

Too Much of a Good Thing (How to Manage GLP-1 Side Effects and What to Do When They Don't Work!)

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Disclosure

Advisory Board: AbbVie; Addition; Altimune; Amgen; AstraZeneca; Autonomy Bio; Biohaven; Boehringer Ingelheim; Carmot/Roche/Regeneron; CinRx; Currax; Eli Lilly; Epitomee Medical; Fractyl Health; i2o Therapeutics; ICON; Kailera; Nestle Healthcare Nutrition; Novo Nordisk; Pfizer; Protagonist Therapeutics; Regor; Souffle; Source Bio; Structure Therapeutics; Tenvie; Viking Therapeutics; Wondr Health; Zealand Pharma

Consultant: Calibrate; PPD; Rhythm; Weight Watchers

Data Monitoring Committee: CinRx; Eli Lilly; Rhythm

Speaker's Bureau: Boehringer Ingelheim; Eli Lilly; Novo Nordisk

Stock Options: Calibrate; Epitomee Medical; Ro



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Objectives

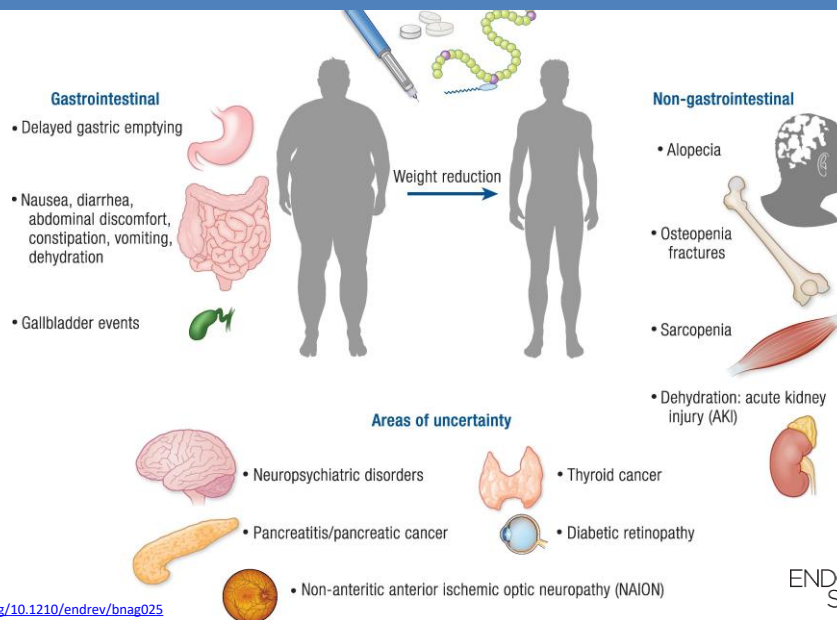
At the end of the presentation, attendees will be able to discuss

1. Safety and tolerability issues due to GLP-1 meds and to weight loss itself;
2. Strategies to lose weight safely while achieving health benefits and avoiding adverse consequences of GLP-1 medications; and
3. Strategies to improve weight loss efficacy in patients who do not respond optimally to GLP-1 medications.



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Safety Considerations with GLP 1 Meds

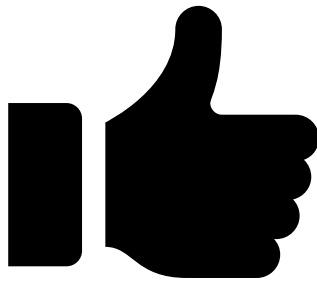


Endocr Rev, bnag025, <https://doi.org/10.1210/endrev/bnag025>

ENDOCRINE
SOCIETY

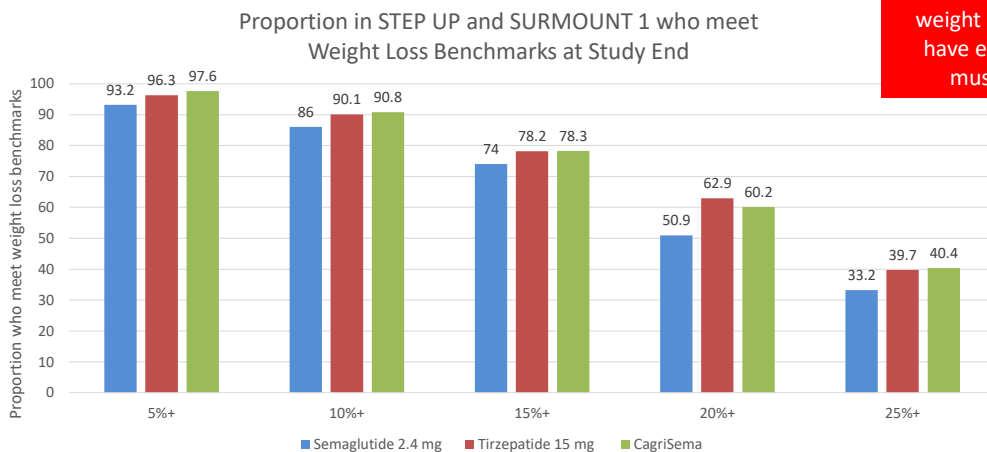
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Importantly: The New GLP-1 Medications Produce Clinically Significant Weight Loss in Almost All Patients



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Categorical Weight Loss with Semaglutide 7.2 mg, Tirzepatide 15 mg and Cagrisema 2.4/2.4 mg



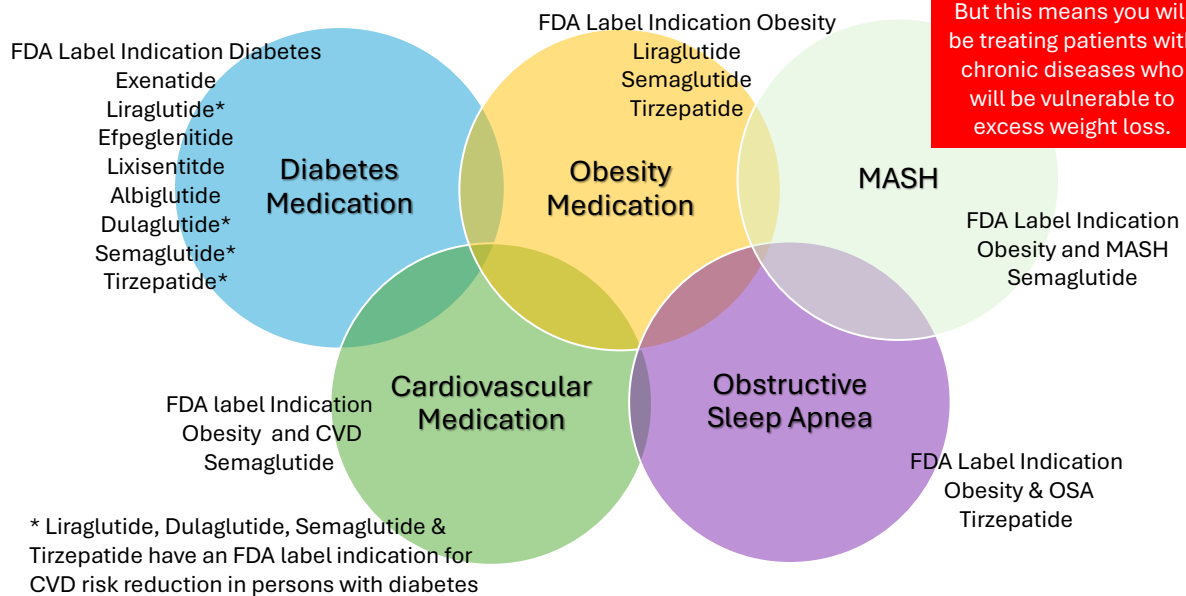
But this means you will be treating patients who can lose unhealthy amounts of weight and who don't have extra bone and muscle to lose.

Wharton S et al. Lancet Diabetes Endocrinol 2025;13:949-963. (STEP UP)
Jastreboff A, et al. N Engl J Med. 2022;387(3):205-216 [SURMOUNT1].
Garvey WT et al. New Engl J Med 2025; 14;393(7):635-647 (REDEFINE 1)

On Treatment Analysis

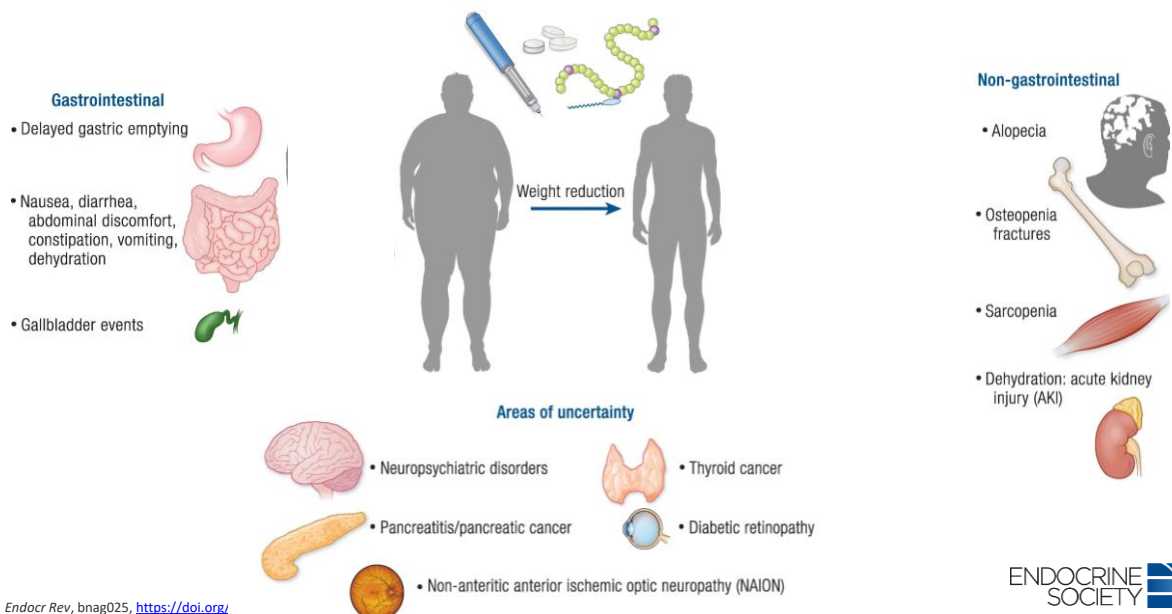
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Make No Mistake: The New GLP-1 Medications Are GOOD! (For Chronic Disease Modifications)



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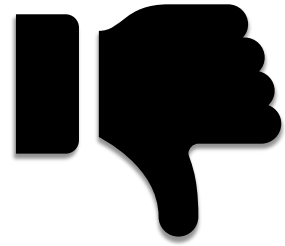
Safety Considerations with GLP 1 Meds



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Safety Issues with GLP-1 Medications (The Labels of All GLP-1 Medications Include....)

- **Boxed warning:** contraindicated in persons with MEN type 2 and in those with personal or family history of medullary thyroid cancer
- Contraindicated in those with allergic reactions (fortunately these are rare)
- Should not be used in pregnancy
- Pancreatitis warning in all labels
- Gall bladder disease (cholelithiasis and cholecystitis)
- Acute renal injury, secondary to dehydration from nausea and vomiting.
- Exacerbation of retinopathy in patients with diabetes and rapid lowering of A1c



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Let's Discuss the Differences in
Safety and Tolerability for the
Available GLP-1s

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Randomized Comparison of Semaglutide (1.7 or 2.4 mg) vs. Tirzepatide (5 or 10 mg)

Selected Tolerability Issues Compared Head to Head

Adverse Event	Tirzepatide N (%)	Semaglutide N (%)
Vomiting	56 (15.0)	80 (21.3)
Fatigue	39 (10.4)	46 (12.2)
Eructation	37(9.9)	29(7.7)
Injection site reaction	32 (8.6)	1 (0.3)
GERD	23(6.1)	40(10.6)
Dyspepsia	22(5.9)	26(7.4)

Table 3. Adverse Events and Safety.*

Variable	Tirzepatide (N=376)	Semaglutide (N=376)	Total (N=752)
number of participants (percent)			
Adverse events that occurred or worsened during the treatment period	287 (76.7)	297 (79.0)	584 (77.8)
Serious adverse events	18 (4.8)	13 (3.5)	31 (4.1)
Adverse events leading to death	0	0	0
Discontinuation from the trial because of adverse events	6 (1.6)	4 (1.1)	10 (1.3)
Discontinuation of the trial because of adverse events	23 (6.1)	30 (8.0)	53 (7.1)
Discontinuation of the trial because of gastro-intestinal adverse events	10 (2.7)	21 (5.6)	31 (4.1)
Adverse events occurring in ≥3% of participants in either group†			
Nausea	163 (43.6)	167 (44.4)	330 (44.0)
Constipation	101 (27.0)	107 (28.5)	208 (27.7)
Diarrhea	66 (17.5)	65 (17.4)	131 (17.4)
Vomiting	56 (15.0)	80 (21.3)	136 (18.1)
Conjunctivitis disease 2019	31 (8.2)	47 (12.5)	78 (10.3)
Fatigue	39 (10.4)	46 (12.2)	85 (11.3)
Eructation	37 (9.9)	29 (7.7)	66 (8.8)
Injection-site reaction	32 (8.6)	1 (0.3)	33 (4.4)
Upper respiratory tract infection	32 (8.6)	43 (11.4)	75 (10.0)
Allegria	31 (8.2)	27 (7.2)	58 (7.7)
Abdominal distension	27 (7.2)	24 (6.4)	51 (6.8)
Headache	27 (7.2)	27 (7.2)	54 (7.2)
Abdominal pain	24 (6.4)	26 (6.9)	50 (6.7)
Diabetes	24 (6.4)	18 (4.8)	42 (5.6)
Gastroesophageal reflux disease	22 (5.9)	40 (10.6)	62 (8.4)
Dyspepsia	22 (5.9)	26 (7.4)	48 (6.7)
Decreased appetite	17 (4.5)	19 (5.1)	36 (4.8)
Nasopharyngitis	17 (4.5)	23 (6.1)	40 (5.3)
Sinusitis	11 (2.9)	21 (5.6)	32 (4.3)
Adverse events leading to discontinuation of the trial treatment‡			
Nausea	5 (1.3)	7 (1.9)	12 (1.6)
Vomiting	3 (0.8)	4 (1.1)	7 (0.9)
Constipation	1 (0.3)	3 (0.8)	4 (0.5)
Diarrhea	1 (0.3)	2 (0.5)	3 (0.4)
Fatigue	1 (0.3)	1 (0.3)	2 (0.3)
Cholelithiasis	0	2 (0.5)	2 (0.3)

* Safety end points were analyzed with the use of data from participants regardless of whether participants adhered to treatment, initiated other antidiabetic medication, or underwent bariatric surgery.
† Adverse events are listed according to preferred terms in the Medical Dictionary for Regulatory Activities, version 24.1.
‡ Events are adverse events that were reported more than once.

Aronne LJ et al. N Engl J Med 2025;393:26-36.

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Oral Semaglutide Safety and Tolerability

- Label is shared with injectable semaglutide and has all the GLP-1 RA important safety information.
- GI side effects are the most common adverse events.
- With oral therapy, 6.9% of patients treated with 25 mg tablets and 5.9% patients treated with placebo permanently discontinued treatment as a result of adverse reactions.
- Oral semaglutide shares and indication for CVD event reduction

25 mg tablets are indicated in combination with a reduced calorie diet and increased physical activity:

- To reduce the risk of major adverse CV events (CV death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established CV disease and either obesity or overweight. (1)
- To reduce excess body weight and maintain weight reduction long term in adults with obesity, or in adults with overweight in the presence of at least one weight-related comorbid condition. (1)

https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/220934Orig1s000lbl.pdf

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Orforglipron Safety and Tolerability

- Label has all the GLP-1 RA important safety information.
- GI side effects are the most common adverse events.
- Discontinuation rates for Adverse Events are 4-8%
- Label has precautions for concomitant inhibitors or inducers of Cyp3A4 enzyme

	Placebo (N=1,576)	5.5 mg once daily (N=1,051)	9 mg once daily (N=1,055)	17.2 mg once daily (N=1,049)
Adverse Reaction	%	%	%	%
Nausea	10	26	34	35
Constipation	9	20	27	24
Diarrhea	11	21	23	25
Vomiting	4	13	21	24
Dyspepsia	4	12	16	13
Abdominal pain*	7	13	14	14
Headache	7	8	9	9
Abdominal distension	3	7	9	8
Fatigue*	4	6	7	9
Eructation	1	6	8	8
Gastroesophageal reflux disease	2	6	6	7
Flatulence	2	5	6	6
Hair loss*	2	4	4	5

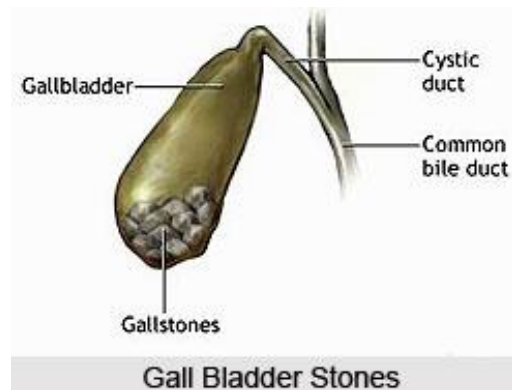
* Includes other related terms.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/220934Orig1s000lbl.pdf

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Managing Gall Bladder Disease

- Obesity increases risk for gall stones.
- Weight loss, especially rapid weight loss, increases risk for gall stones and acute gall bladder disease.
- The risk of gallbladder disease with GLP 1 medications is greater than that which can be attributed to weight loss.
- Have a high index of suspicion. In clinical trials, ~3% have gall bladder disease.
- Treat appropriately.



Everhart JE. Et al. Ann Intern Med. 1993 Nov 15;119(10):1029-35.

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Dealing with Nausea and Vomiting

- Nausea is common – in up to half of patients
 - Vomiting less common
 - Dose-related, occurs when starting or increasing dose
 - Titrate! Many patients do not need top dose
 - Occurs on first or second day
 - If nausea lasts more than a day or is severe, don't titrate up, stay on it
 - If nausea and vomiting are severe, reduce the dose
 - **Severe vomiting can trigger acute renal failure: don't let your patient become dehydrated**
- Diarrhea and Constipation possible (treat symptomatically)
- Delayed gastric emptying
 - Can worsen GERD
 - Antacids and proton pump inhibitors



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Dealing with On-Target Side Effects: Risk of Aspiration with Anesthesia

2025 Consensus Recommendation

- fast from solid foods for 24 hours and stick to clear liquids prior to a procedure requiring anesthesia.

Anesthesiologist may want patients off GLP-1 for 1-2 weeks.

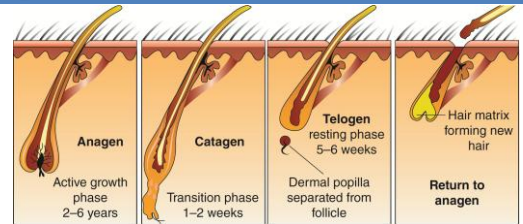


Oprea AD, et al. Perioperative management of patients taking glucagon-like peptide 1 receptor agonists: Society for Perioperative Assessment and Quality Improvement (SPAQI) multidisciplinary consensus statement. British Journal of Anesthesia, Volume 135, Issue 1, 48 - 78

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Dealing with Side Effects of Robust Weight Loss: Hair Shedding

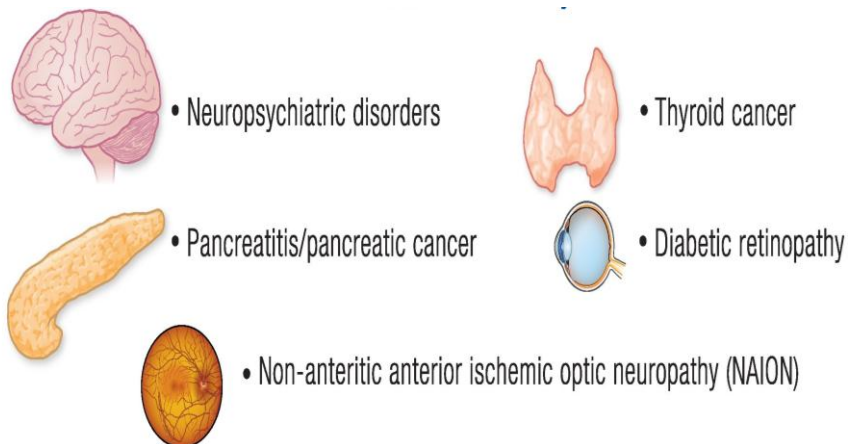
- Telogen effluvium (Hair shedding)
- Hair follicles are in
 - Anagen phase (active growth, 90%)
 - Catagen phase (transition phase, 1%)
 - Telogen phase (resting, 10%)
- With rapid weight loss and robust weight loss (~15% over 3.5 months), hair shedding can occur.
 - Regrowth usually occurs at about 6-12 months
- Other causes anesthesia, childbirth, nutritional deficiency, chemotherapy, hypothyroidism



Asghar F, et al. Telogen Effluvium: A Review of the Literature. Cureus. 2020 May 27;12(5):e8320.

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Areas of Uncertainty



Endocr Rev, bnag025, <https://doi.org/10.1210/endo/bnag025>

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Mental Health Adverse Outcomes Review of 32 Studies

“Post-bariatric surgery patients had higher self-harm/suicide attempt risk compared to age-, sex-, and BMI-matched controls.”

Castaneda D, Popov VB, Wander P, Thompson CC. Risk of Suicide and Self-harm Is Increased After Bariatric Surgery-a Systematic Review and Meta-analysis. *Obes Surg.* 2019 Jan;29(1):322-333.

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Robust Weight Loss with Newer OMMs

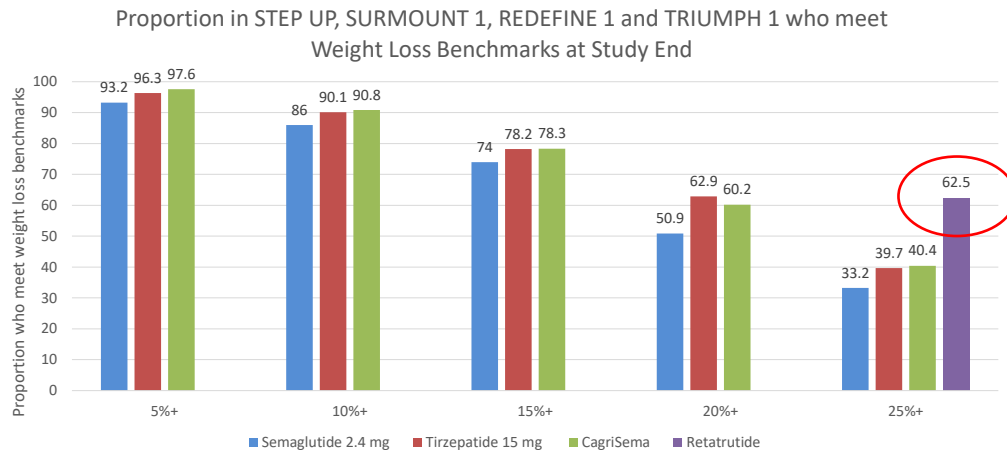
Some patients will experience profound reduction in appetite with newer OMMs.

It is important to assure adequate nutritional intake in those patients.

OMM = Obesity Management Medications

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Categorical Weight Loss with Semaglutide 7.2 mg, Tirzepatide 15 mg and Cagrisema 2.4/2.4 mg and Retatrutide 12 mg



Wharton S et al. Lancet Diabetes Endocrinol 2025;13:949–963. (STEP UP)

Jastreboff A, et al. N Engl J Med. 2022;387(3):205–216 [SURMOUNT1].

Garvey WT et al. New Engl J Med 2025; 14:393(7):635–647 (REDEFINE 1)

<https://investor.lilly.com/news-releases/news-release-details/lillys-triple-agonist-retatrutide-delivered-powerful-weight-loss>

On Treatment Analysis

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AACE/TOS/ASMBS/OMA/ASA 2019 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*

Jeffrey I. Mechanick, MD, FACP, FACN, MACE¹; Caroline Apovian, MD²; Stacy Brethauer, MD³; W. Timothy Garvey, MD, FACE⁴; Aaron M. Joffe, DO, FCCM⁵; Julie Kim, MD⁶; Robert F. Kushner, MD⁷; Richard Lindquist, MD, FAASP⁸; Rachel Pessah-Pollack, MD, FACE⁹; Jennifer Seger, MD¹⁰; Richard D. Urman, MD, MBA, CPE¹¹; Stephanie Adams, PhD¹²; John B. Cleek, MD¹³; Riccardo Correa, MD, FACE¹⁴; M. Kathleen Figaro, MD, MS, FACE¹⁵; Karen Flanders, MSN, CNP, CBN¹⁶; Jayleen Grams, MD, PhD¹⁷; Daniel L. Hurley, MD, FACE¹⁸; Shanu Kothari, MD, FACS, FASMB¹⁹; Michael V. Seger, MD, FACS, FASMB²⁰; Christopher D. Still, DO, FACN, FACP²¹

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Donna Ryan, MD
Too Much of a Good Thing

AACE/TOS/ASMBS/OMA/ASA 2019 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*

When patients lose as much weight as bariatric surgery, we must have a similar approach.

Jeffrey I. Mechanick, MD, FACP, FACN, MACE¹; Caroline Apovian, MD²; Stacy Brethauer, MD³; W. Timothy Garvey, MD, FACE⁴; Aaron M. Joffe, DO, FCCM⁵; Julie Kim, MD⁶; Robert F. Kushner, MD⁷; Richard Lindquist, MD, FAASP⁸; Rachel Pessah-Pollack, MD, FACE⁹; Jennifer Seger, MD¹⁰; Richard D. Urman, MD, MBA, CPE¹¹; Stephanie Adams, PhD¹²; John B. Cleek, MD¹³; Riccardo Correa, MD, FACE¹⁴; M. Kathleen Figaro, MD, MS, FACE¹⁵; Karen Flanders, MSN, CNP, CBN¹⁶; Jayleen Grams, MD, PhD¹⁷; Daniel L. Hurley, MD, FACE¹⁸; Shanu Kothari, MD, FACS, FASMBS¹⁹; Michael V. Seger, MD, FACS, FASMBS²⁰; Christopher D. Still, DO, FACN, FACP²¹

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Why Weight Loss Safety Measures Are Important: The Bariatric Surgery Example

- Bariatric surgery: Most patients over 40 kg/m², and almost all >35 kg/m²
- Follow-up schedule for Surgical Procedures

Bariatric surgery patients meet with a dietitian, take supplements, and have strict exercise regimens.

Procedure	Initial	Interval Until Stable	Once stable
LAGB	1 month	Every 1-2 months	Every 12 months
LSG	1 month	Every 3-6 months	Every 12 months
RYGB	1 month	Every 3 months	Every 6-12 months
BPD/DS biliopancreatic diversion with duodenal switch	1 month	Every 3 months	Every 6 months

Mechanick J, et al. *Endocr Pract.* 2019;25(Suppl 2):1-75.

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Acute Consequences of Negative Energy Balance

Acute Effects

- Reduction in insulin needs
 - Sulfonylureas and insulin pose danger of hypoglycemia
- Depletion of glycogen stores
 - Rapid water mobilization, diuresis
 - Diuretics may pose danger of hypotension
- Diuresis and electrolyte imbalance
 - Cardiac arrhythmia
- Constipation



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Recommendations



STOP OR REDUCE THE
INSULIN SECRETAGOGUES
FOR PATIENTS WHO ARE IN
NEGATIVE ENERGY BALANCE



STOP OR REDUCE THE
DIURETICS FOR PATIENTS
WHO ARE LOSING WEIGHT
RAPIDLY



MONITOR THE PATIENT AND
INTERVENE IF LOSS IS TOO
RAPID

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Consequences of Rapid Weight Loss

Lack of high-quality protein: heart failure and sudden death associated with starvation diets (maintain intake >500 kcal/d - >900 kcal/day is preferable - and use high-quality protein source)

Gall bladder disease

Rapid reduction in glycemia may exacerbate retinopathy

Loss of lean body mass

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How Many Calories in a Pound of Fat Lost?



NIH Public Access

Author Manuscript

Int J Obes (Lond). Author manuscript; available in PMC 2008 September 1.

Published in final edited form as:

Int J Obes (Lond). 2008 March ; 32(3): 573-576.

What is the Required Energy Deficit per unit Weight Loss?

Kevin D. Hall

Laboratory of Biological Modeling, National Institute of Diabetes & Digestive & Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892

Abstract

One of the most pervasive weight loss rules is that a cumulative energy deficit of 3500 kcal is required per pound of body weight loss, or equivalently 32.2 MJ per kg. Under what conditions is it appropriate to use this rule of thumb and what are the factors that determine the cumulative energy deficit required per unit weight loss? Here, I examine this question using a modification of the classic Forbes equation that predicts the composition of weight loss as a function of the initial body fat and magnitude of weight loss. The resulting model predicts that a larger cumulative energy deficit is required per unit weight loss for people with greater initial body fat - a prediction supported by published weight loss data from obese and lean subjects. This may also explain why men can lose more weight than women for a given energy deficit since women typically have more body fat than men of similar body weight. Furthermore, additional weight loss is predicted to be associated with a lower average cumulative energy deficit since a greater proportion of the weight loss is predicted to result from loss of lean body mass which has a relatively low energy density in comparison with body fat. The rule of thumb approximately matches the predicted energy density of lost weight in obese subjects with an initial body fat above 30 kg but overestimates the cumulative energy deficit required per unit weight loss for people with lower initial body fat.

"The rule of thumb approximately matches the predicted energy density of lost weight in obese subjects with an initial body fat above 30 kg but overestimates the cumulative energy deficit required per unit weight loss for people with lower initial body fat."

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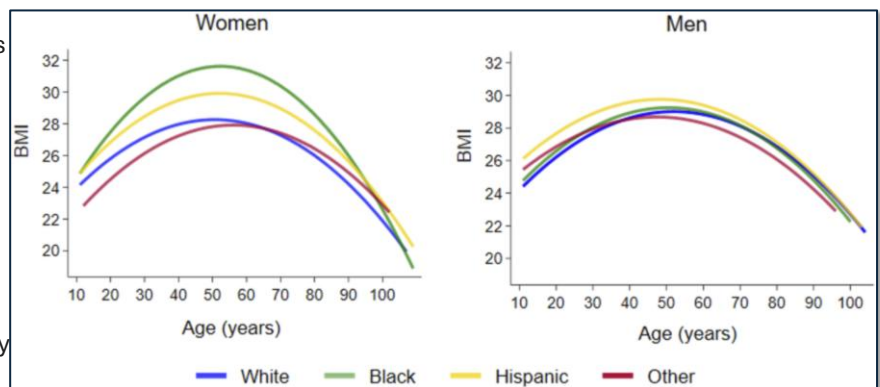
Who Is at Risk for Too Much Weight Loss?

- Lower BMI (<35)
- Older individuals (because they start with lower lean mass)
- Older women (because of the higher risk of osteoporosis)
- Women (because of the cultural drive for slimness driving unrealistic body image)
- South Asian phenotype (because they start with lower lean mass)

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Body Weight Changes Across the Lifespan

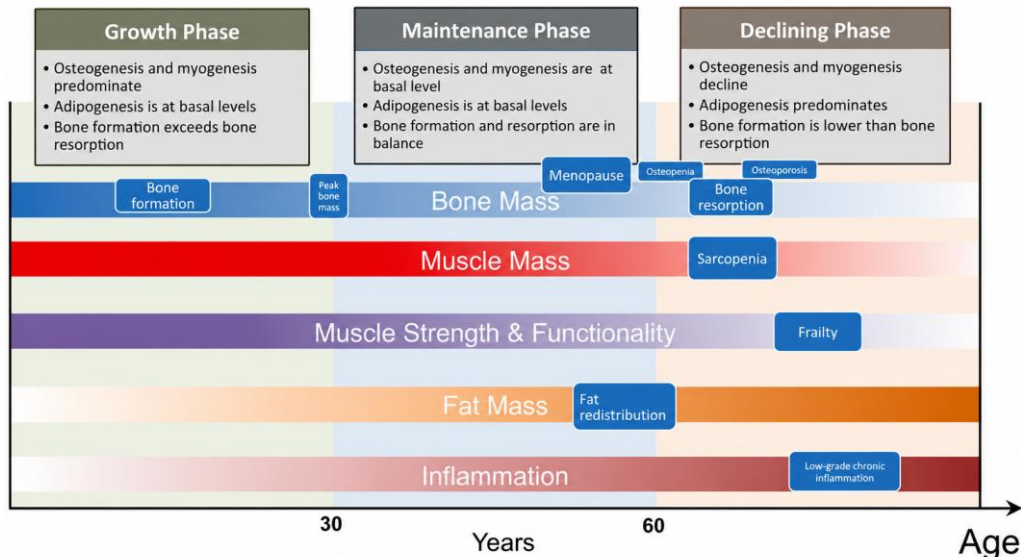
- Weight increases through age ~65 years and decreases thereafter
- On average, muscle mass declines with age, and even in older persons with stable weight, muscle mass is replaced by fat mass over time.
- Younger persons with obesity have increased lean mass. With aging, sarcopenic obesity can occur.



Yang, Y.C et al.. *Proc. Natl. Acad. Sci. USA* **2021**, 118, e2020167118.
 Alley DE, et al.. *J Gerontol A Biol Sci Med Sci*. 2008 Nov;63(11):1257-9.

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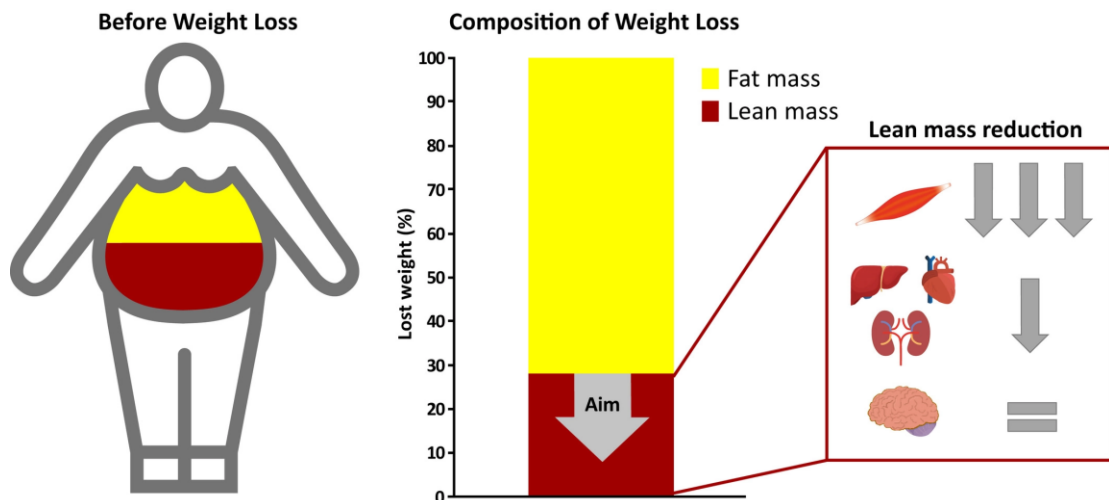
What Happens to Body Composition Across the Lifespan?



Journal of Endocrinology. <http://joe.endocrinology-journals.org> DOI: 10.1530/JOE-16-0603

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Body Composition Changes with Weight Loss Loss of Lean AND Fat Is Inevitable

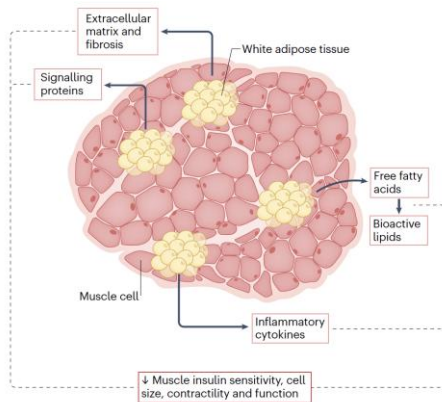


Christoffersen BØ, et al. Obesity (Silver Spring). 2022 Apr;30(4):841-857.

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Muscle Fat Infiltration with Aging Related to Poor Muscle Composition, Quality and Quantity

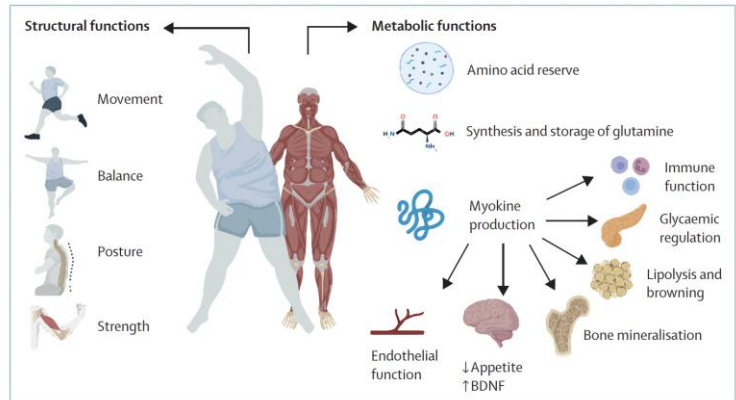
Muscle quality



Kahn DE, Bergman BC; *Diabetes* 2022

Goodpaster et al; *Nature Reviews Endocrinology* 2023

Muscle function & metabolic functions



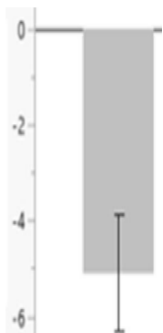
Slide courtesy E Ravussin ADA 2026

Prado, et al.; *Lancet Diabetes Endocrinol* 12; 2024

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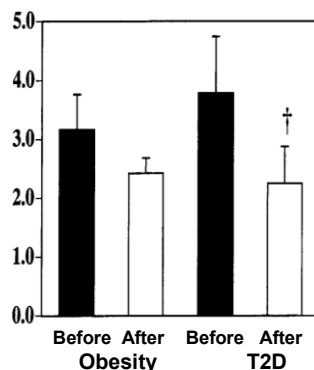
Effect of Weight Loss on Skeletal Muscle “Quality” It Is Possible to Lose Weight and Have Improved Muscle Function

**Intermuscular
Adipose Tissue after
10% Weight Loss (cm³)**



A. Goss et al.
Nutr Metab 2020

**Intramuscular triglyceride
before and after 14%
weight loss (%)**



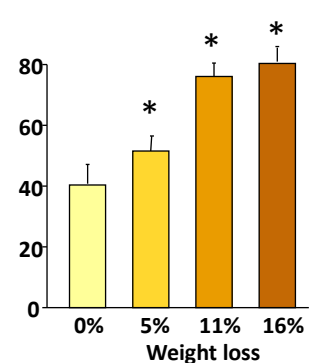
B. Goodpaster et al.
Metabolism 2000

**Skeletal muscle capillaries
before and after
20% weight loss**

	Pre	Post	% Δ
Capillary to fiber ratio	1.9	2.5	32
Capillary density (cap/mm ²)	634	974	54

P. Kern et al.
JCEM 1999

**Glucose rate of disposal
during insulin infusion
(umol/kg FFM/min)**



Magkos F et al.
Cell Metab 2016

Slide courtesy S Klein ADA 2026

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ARS Question #1

When Weight Is Lost Through Lifestyle Intervention or Medications, What Percentage of the Lost Weight as Fat-Free Mass Is Considered an Adaptive Response?

- A. 10%
- B. 25%
- C. 35%
- D. 45%



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Forbes' Rule – Quarter FFM Rule

Published in final edited form as:

Obes Rev. 2014 April ; 15(4): 310–321. doi:10.1111/obr.12143.

Weight Loss Composition is One-Fourth Fat-Free Mass: A Critical Review and Critique of This Widely Cited Rule

Steven B. Heymsfield¹, M. C. Cristina Gonzalez², Wei Shen³, Leanne Redman¹, and Dia Thomas⁴

¹Pennington Biomedical Research Center, Baton Rouge, LA, USA

²Post Graduate Program in Health and Behavior, Catholic University of Brasilia, Brazil

³New York Obesity Research Center, St. Luke's-Roosevelt Hospital, College of Physicians and Surgeons, NY, NY, USA

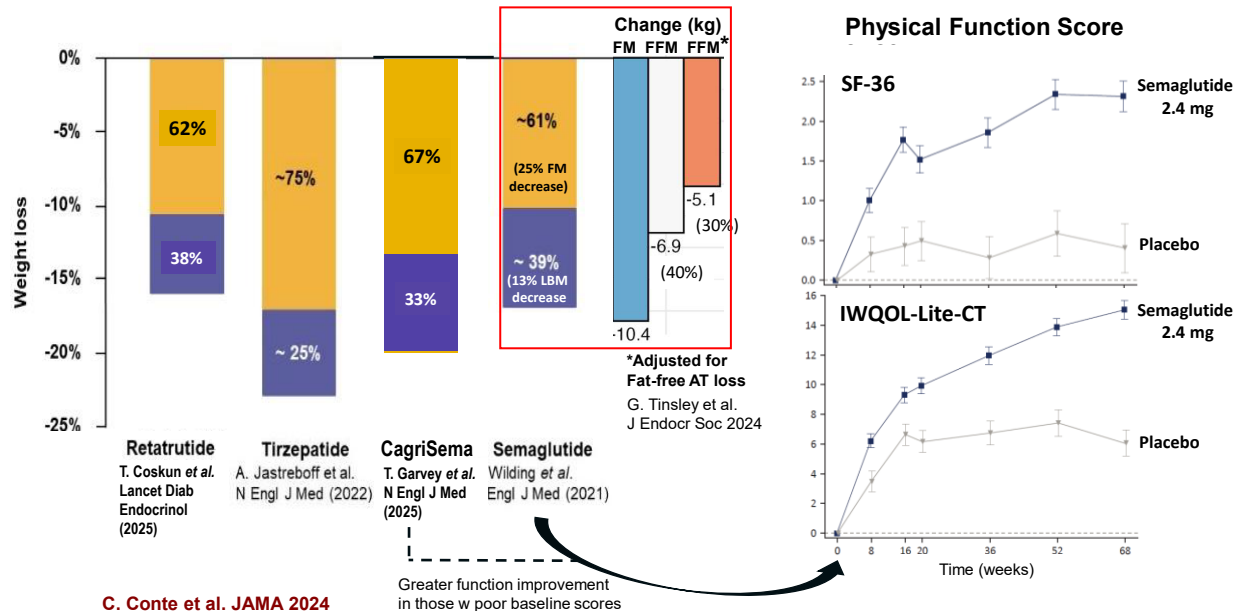
⁴Department of Mathematical Sciences, Montclair State University, Montclair, NJ, USA

Of weight that is lost, 25% is fat free mass

An orange starburst graphic with a black outline, containing the text 'Of weight that is lost, 25% is fat free mass'.

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What Do the Data Show? Changes in FFM/LBM After GLP-1 Therapy



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Comments: That Was Reassuring, But...

- Mean data are reported in clinical trials. We need data in **individuals who are at risk... who do not have lean mass to lose**
- At risk:
 - Those with central adiposity and low lean mass
 - Those with sarcopenic obesity
 - Older individuals
 - Individuals who start with lower BMI

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Interventions to Maintain Muscle Mass and Function/Strength

Exercise Training

PERSPECTIVE JAMA Published online May 4, 2026

The Conundrum of Exercise for Weight Management in the GLP-1 Receptor Agonist Era

Daniel E. Lieberman, PhD; Daniel H. Aslan, PhD; Steven B. Heymsfield, MD

Lieberman et al; JAMA 2026

- Only 20% of patients are prescribed exercise
- Poor adherence to adequately prescribed doses
- Exercise promote fat oxidation
- Exercise may increase short-term RMR
- **Often ineffective because of low adherence**
- **Resistance exercise to maintain muscle mass**

High Protein Diet / Supplement



From the Society

Nutritional priorities to support GLP-1 therapy for obesity: a joint Advisory from the American College of Lifestyle Medicine, the American Society for Nutrition, the Obesity Medicine Association, and The Obesity Society

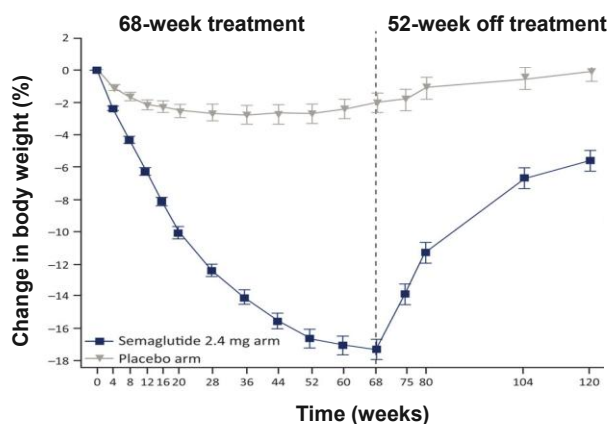
Darush Mozaffarian^{1,2}, Monica Agarwal³, Monica Agarwal³, Lydia Alexander⁴, Caroline M Apovian⁵, Shagun Bindlish⁶, Jonathan Bonnet⁷, W Scott Batsch⁸, Sandra Christensen⁹, Eugenia Gianos¹⁰, Mahima Gulati¹¹, Alka Gupta^{12,13}, Debbie Horn¹⁴, Ryan M Kane^{15,16}, Jandeep Saluja¹⁷, Deepa Samdhi¹⁸, Fatima Cody Stanford^{19,20}, Emily A Callahan¹

the optimal approach. A protein intake of 1.5 g per kilogram of lean body mass (FFM) per day is considered more accurate but requires body composition data for precise calculation [166]. **Alternatively, setting an absolute protein target of 80–120 g/d, or 16%–24% energy on a 2000 kcal/d diet, may enhance adherence while ensuring adequate intake.**

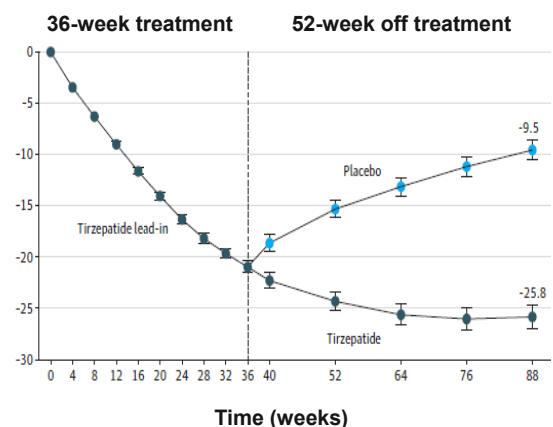
Mozaffarian et al; Am J Clin Nutr. 2025

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Effect of Discontinuing GLP-1 Agonist Therapy on Body Weight



JPH Wilding et al. Diabetes Obes Metab 2022

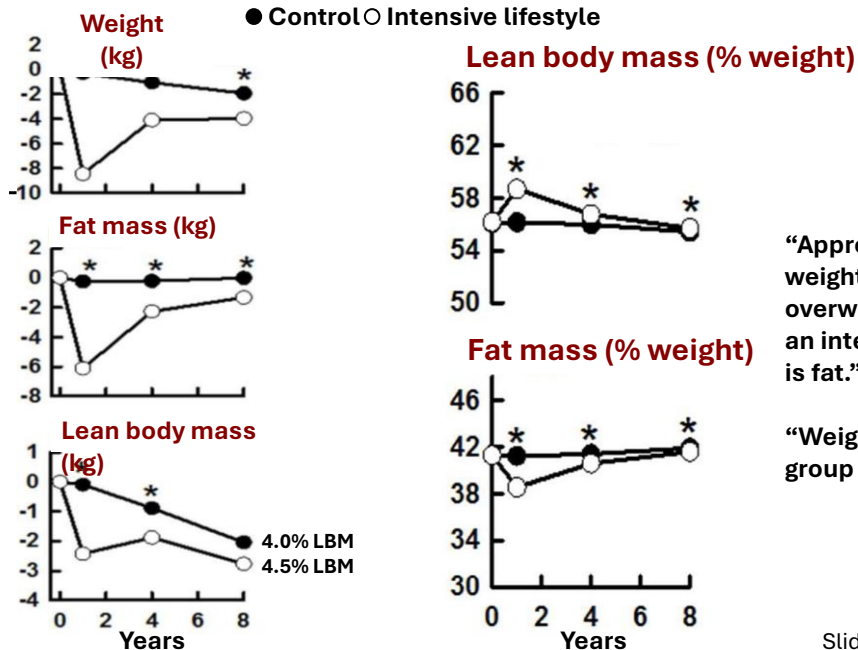


L. Aronne et al. JAMA 2024

Slide courtesy S Klein ADA 2026

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Body Composition after Weight Loss and Regain in Look AHEAD (T2D)



5,145 participants
Baseline age=59 yrs old
4-5% muscle loss/decade

“Approximately two-thirds of the weight-loss among obese or overweight diabetic persons via an intensive lifestyle intervention is fat.”

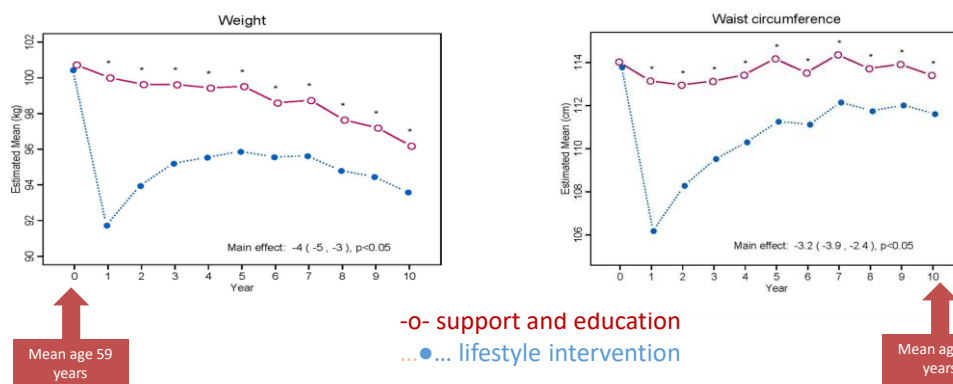
“Weight regain in the intervention group is nearly 100% fat mass.”

H. Pownall et al. Obesity 2015

Slide courtesy S Klein ADA 2026

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Look AHEAD: Weight Loss Over 10 Years in 5145 Patients with T2DM



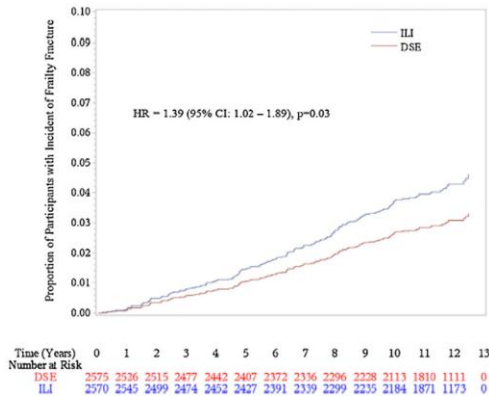
T2DM = type 2 diabetes mellitus.

Look AHEAD Research Group, et al. *N Engl J Med.* 2013;369(2):145-154.

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Frailty Fractures in Weight Loss

Increased Risk of Frailty Fractures in Look AHEAD Intensive Lifestyle Intervention



Kushner RK et al.

Increased Risk of Fractures in SELECT Cardiovascular Outcome Trial

- SELECT study hip and pelvic fractures from SAE reports
- Average age 61.5 years at start
- Average weight loss 9.3%
- Female patients
 - 1.0% (24/2448) vs 0.2% (5/2424)
- Patients age 75+
 - 2.4% (17/703) vs. 0.6% (4/663)

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What Is the Evidence of Fracture Risk in Special Populations Taking GLP-1 RAs?

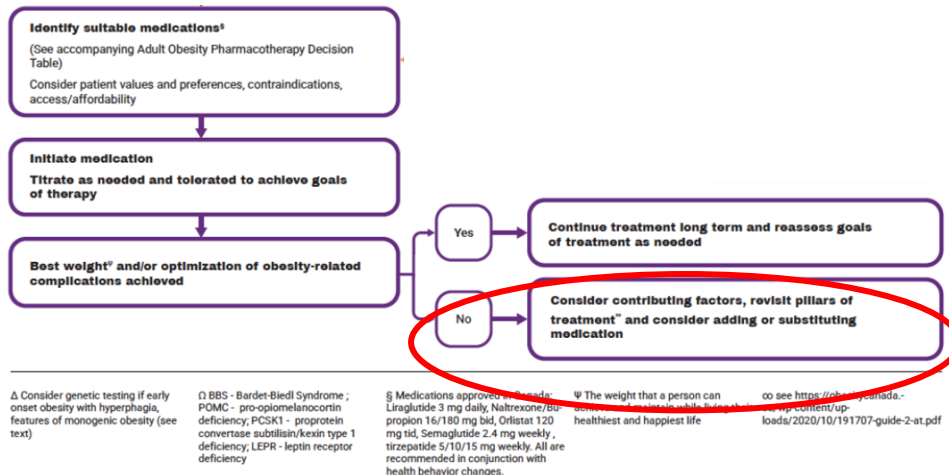
	Semaglutide 2.4 mg	Placebo
Fractures of Hip and Pelvis in female patients	24/2448 (1.0%)	5/2424 (0.2%)
Fractures of Hip and Pelvis in patients ≥75 years	17/703 (2.4%)	4/663 (0.6%)

Subgroup Analyses of SAE fractures from the SELECT trial in the Wegovy® Label

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Adult Obesity Pharmacotherapy Decision Tool

What Do You Do When Patients Have Less than Optimal Response?



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Case Study

- Lindsey is a 40-year-old mother of 2 who works as a real estate agent. She had gestational diabetes with each of her pregnancies and gained 60 pounds since finishing college. She was recently found to have obesity (weight 180, BMI 31), hypertension and pre-diabetes. Her NP put her on metformin, but she had diarrhea and stopped. She is also on hydrochlorothiazide, amlodipine and rosuvastatin.
- She went to a medspa to lose weight and is started on a vial that is labeled tirzepatide and told to self-administer at home. She takes the first dose and has severe nausea and vomiting. She goes to the ER and is given IV fluids and released. She took several times the recommended dose. She comes to see you 6 days later because her friend said she needed a weight loss expert.
- She says, "I don't have vomiting, but I don't feel like eating anything. That's a good thing because I already lost 6 pounds. But every time I stand up I feel dizzy."

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Case #1 - ARS Question #2

What Is Your Move?

- A. Check Lindsey's BP for orthostatic hypotension. If it's low, you are going to reduce her BP meds.
- B. Tell her she is doing great and show her how to inject the proper dose from her vial.
- C. Tell her she must not take the medication in the vial. Ask her to discard it. Prescribe tirzepatide 2.5 mg in a single dose pen.



CONTINUING EDUCATION COMPANY

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Acute Consequences of Negative Energy Balance

- Depletion of glycogen stores
 - Rapid water mobilization, diuresis
 - Diuretics may pose danger of hypotension
- Diuresis and electrolyte imbalance
 - Cardiac arrhythmia
- Reduction in insulin needs
 - Sulfonylureas and insulin pose danger of hypoglycemia
- Constipation

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Case 1. Continued

Lindsey returns in a week for a consultation visit. She agrees to undertake a weight management effort to achieve her goal of normoglycemia, reduced medications for blood pressure and lipids and feeling better about herself and fitting in her clothes.

You prescribe tirzepatide 2.5 mg in a single injection pen. What do you tell her about how to avoid vomiting and other side effects?



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What to Say to Patients Before They Start

- This medicine makes you feel full. You will feel effects in 12-24 hours.
- You can't eat like you used to. No big meals. No rich foods. No bedtime eating.
- Fill your plate only half full. Eat more salads and soups. But you must eat at least 800 to 1000 calories a day and you must eat protein (60 G minimum)
- You can use OTC nausea meds.
- Your nausea must be better before you take another injection.
- You may lose your taste for alcohol. Go with the flow.
- We are watching how fast and how much you lose. We don't increase the dose until you feel no nausea and you stop losing weight.

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Dealing with on-Target Side Effects: Nausea and Vomiting

- Nausea is common – in up to half of patients; Vomiting less common
 - Dose-related, occurs when starting or increasing dose
 - Titrate! Many patients do not need top dose
 - Occurs on first or second day. Tell patients to expect it and modify diet.
 - If nausea lasts more than a day or is severe, don't titrate up, stay on the dose
 - If nausea and vomiting are severe, ~~reduce the dose~~
 - **Severe vomiting can trigger acute renal failure: don't let your patient become dehydrated**
 - Diarrhea and Constipation possible (treat symptomatically)
 - Delayed gastric emptying
 - Can worsen GERD
 - Antacids and proton pump inhibitors

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Case 1. Continued

- Lindsey checks in with you at 8 weeks and is doing well. She is losing weight, no longer has symptoms, except for constipation, relieved by Metamucil and mild nausea for a day or two after her dose increase. After 4 weeks, she increased to 5 mg tirzepatide with minimal nausea. At 8 weeks before the next dose increase she reports 15 pounds weight loss. She says, "I still don't have much appetite."
- Is this too much weight loss?
- How can you judge too rapid and too much weight loss?



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Patients May Lose 5 Pounds or More in the First Week. This Exceeds the Energy Deficit You Cite. Why?????

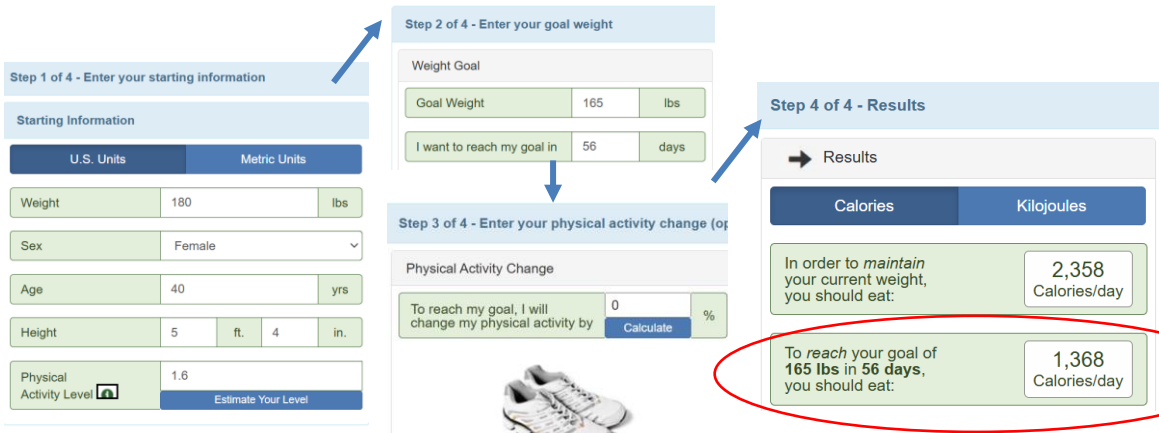
- Glycogen depletion causes water loss. Every molecule of glycogen is stored with 2 molecules of water.
- Fat is anhydrous.
- Initial weight loss is loss of both water and fat.
- Weight loss slows over time - liver glycogen is repleted.
- Over time, weight loss is reflective of the energy deficit.

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<https://www.niddk.nih.gov/bwp>

Let's Use Body Weight Planner

- Lindsey lost 15 pounds in 8 weeks (56 days). This is 52,500 kcal or 937 kcal per day.



Step 1 of 4 - Enter your starting information

Starting Information

U.S. Units Metric Units

Weight 180 lbs

Sex Female

Age 40 yrs

Height 5 ft. 4 in.

Physical Activity Level 1.6

Step 2 of 4 - Enter your goal weight

Weight Goal

Goal Weight 165 lbs

I want to reach my goal in 56 days

Step 3 of 4 - Enter your physical activity change (optional)

Physical Activity Change

To reach my goal, I will change my physical activity by 0 %

Step 4 of 4 - Results

Results

Calories Kilojoules

In order to *maintain* your current weight, you should eat: 2,358 Calories/day

To reach your goal of 165 lbs in 56 days, you should eat: 1,368 Calories/day

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Or You Can Keep the Weight Loss Between ½
Pound and 2 Pounds Per Week.

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Case 1. Continued

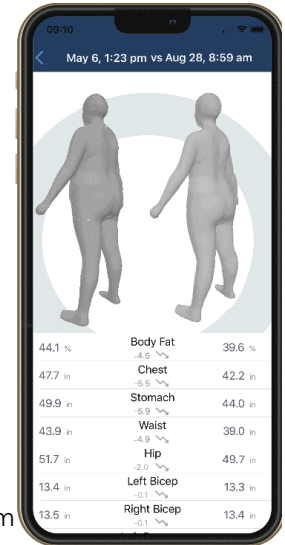
- Today, after 9 months of treatment, Lindsay's A1c is normal and she weighs 135 pounds (BMI 23.2). She says, "I feel great. I am eating healthy – all clean foods. But I don't exercise."
- Is this weight loss too fast? (We checked in with the body weight planner – she can achieve this with intake of 1526 kcal/d. Or we can say this was 45 pounds in 36 weeks, which is acceptable.)
- Is this too much weight loss?
- What do you think about the lack of exercise?



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How to Avoid Too Much Weight Loss...

- Start at a low dose.
- Stay at the lowest effective dose.
- Remember weight loss can continue for >1 year.
- If BMI goes too low, reduce the dose.
- Use guardrails: BMI 22 (rather than 18.5).
- Use percentage body fat (impedance or digital anthropometry) and waist circumference as guides for when enough weight loss has been achieved.



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Case 1. Continued

At the last visit, you reduced Lindsay's dose of tirzepatide to 10 mg and her weight stabilized. She comes in today for the one-year visit.

- Lindsey's annual visit shows remarkable health improvement. Her A1c is 5%. Her blood pressure, lipids and chem profile are normal.
- Lindsey says, "I feel great! I will never go back to my old diet. I know what to eat. I am ready to quit these shots. I no longer have prediabetes, I no longer have any health problems. I've got this! Why should I take medicine? I am totally healthy."



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