who completed a 20-week run-in period with subcutaneous semaglutide, 2.4 mg once weekly, maintaining treatment with semaglutide compared with switching to placebo resulted in continued weight loss over the following 48 weeks.

Continued use of GLP-1 RA is needed to maintain weight loss: STEP 4 trial



Rubino D et alJAMA. 2021 Apr 13;325(14):1414-1425. doi: 10.1001/jama.2021.3224. PMID: 33755728; PMCID: PMC7988425.

SEMAGLUTIDE: STUDIES. STEP 8

OBJECTIVE To compare the efficacy and adverse event profiles of once-weekly subcutaneous semaglutide, 2.4 mg, vs once-daily subcutaneous liraglutide, 3.0 mg (both with diet and physical activity), in people with overweight or obesity.

DESIGN, SETTING, AND PARTICIPANTS Randomized, open-label, 68-week, phase 3b trial conducted at 19 US sites from September 2019 (enrollment: September 11-November 26) to May 2021 (end of follow-up: May 11) in adults with body mass index of 30 or greater or 27 or greater with 1 or more weight-related comorbidities, without diabetes (N = 338).

INTERVENTIONS Participants were randomized (3:1:3:1) to receive once-weekly subcutaneous semaglutide, 2.4 mg (16-week escalation; n = 126), or matching placebo, or once-daily subcutaneous liraglutide, 3.0 mg (4-week escalation; n = 127), or matching placebo, plus diet and physical activity. Participants unable to tolerate 2.4 mg of semaglutide could receive 1.7 mg; participants unable to tolerate 3.0 mg of liraglutide discontinued treatment and could restart the 4-week titration. Placebo groups were pooled (n = 85).

MAIN OUTCOMES AND MEASURES The primary end point was percentage change in body weight, and confirmatory secondary end points were achievement of 10% or more, 15% or more, and 20% or more weight loss, assessed for semaglutide vs liraglutide at week 68. Semaglutide vs liraglutide comparisons were open-label, with active treatment groups double-blinded against matched placebo groups. Comparisons of active treatments vs pooled placebo were supportive secondary end points.

RESULTS Of 338 randomized participants (mean [SD] age, 49 [13] years; 265 women [78.4%]; mean [SD] body weight, 104.5 [23.8] kg; mean [SD] body mass index, 37.5 [6.8]), 319 (94.4%) completed the trial, and 271 (80.2%) completed treatment. The mean weight change from baseline was −15.8% with semaglutide vs −6.4% with liraglutide (difference, −9.4 percentage points [95% CI, −12.0 to −6.8]; $P < .001$); weight change with pooled placebo was −1.9%. Participants had significantly greater odds of achieving 10% or more, 15% or more, and 20% or more weight loss with semaglutide vs liraglutide (70.9% of participants vs 25.6% [odds ratio, 6.3 {95% CI, 3.5 to 11.2}], 55.6% vs 12.0% [odds ratio, 7.9 {95% CI, 4.1 to 15.4}], and 38.5% vs 6.0% [odds ratio, 8.2 {95% CI, 3.5 to 19.1}], respectively; all $P < .001$). Proportions of participants discontinuing treatment for any reason were 13.5% with semaglutide and 27.6% with liraglutide. Gastrointestinal adverse events were reported by 84.1% with semaglutide and 82.7% with liraglutide.

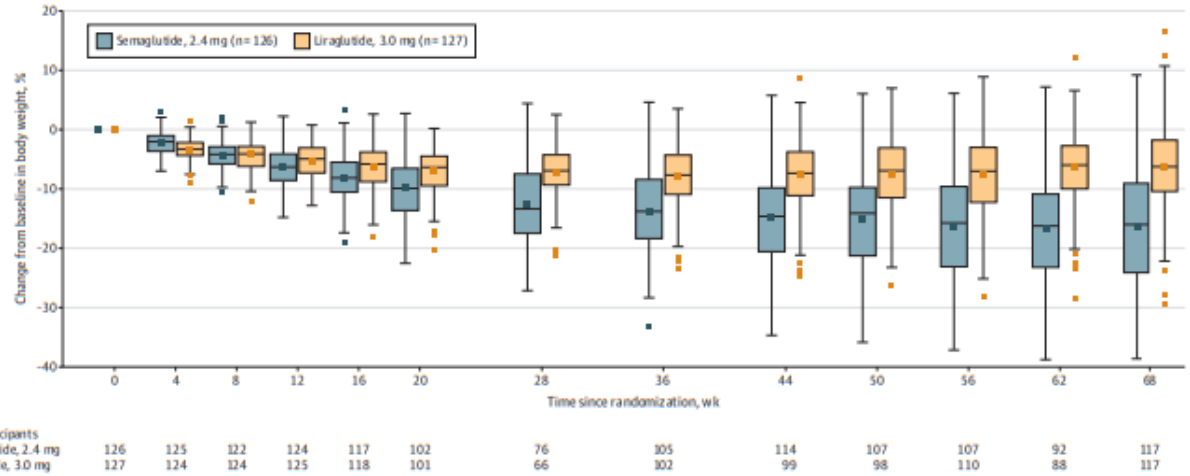
CONCLUSIONS AND RELEVANCE Among adults with overweight or obesity without diabetes, once-weekly subcutaneous semaglutide compared with once-daily subcutaneous liraglutide, added to counseling for diet and physical activity, resulted in significantly greater weight loss at 68 weeks.

JAMA | Original Investigation

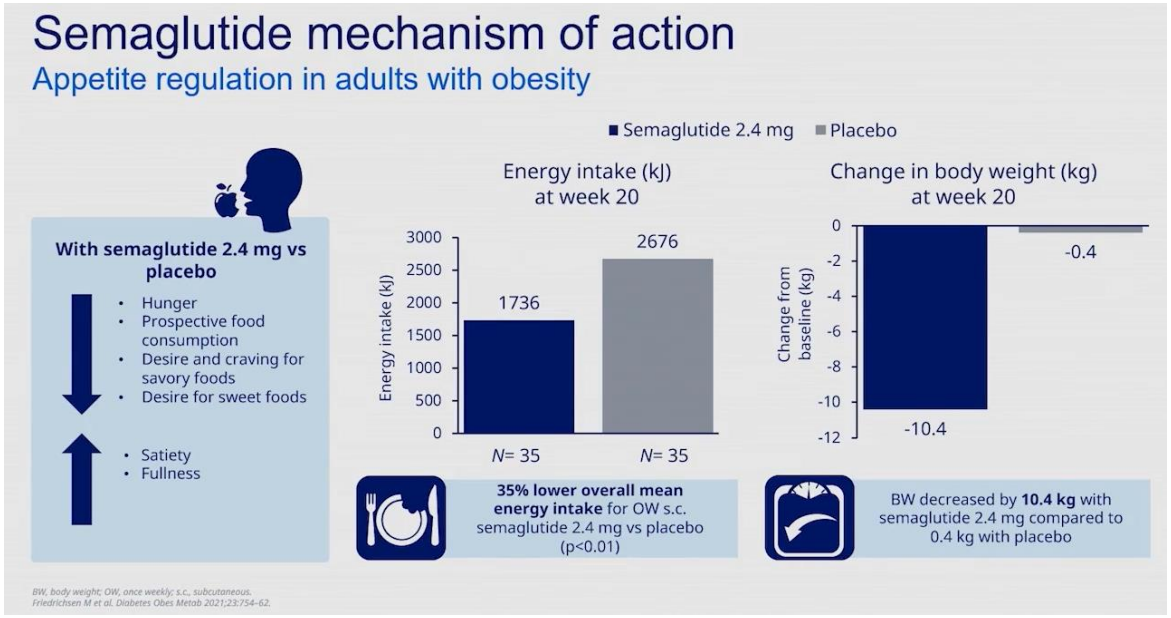
Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes
The STEP 8 Randomized Clinical Trial

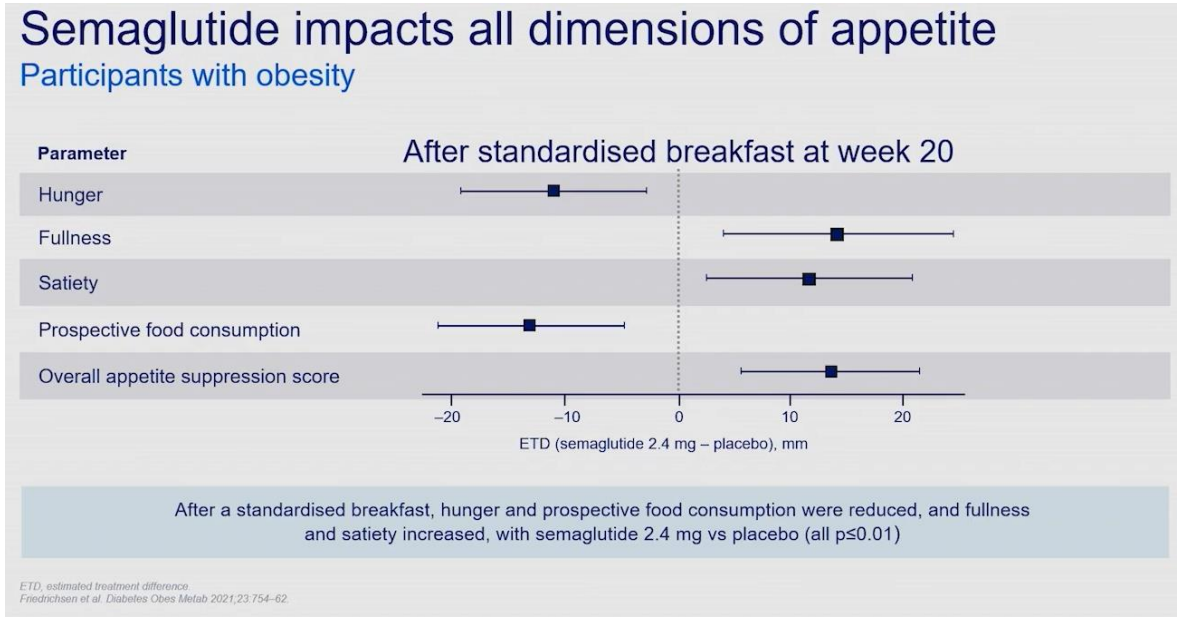
Domenica M. Rubino, MD; Frank L. Greenway, MD; Usman Khalid, MD, PhD; Patrick M. O'Neil, PhD; Julio Rosenstock, MD; Rasmus Sørrig, MD, PhD; Thomas A. Wadden, PhD; Alicja Wizert, PhD; W. Timothy Garvey, MD; for the STEP 8 Investigators

Figure 2. Percentage Change in Body Weight From Baseline to Week 68 (Observed In-Trial Data; Full Analysis Set)



SEMAGLUTIDE: STUDIES APPETITE-RELATED





OTHER TREATMENTS

Molecules on the horizon and in the pipeline

Next, we look at five of the investigational anti-obesity treatment molecules that are either newly available in 2021 and 2022, or nearest to becoming available, and which appear to have the potential to bridge the gap between 5-10% total body weight loss and perhaps meet larger patient/provider and medical therapy efficacy goals:

- **Semaglutide:** An injectable GLP-1 receptor agonist
- **Setmelanotide:** A newly-approved medication for the treatment of obesity caused by rare genetic disorders in appetite signalling
- **Tirzepatide:** A dual agonist medication that targets both GLP-1 receptors and GIP
- **Bimagrumab:** A human monoclonal antibody that preferentially improves body composition via muscle mass gain as well as providing weight loss
- **Cagrisema:** A combination of an amylin analogue and semaglutide

LIRAGLUTIDE 3 MG (SAXENDA®)

Fig.1

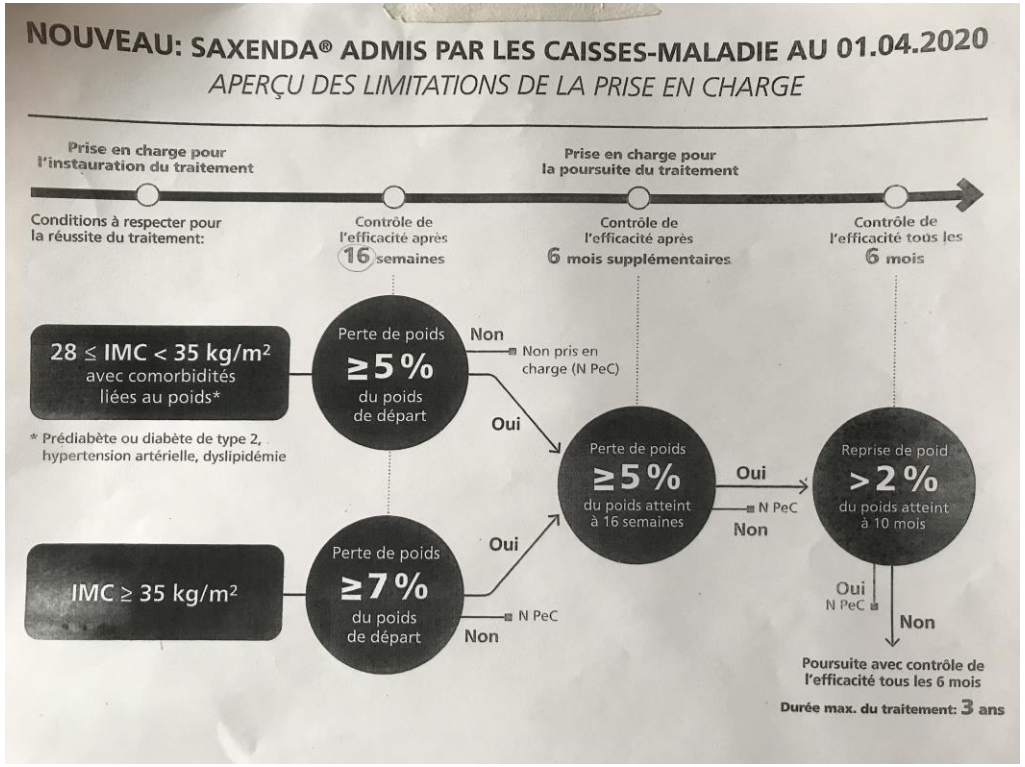


Fig 2

- 1x/jour sc
- **BMI ≥ 35 Kg/m2 ou ≥ 28 Kg/m2 si pré-DM, HTA ou HCT**
- **Remboursé depuis 2020 uniquement si prescrit par des specialists**
  - **Algorythme visible dans la figure 2**
- Durée max 3 ans ….

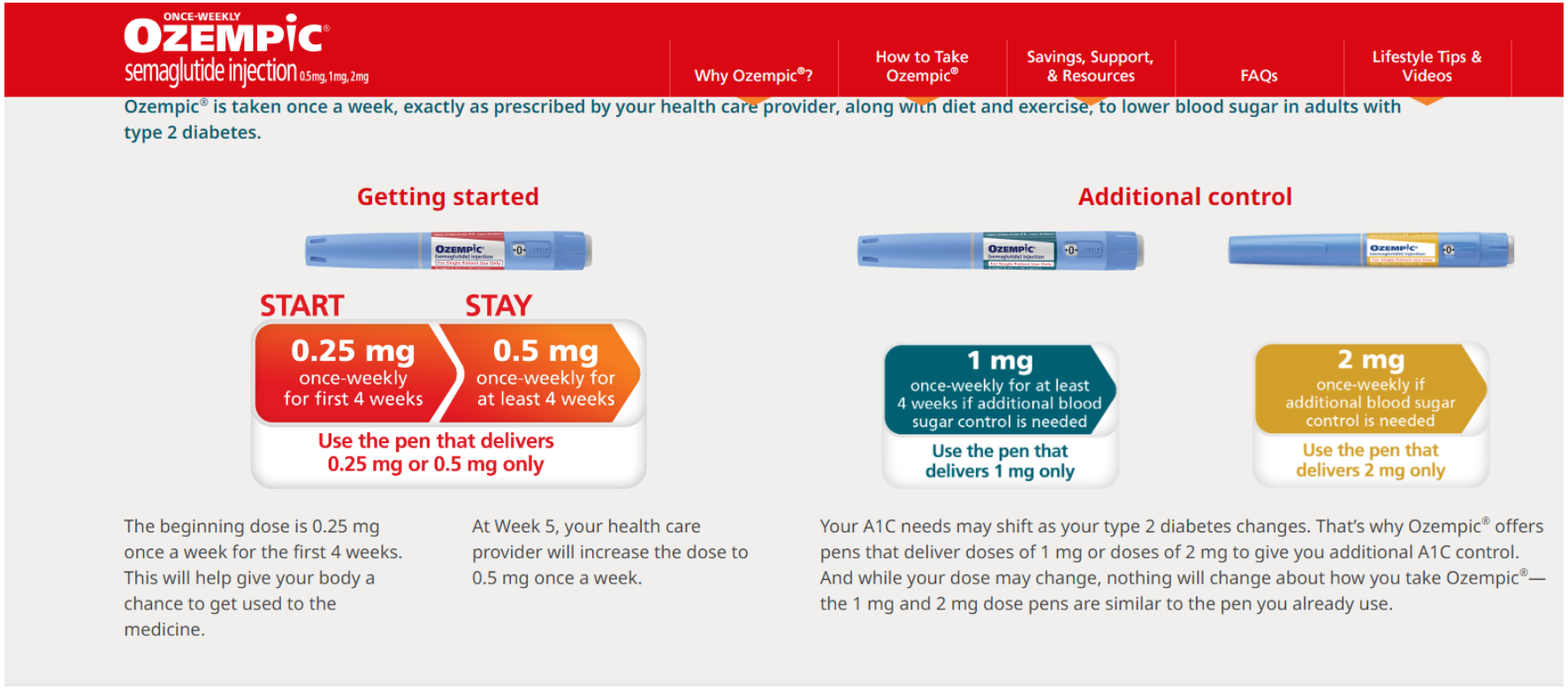
LIRAGLUTIDE (SAXENDA®) IN ADOLESCENTS

- Liraglutide 3 mg (Saxenda©) est autorisé chez les adolescents à partir de 12 ans
- Poids ≥ 60 kg et une obésité selon les valeurs limites acceptées au niveau international (correspond à l'IMC ≥ 30 kg/m^2 chez les adultes)
- Pas de remboursement par les caisses-maladie

SEMAGLUTIDE (WEGOVY®)

- Prévu pour mars-avril 2023
- Conditions de remboursement en train d'être discutées avec OFSP
  - Probablement cut-offs pondéraux à respecter comme le Saxenda

SEMAGLUTIDE (OZEMPIC®)

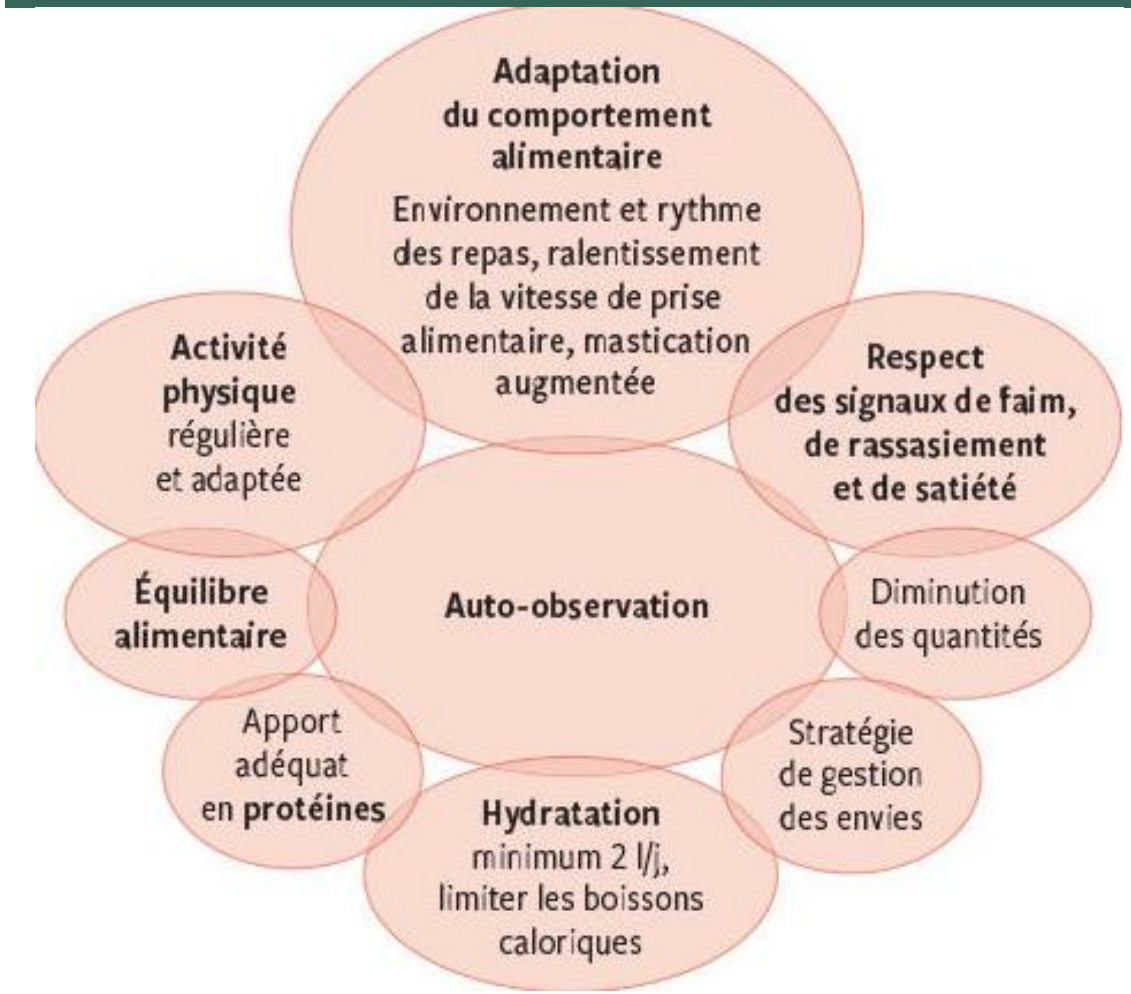


- Validé uniquement pour les personnes souffrant de DMT2
- Ne pas prescrire off-label (rupture de stock en Suisse en janvier 2023) pour obésité sans DMT2
- En 2ème ligne après la Metformine (association précoce)
- Si doutes, ne pas hésiter à demander à un collègue diabétologue

DESPITE OBESITY BEING A CHRONIC DISEASE …

- Remboursés en Suisse pour max 3 ans
- Drop-out 1x → drop-out définitif
- **Comment augmenter les chances de succès pour éviter les drop-out?**
- **Comment faire face à l'interruption de la prise en charge après 3 ans?**

MULTIDISCIPLINARY APPROACH



A l'heure actuelle pas de données quantitatives mais selon l'expérience clinique romande …

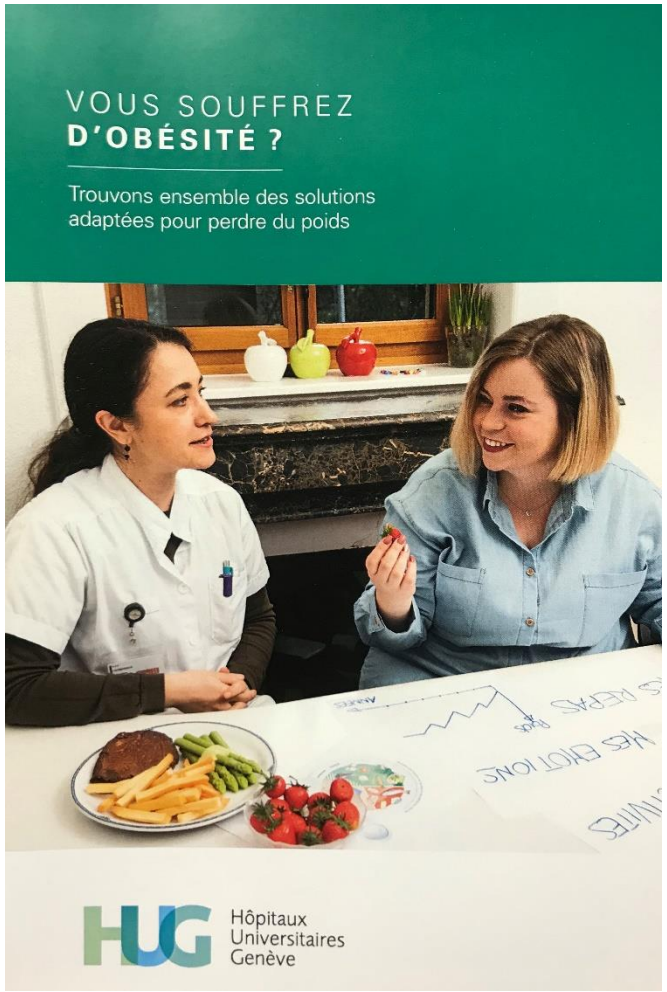
NUTRITION-OBÉSITÉ

Liraglutide dans le traitement de l'obésité : une prise en charge multidisciplinaire

Séverine Nest , Patricia Gilet , Véronique Di Vetta , Fanny Dudin , Johanna Frantz , Lucie Favre

DOI: 10.53738/REVMED.2022.18.774.516

EDUCATION THERAPEUTIQUE DU PATIENT AUX HUG



OBÉSITÉ ET DIABÈTE

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→ info.contrepoids@hcuge.ch

Mission du programme Contrepoids

Contrepoids est un programme de soins qui s'intéresse à la prévention et au traitement de l'obésité qui, par les problèmes de santé et de morbidité qu'elle engendre, est devenue un enjeu de santé publique majeur.

Novateur en Suisse, Contrepoids sert de modèle pour :

- Promouvoir la santé présente et future ;
- Réduire les conséquences et les coûts considérables provoqués par l'obésité.

Les objectifs

- Offrir une prise en charge optimale à l'ensemble des patients souffrant d'un excès de poids ou d'obésité ;
- Améliorer la formation des soignants et encourager les recherches cliniques dans ce domaine ;
- Promouvoir l'activité physique et une alimentation saine auprès de l'ensemble du personnel.

Futurs parents, enfants, parents, grands-parents, arrières grands-parents, mais aussi les gouvernements, communautés, institutions de santé, écoles et entreprises ... ont chacun leur rôle à jouer.

Merci pour votre attention