Addressing Obesity in Diabetes: Why Weight?
(Holistic Management of Diabetes)

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CONTINUING EDUCATION COMPANY

1

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Holistic Management of Diabetes

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2

Disclosure

Advisory Board: Abbott; Eli Lilly; MannKind; Novo Nordisk

Consultant: Eli Lilly; Novo Nordisk

Research Grant: AbbVie; Bayer Pharmaceuticals; Eli Lilly; Novo Nordisk

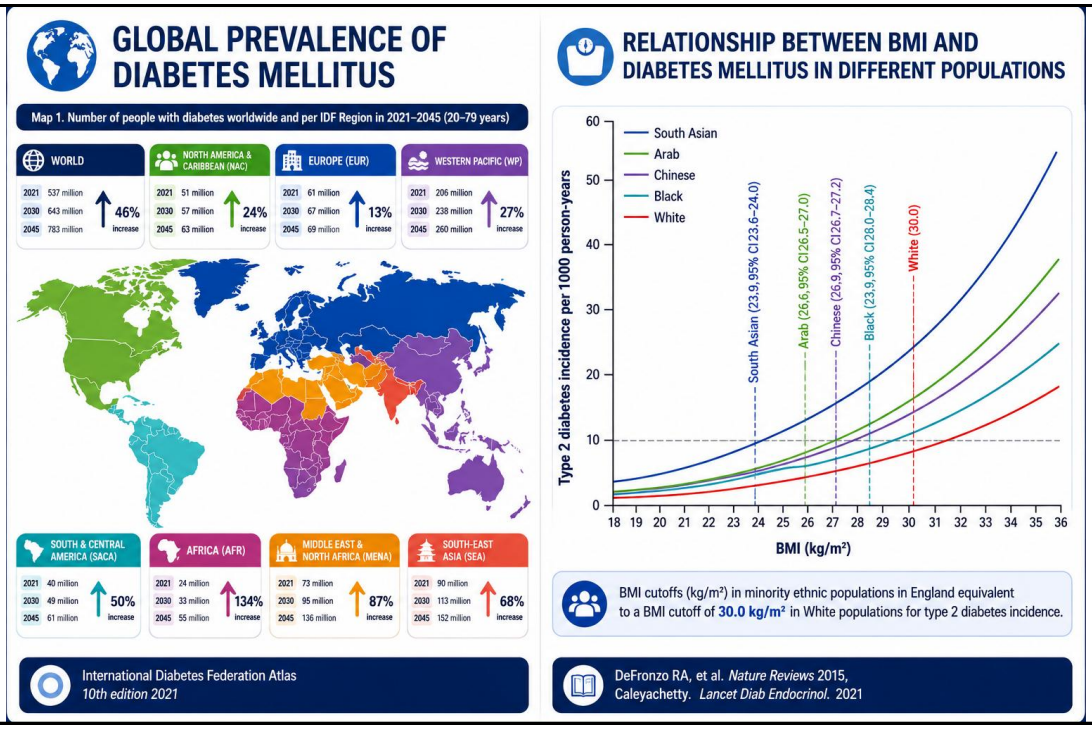
Speaker's Bureau: Abbott; Eli Lilly; MannKind; Novo Nordisk

Definition of Holistic
(Oxford Language Dictionary)

Characterized by the belief that the parts of something are **interconnected** and can be explained only by reference to the whole.

Characterized by the treatment of the **whole person**, taking into account mental and social factors, rather than just the symptoms of an illness.

In essence, holistic means seeing and treating the whole person — mind, body, and social context — as interconnected.


GLOBAL PREVALENCE OF DIABETES MELLITUS
Map 1. Number of people with diabetes worldwide and per IDF Region in 2021–2045 (20–79 years)
WORLD
2021 537 million
2030 643 million
2045 783 million
46% increase
NORTH AMERICA & CARIBBEAN (NAC)
2021 51 million
2030 57 million
2045 63 million
24% increase
EUROPE (EUR)
2021 61 million
2030 67 million
2045 69 million
13% increase
WESTERN PACIFIC (WP)
2021 206 million
2030 238 million
2045 260 million
27% increase
SOUTH & CENTRAL AMERICA (SACA)
2021 40 million
2030 49 million
2045 61 million
50% increase
AFRICA (AFR)
2021 24 million
2030 33 million
2045 55 million
134% increase
MIDDLE EAST & NORTH AFRICA (MENA)
2021 73 million
2030 95 million
2045 136 million
87% increase
SOUTH-EAST ASIA (SEA)
2021 90 million
2030 113 million
2045 152 million
68% increase
International Diabetes Federation Atlas
10th edition 2021
RELATIONSHIP BETWEEN BMI AND DIABETES MELLITUS IN DIFFERENT POPULATIONS
South Asian
Arab
Chinese
Black
White
Type 2 diabetes incidence per 1000 person-years
BMI (kg/m²)
South Asian (23.9, 95% CI 23.6–24.0)
Arab (26.6, 95% CI 26.5–27.0)
Chinese (26.9, 95% CI 26.7–27.2)
Black (23.9, 95% CI 28.0–28.4)
White (30.0)
BMI cutoffs (kg/m²) in minority ethnic populations in England equivalent to a BMI cutoff of 30.0 kg/m² in White populations for type 2 diabetes incidence.
DeFronzo RA, et al. Nature Reviews 2015,
Caleyachetty. Lancet Diab Endocrinol. 2021

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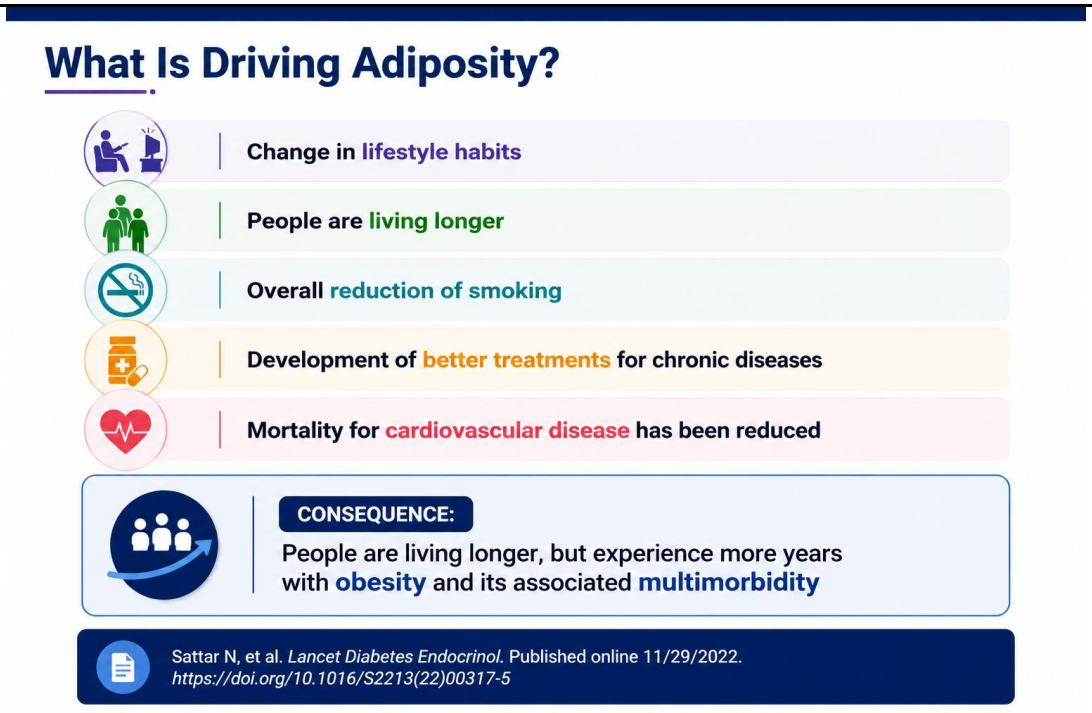
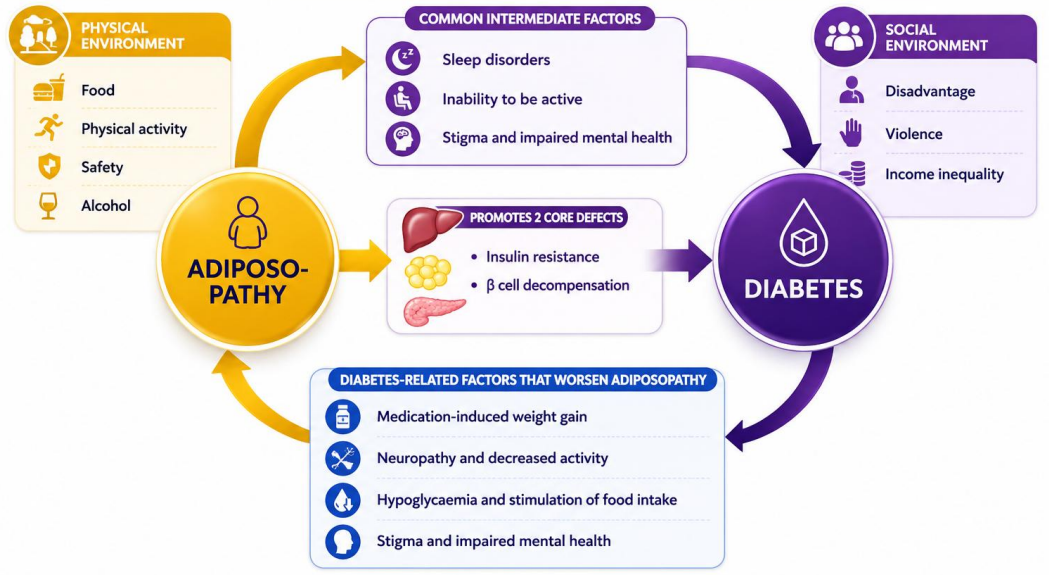

What Is Driving Adiposity?
Change in lifestyle habits
People are living longer
Overall reduction of smoking
Development of better treatments for chronic diseases
Mortality for cardiovascular disease has been reduced
CONSEQUENCE:
People are living longer, but experience more years with obesity and its associated multimorbidity
Sattar N, et al. Lancet Diabetes Endocrinol. Published online 11/29/2022.
https://doi.org/10.1016/S2213(22)00317-5

6

Holistic View of Interplay between Obesity (Adiposopathy) and Diabetes: Synergistic and Syndemic



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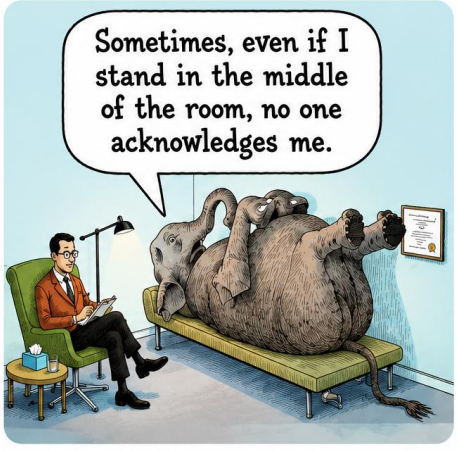
Long-term goals for our patients with type 2 diabetes

1 Prevent sequelae of micro- and macrovascular complications of diabetes

Focus on optimal control of key risk factors:

- **A1c** (Blood Glucose)
- **BP** (Blood Pressure)
- **Cholesterol** (Lipid Management)



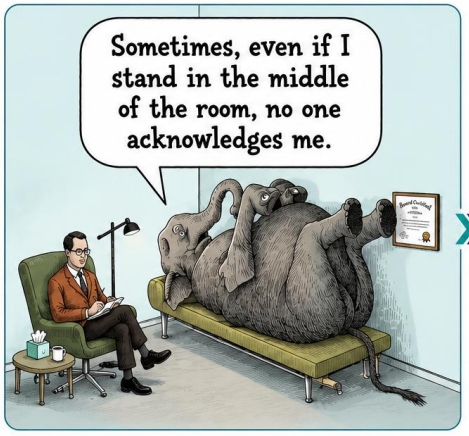
2 Address social and psychological impact of diabetes and its treatment

Holistic care includes emotional well-being, social support, and individualized treatment that fits the patient's life.

Our goal: Help patients live longer, healthier lives – free from complications and empowered in body and mind.

8

What else are we missing?



Adiposity

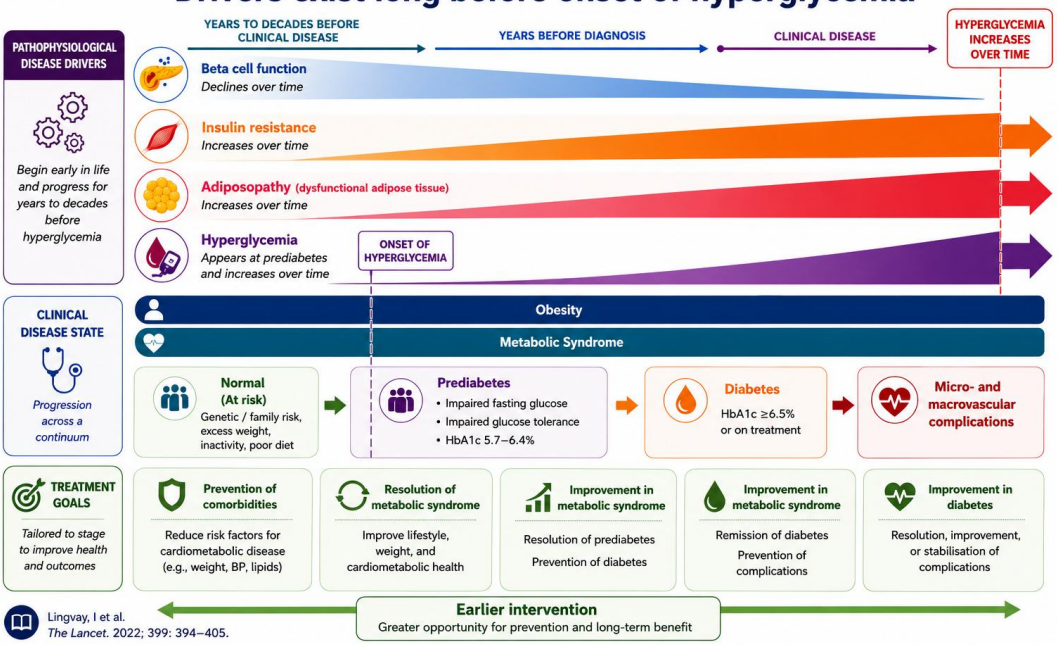
A critical piece we cannot overlook

- Is a major risk factor for many of the **traditional** and **nontraditional** and complications of diabetes
- Is a major risk factor for many of the **comorbidities** that affect people with diabetes
- Has major **social** and **psychological impact** on our patients

The Takeaway: Addressing adiposity is essential for improving health outcomes, quality of life, and overall well-being in people with type 2 diabetes.

9

The disease continuum of T2D: Drivers exist long before onset of hyperglycemia



10

Type 2 diabetes is only one of many conditions related to obesity

Obesity is a chronic, relapsing, multifactorial disease that is associated with **numerous complications and a wide range of related diseases.**[1–3]

Obesity Complications*

- OA (knee, hip)
- OSA
- Obesity hypoventilation syndrome
- Lymphedema
- Stress urinary incontinence
- GERD
- Prediabetes and metabolic syndrome
- MASLD
- Obesity glomerulopathy, CKD
- HFpEF
- ASCVD
- Thromboembolism
- Idiopathic intracranial hypertension
- Disability limiting activities of daily living

Obesity-Related Diseases*

- T2D
- MASH
- HFrEF
- Atrial fibrillation
- Certain cancers
- Cholelithiasis, cholecystitis
- Asthma
- Depression, anxiety
- Internalized weight bias
- Stigmatization
- Disordered eating
- Cognitive decline, dementia
- Inflammatory skin diseases
- Intertrigo

*There can be overlap between complications and related diseases depending on the pathophysiological role of obesity in individual patients. See Box A for definitions.

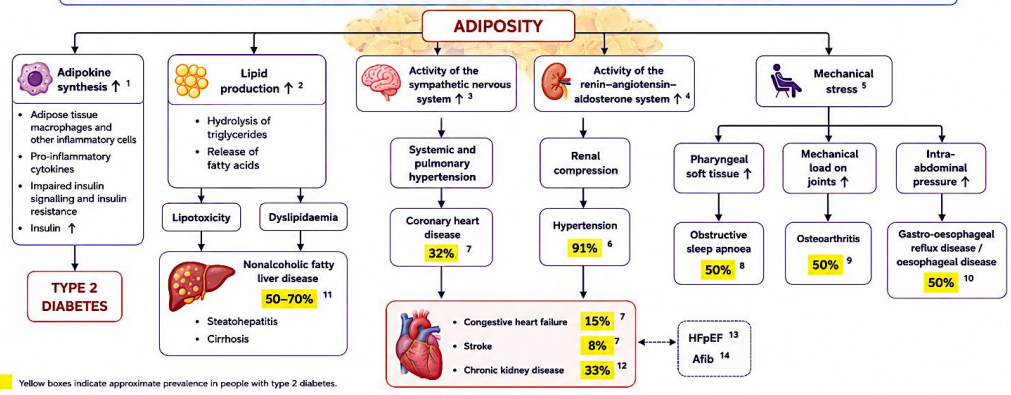
References:

1. Rubino D, et al. Joint international consensus statement for ending stigma of obesity. *Nat Med.* 2020;26:485–497.
2. Mechanick JI, et al. Clinical practice guidelines for the prevention, diagnosis, and treatment of obesity. *Endocr Pract.* 2020;26(Suppl 1):1–107.
3. American Diabetes Association Professional Practice Committee. Standards of Care in Diabetes—2024. *Diabetes Care.* 2024;47(Suppl 1):S145–S158.

11

Adiposity and complications in people with T2D

Adiposity drives multiple pathophysiologic pathways that contribute to cardiometabolic, renal, hepatic, musculoskeletal, pulmonary and gastrointestinal complications in people with type 2 diabetes.



Yellow boxes indicate approximate prevalence in people with type 2 diabetes.

*There can be overlap between complications and related diseases depending on the pathophysiological role of obesity in individual patients.

References

1. Bluher M. Obesity: global epidemiology and pathogenesis. *Nat Rev Endocrinol.* 2019;15:288–298.
2. Mucio DM. Metabolic inflexibility: when mitochondrial indecision leads to metabolic gridlock. *Cell.* 2014;159:1253–1262.
3. Hall JE et al. Obesity-induced hypertension: interactions of neurohumoral and renal mechanisms. *Circ Res.* 2015;116:991–1006.
4. Carey RM, Siragy HM. The intrarenal renin–angiotensin–aldosterone system and diabetic nephropathy. *Trends Endocrinol Metab.* 2003;14:274–281.
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6. Cheung BM, Li C. Diabetes and hypertension: is there a common metabolic pathway? *Curr Atheroscler Rep.* 2010;12:160–166.
7. Einarson TR et al. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. *Cardiovasc Diabetol.* 2018;17:83.
8. Foster GD et al. A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes. *Am J Respir Crit Care Med.* 2009;179:508–513.
9. Louati K et al. Association between obesity and osteoarthritis of the knee: a systematic literature review and meta-analysis. *RMD Open.* 2015;1:e000077.
10. Hampel H et al. The association between obesity and gastroesophageal reflux disease: A systematic review and meta-analysis. *Ann Intern Med.* 2005;143:199–211.
11. Younossi ZM et al. The global epidemiology of NAFLD and NASH. *Hepatology.* 2016;64:73–84.
12. Afkarian M et al. Kidney disease and increased mortality in type 2 diabetes. *J Am Soc Nephrol.* 2016;27:3027–3032.
13. Dunlay SM et al. Type 2 diabetes mellitus and heart failure with preserved ejection fraction. *JACC Heart Fail.* 2019;7:329–340.
14. Kannel WB et al. Obesity and risk of atrial fibrillation: the Framingham Study. *Am J Cardiol.* 1997;80:29–32.

Afib, atrial fibrillation; CKD, chronic kidney disease; HFpEF, heart failure with preserved ejection fraction; OSA, obstructive sleep apnoea; T2D, type 2 diabetes.

12

Obesity stigma, bias and discrimination.

- There exists consistent weight bias and stigmatization exist in employment, health care, schools, the media, and interpersonal relationships.
- For overweight and obese youth, weight stigmatization translates into pervasive victimization, teasing, and bullying.
- Results in depression, anxiety, low self-esteem, body dissatisfaction, suicidal ideation, poor academic performance, lower physical activity, maladaptive eating behaviors, and avoidance of health care.

Addressing weight stigma is essential to improving mental health, quality of life, and outcomes for individuals with obesity.

12 | Puhl R & King K: Best Pract Res Clin Endocrinol Metab 2013 Apr;27(2):117-27.

13

But What About Type 1 Diabetes?

The prevalence of overweight (30–40%) and obesity (15–30%) for people with type 1 diabetes is comparable to that for the general adult population

A diagnosis of type 1 diabetes does not preclude also having features classically associated with type 2 diabetes (e.g., insulin resistance, obesity, and other metabolic abnormalities), and until more

Using GLP-1 RA Approved for Weight Loss Is Not Off-label for T1D

Standards of Care in Diabetes—2026

American Diabetes Association.

ISSN 0149-5992

having features of both type 1 and type 2 diabetes to facilitate access to glucose monitoring systems and appropriate treatment (e.g., glucagon-like peptide 1 receptor agonist [GLP-1 RA] or sodium–glucose cotransporter 2 [SGLT2] inhibitor therapies for potential weight and other cardiometabolic benefits).

14

Obesity is associated with increased risk for traditional complications in type 1 and type 2 diabetes

National Program for Prevention and Control of Diabetes

N = 111,380 with diabetes studied 2016 – 2021

10,641 T1D – **3,187** Obese

101,189 T2D – **51,873** Obese

RESULTS
Obesity associated with increased risk (HR)

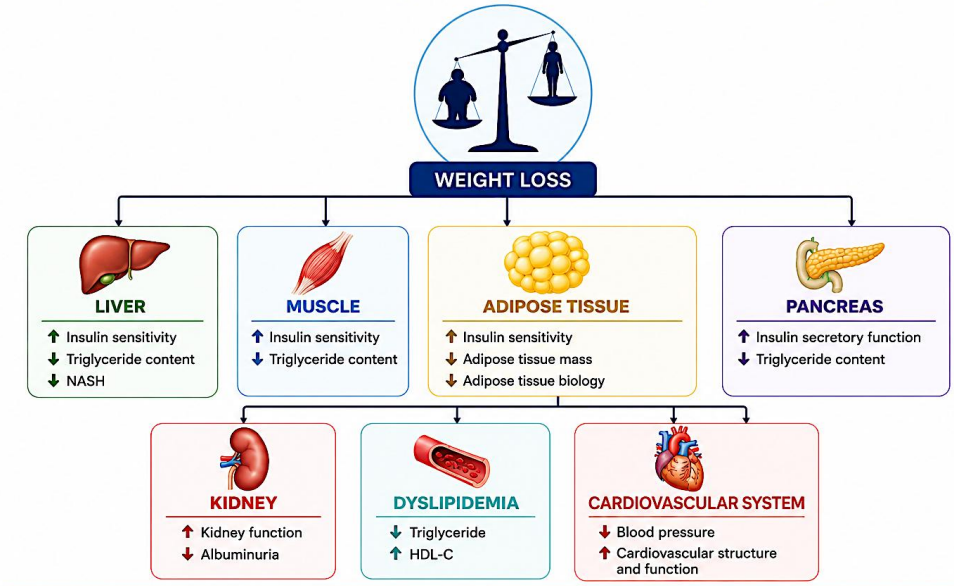
	T1D	T2D
CVD	1.75	1.62
Neuropathy	1.56	1.98
Nephropathy	1.80	1.21
Retinopathy	1.92	NS

Abbreviation: CVD, cardiovascular disease; HR, hazard ratio; NS, not significant; T1D, type 1 diabetes; T2D, type 2 diabetes.

Moosaie F et al. *Prim Care Diabetes* 2022;16:101402.

15

Effects of Weight Loss on Multiple Organs



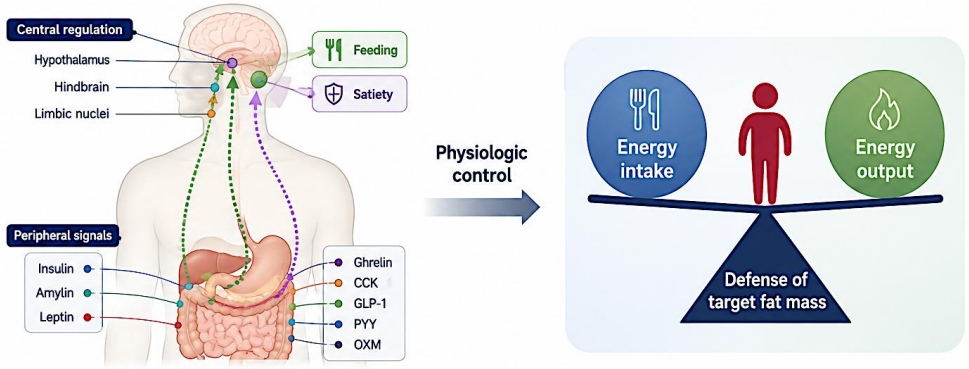
Weight loss favorably affects multiple organs and systems, improving metabolic health and reducing cardiovascular risk.

Magkos F, et al. *Cell Metab.* 2016;23(1):1-6.

16

Body fat mass is tightly regulated by an entero-CNS axis

The hypothalamus, hindbrain and limbic nuclei regulate appetitive drives and thermogenic energy expenditure



>80% of obesity-associated genes are selectively expressed in the nervous system

Adapted from Morton GJ et al., *Nat Rev Neurosci.* 2014;15:367–378.

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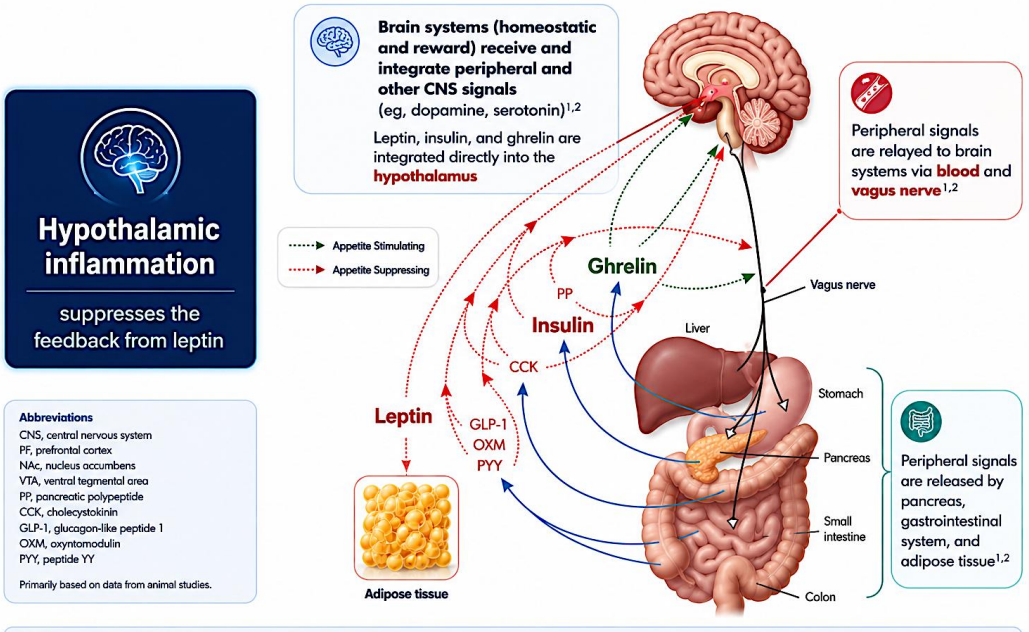
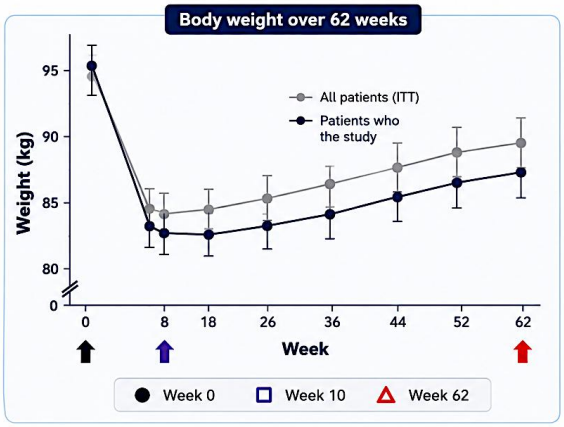


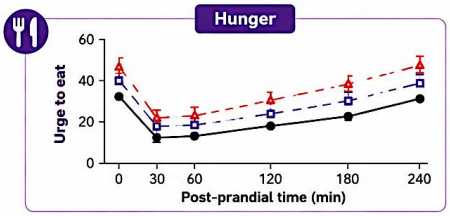
1. Yu JH et al. *Diabetes Metab J.* 2012;36(6):391-398.
2. Mendieta-Zerón H et al. *Gen Comp Endocrinol.* 2008;155:481-495.

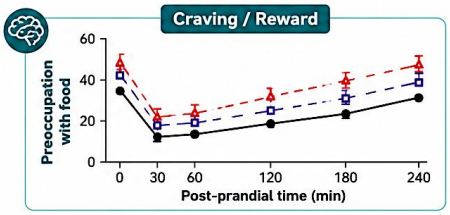
18

Why is weight usually regained after diet?

Sustained physiological adaptations drive hunger and food preoccupation, promoting weight regain







After initial weight loss, weight is progressively regained over time.

Hunger increases significantly after weight loss and over time.

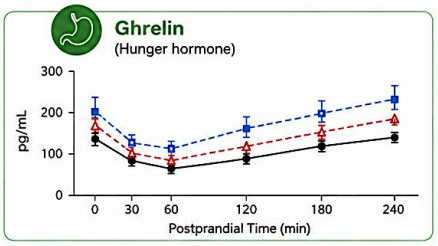
Craving and preoccupation with food remain elevated, driving weight regain.

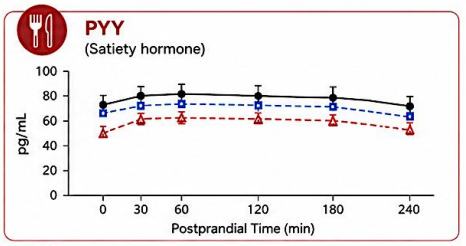
Sumithran P et *al.*, *NEJM* 2011;365:1597–1604.

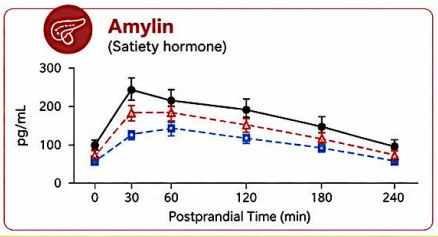
19

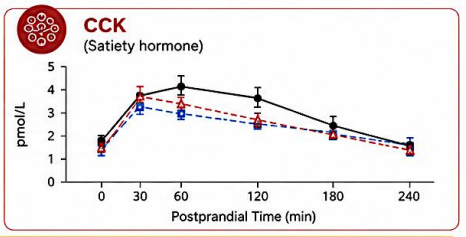
Gut hormones persistently oppose restriction diet-induced weight loss

Levels of satiety hormones drop from baseline and remain lower throughout the 62 weeks of the study, whereas **Gherlin levels rise**.









Key takeaway:
Restriction diets trigger sustained hormonal adaptations that increase hunger and reduce satiety, driving food-seeking behavior and contributing to **weight regain**.

Sumithran P et al., *NEJM* 2011;365:1597–1604.

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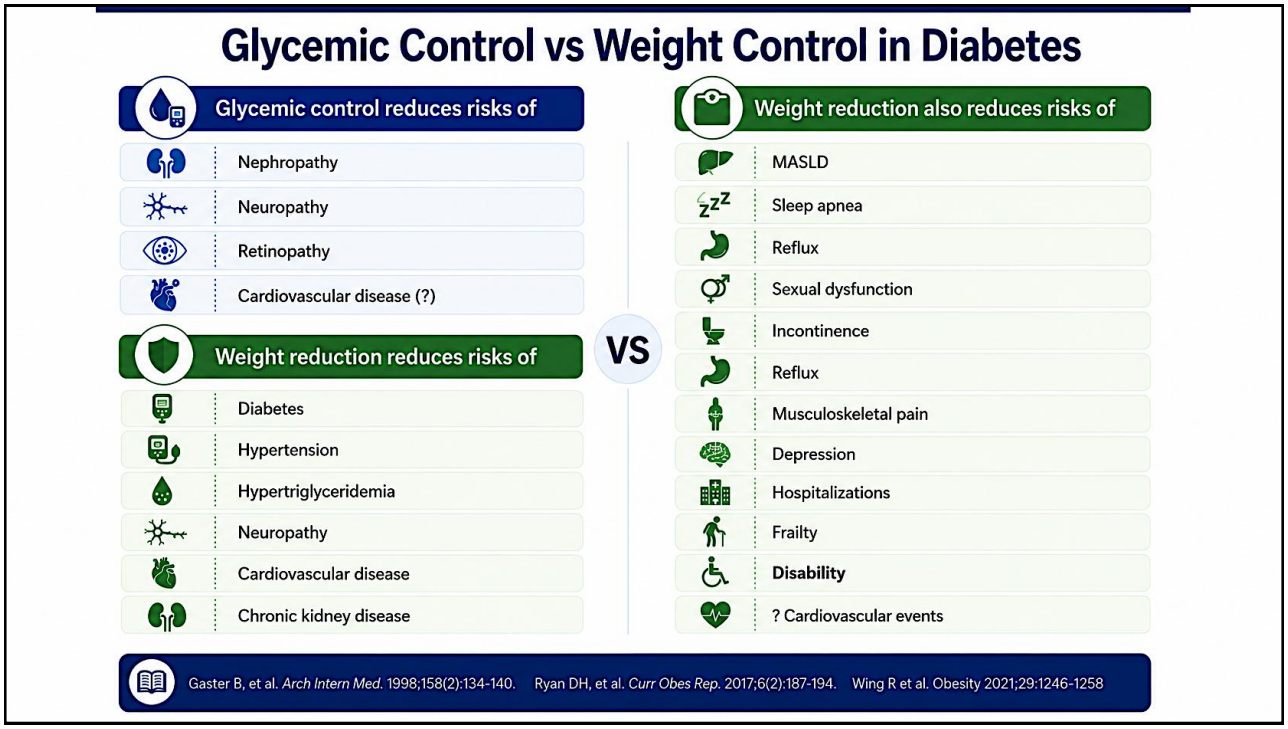
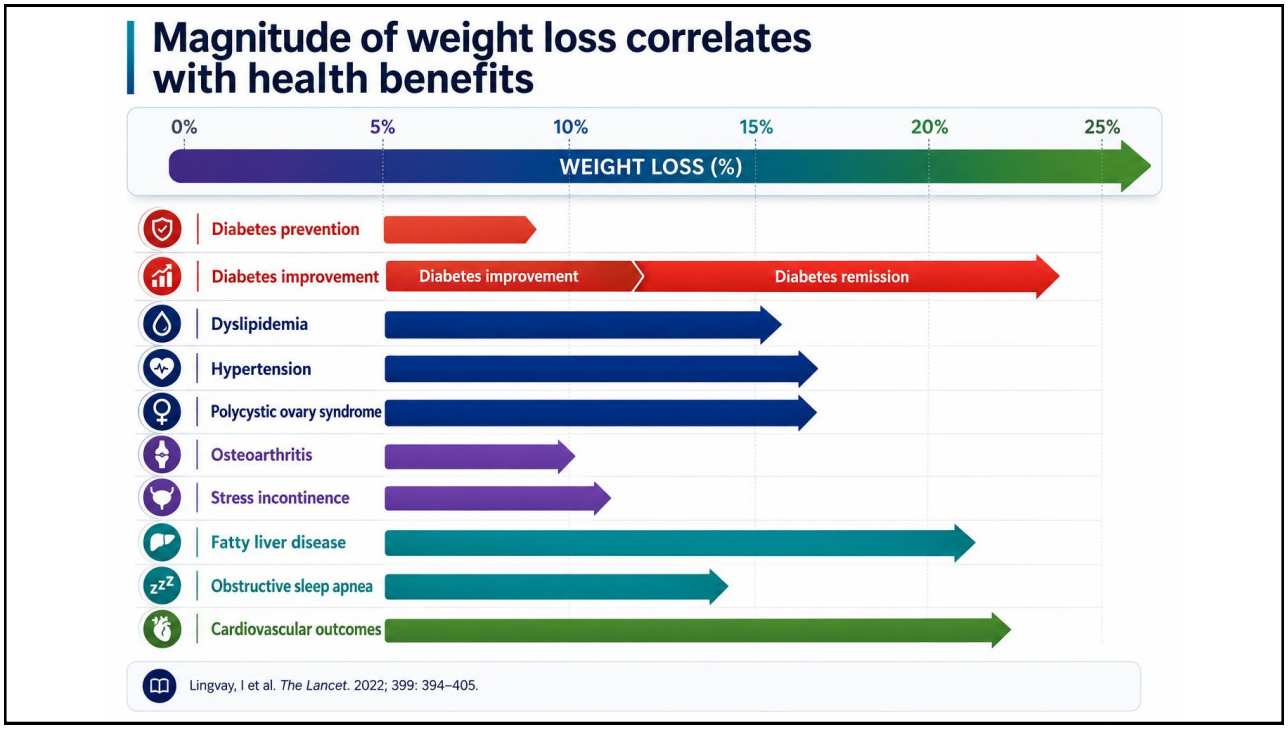

Glycemic Control vs Weight Control in Diabetes
Glycemic control reduces risks of
Nephropathy
Neuropathy
Retinopathy
Cardiovascular disease (?)
Weight reduction reduces risks of
Diabetes
Hypertension
Hypertriglyceridemia
Neuropathy
Cardiovascular disease
Chronic kidney disease
VS
Weight reduction also reduces risks of
MASLD
Sleep apnea
Reflux
Sexual dysfunction
Incontinence
Reflux
Musculoskeletal pain
Depression
Hospitalizations
Frailty
Disability
? Cardiovascular events
Gaster B, et al. Arch Intern Med. 1998;158(2):134-140. Ryan DH, et al. Curr Obes Rep. 2017;6(2):187-194. Wing R et al. Obesity 2021;29:1246-1258

21


Magnitude of weight loss correlates with health benefits
0%
5%
10%
15%
20%
25%
WEIGHT LOSS (%)
Diabetes prevention
Diabetes improvement
Diabetes improvement
Diabetes remission
Dyslipidemia
Hypertension
Polycystic ovary syndrome
Osteoarthritis
Stress incontinence
Fatty liver disease
Obstructive sleep apnea
Cardiovascular outcomes
Lingvay, I et al. The Lancet. 2022; 399: 394–405.

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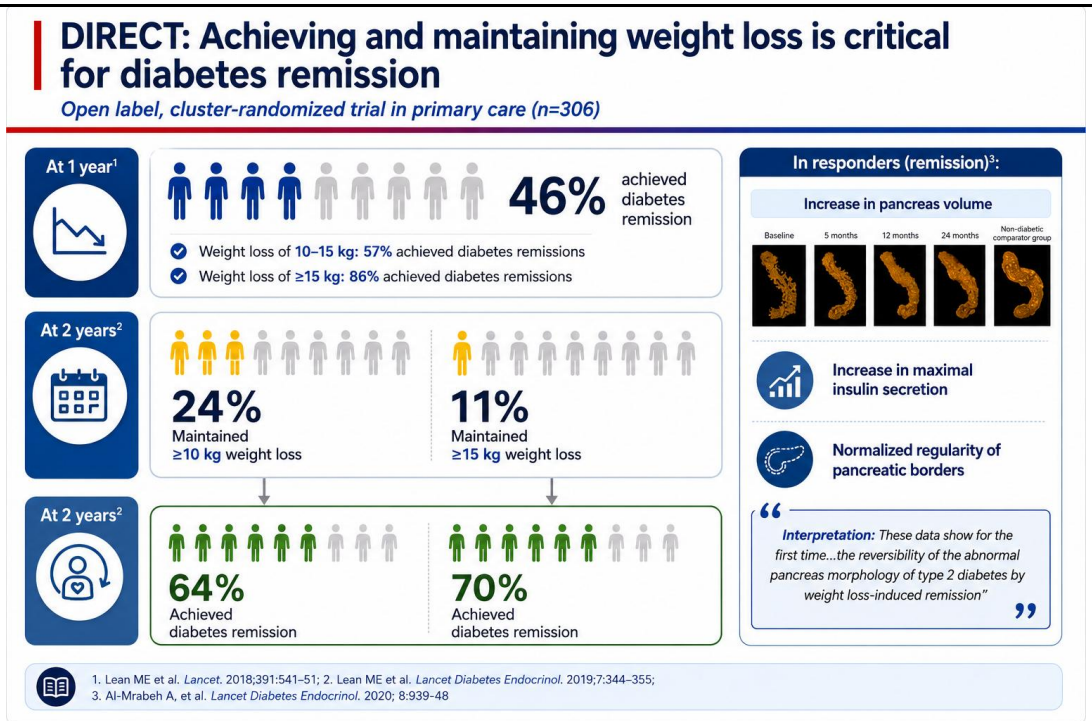


23

Look AHEAD: Weight loss magnitude and cardiovascular outcomes

Weight Change Groups (percent weight loss in first year)

Look AHEAD	Gain / Stable (<2% loss)	Small Loss (2 to 5%)	Medium Loss (5 to 10%)	Large Loss (>10%)	P Value	Test for Trend
N (%)	1972 (40.3%)	914 (18.7%)	1000 (20.4%)	1013 (20.7%)		
BMI (mean kg/m²)	35.9	35.8	35.8	36.1	0.34	—
1-y Change in weight (mean %)	+1.6	−3.5	−7.3	−15.8	NA	—
Primary Outcome						
Events / person years	289 / 17075	141 / 7870	154 / 8570	128 / 8942		
Crude rate /100 person years	1.69	1.79	1.80	1.43		
Unadjusted HR (95% C.I.)	1.0	1.07 (0.88 – 1.31)	1.07 (0.88 – 1.31)	0.83 (0.67 – 1.02)	0.21	—
Adjusted HR* (95% C.I.)	1.0	1.08 (0.88 – 1.33)	1.16 (0.95 – 1.42)	0.79 (0.64 – 0.98)	0.17	—
Secondary Outcome						
Events / person years	422 / 16699	206 / 7657	203 / 8411	186 / 8792		
Crude rate /100 person years	2.53	2.69	2.41	2.12		
Unadjusted HR (95% C.I.)	1.0	1.08 (0.91 – 1.27)	0.96 (0.81 – 1.13)	0.83 (0.70 – 0.99)	0.04	—
Adjusted HR* (95% C.I.)	1.0	1.05 (0.88 – 1.25)	0.97 (0.82 – 1.16)	0.76 (0.63 – 0.91)	0.006	—

Primary outcome: composite of death from cardiovascular causes, non-fatal AMI, non-fatal stroke, or admission to hospital for angina.

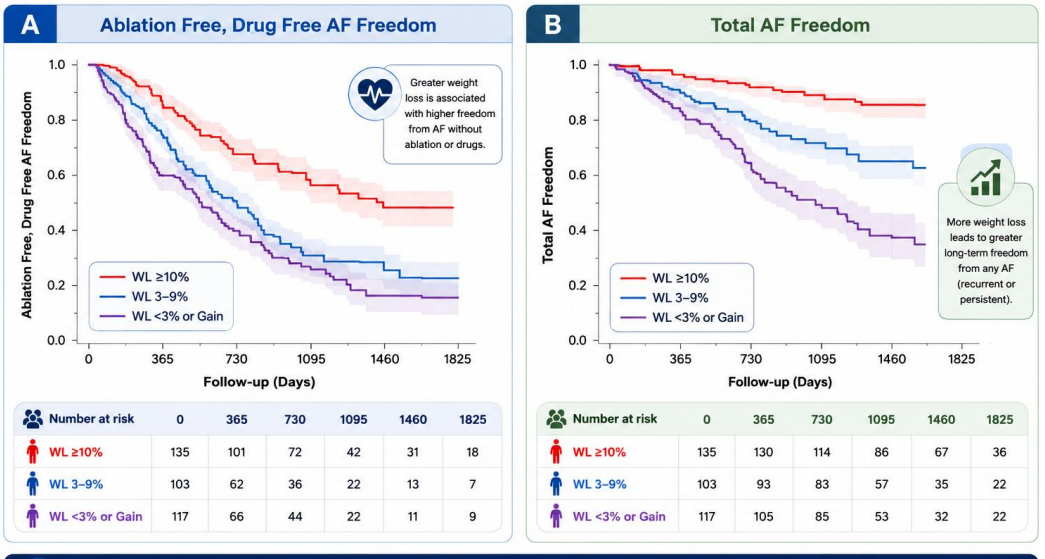
Secondary outcome: primary + CABG, carotid endarterectomy, PCI, hospitalisation for CHF, PVD, or total mortality.

★ **Adjusted for** sex, age, baseline weight, fitness, history of CVD, insulin use, diabetes duration, smoking status, LDL, blood pressure

Gregg *Lancet Diab Endocrinol* 2016

24

Weight Loss Decreases Recurrent Atrial Fibrillation

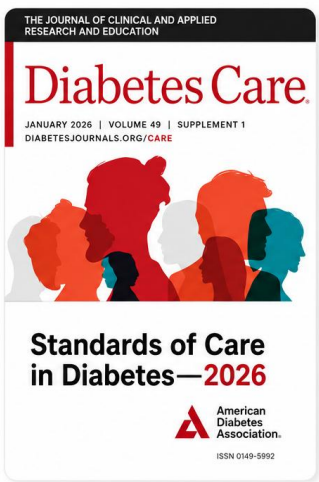


Key Takeaway: Achieving ≥10% weight loss is associated with substantially higher freedom from atrial fibrillation compared with lesser weight loss or weight gain.

Pathak J, et al. J Am Coll Cardiol. 2015;65(20):2159–2169.

25

ADA Recommendations for Management of Obesity in Diabetes



8.2a **Screen for overweight and obesity using BMI annually.**
To confirm excess adiposity, additional assessments of body fat using **anthropometric assessments** (e.g., waist-to-hip ratio) or **direct measurements** (e.g., dual-energy X-ray absorptiometry, bioelectrical impedance analysis) could be considered **where available/feasible**.

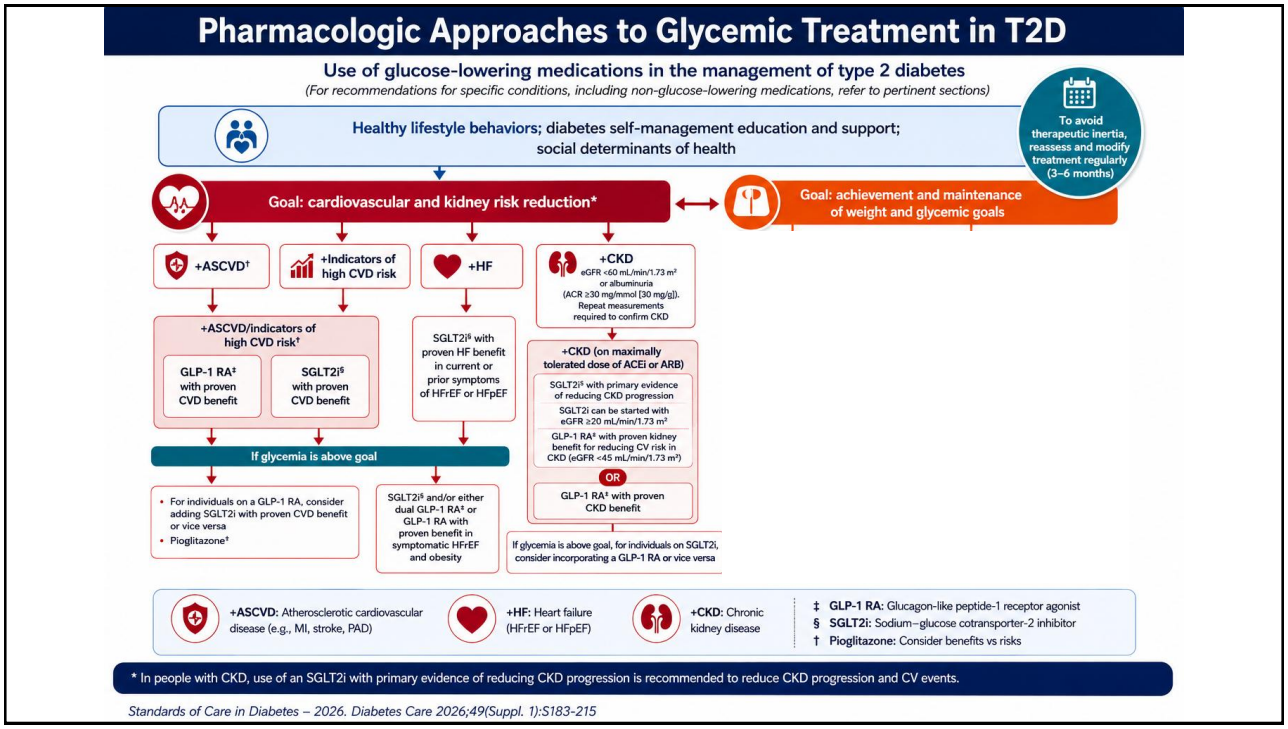
8.4 In people with type 2 diabetes and overweight or obesity, **weight management** should represent a **primary goal** of treatment along with glycemic management.

8.6 **Individualize** initial treatment approaches for obesity (i.e., lifestyle and nutritional therapy, pharmacologic therapy, or metabolic surgery) **based on the person's** medical history, life circumstances, and preferences. **Consider combining** treatment approaches if appropriate.

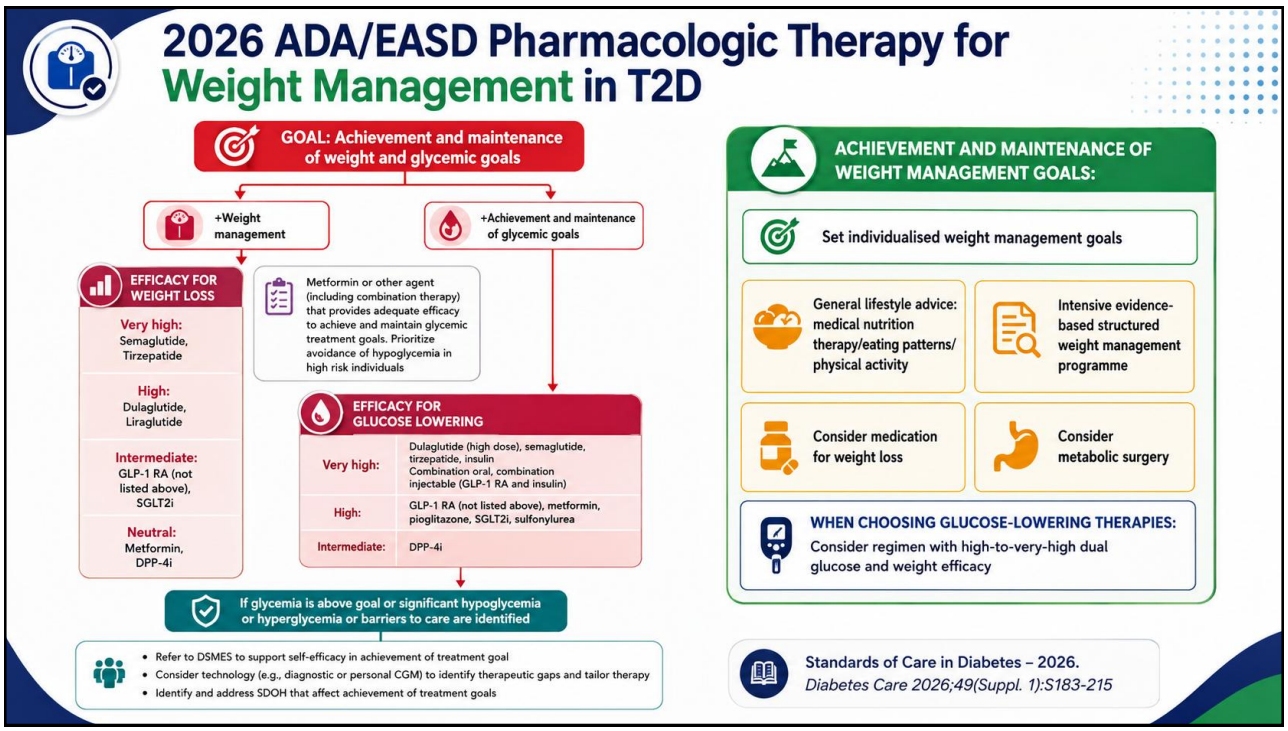
Key Takeaway: Obesity management is essential in type 2 diabetes. Screen, prioritize, and personalize to improve outcomes.

Improves Health | Reduces Complications | Enhances Quality of Life

26


Pharmacologic Approaches to Glycemic Treatment in T2D
Use of glucose-lowering medications in the management of type 2 diabetes
(For recommendations for specific conditions, including non-glucose-lowering medications, refer to pertinent sections)
Healthy lifestyle behaviors; diabetes self-management education and support; social determinants of health
To avoid therapeutic inertia, reassess and modify treatment regularly (3–6 months)
Goal: cardiovascular and kidney risk reduction*
Goal: achievement and maintenance of weight and glycemic goals
+ASCVD†
+Indicators of high CVD risk
+HF
+CKD
eGFR <60 mL/min/1.73 m² or albuminuria (ACR ≥30 mg/mmol [30 mg/g]). Repeat measurements required to confirm CKD
+ASCVD/indicators of high CVD risk†
GLP-1 RA‡ with proven CVD benefit
SGLT2i§ with proven CVD benefit
SGLT2i§ with proven HF benefit in current or prior symptoms of HFrEF or HFpEF
+CKD (on maximally tolerated dose of ACEi or ARB)
SGLT2i§ with primary evidence of reducing CKD progression
SGLT2i can be started with eGFR ≥20 mL/min/1.73 m²
GLP-1 RA‡ with proven kidney benefit for reducing CV risk in CKD (eGFR <45 mL/min/1.73 m²)
OR
GLP-1 RA‡ with proven CKD benefit
If glycemia is above goal
For individuals on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
Pioglitazone†
SGLT2i§ and/or either dual GLP-1 RA‡ or GLP-1 RA with proven benefit in symptomatic HFrEF and obesity
If glycemia is above goal, for individuals on SGLT2i, consider incorporating a GLP-1 RA or vice versa
+ASCVD: Atherosclerotic cardiovascular disease (e.g., MI, stroke, PAD)
+HF: Heart failure (HFrEF or HFpEF)
+CKD: Chronic kidney disease
‡ GLP-1 RA: Glucagon-like peptide-1 receptor agonist
§ SGLT2i: Sodium–glucose cotransporter-2 inhibitor
† Pioglitazone: Consider benefits vs risks
* In people with CKD, use of an SGLT2i with primary evidence of reducing CKD progression is recommended to reduce CKD progression and CV events.
Standards of Care in Diabetes – 2026. Diabetes Care 2026;49(Suppl. 1):S183-215

27


2026 ADA/EASD Pharmacologic Therapy for Weight Management in T2D
GOAL: Achievement and maintenance of weight and glycemic goals
+Weight management
+Achievement and maintenance of glycemic goals
EFFICACY FOR WEIGHT LOSS
Very high: Semaglutide, Tirzepatide
High: Dulaglutide, Liraglutide
Intermediate: GLP-1 RA (not listed above), SGLT2i
Neutral: Metformin, DPP-4i
Metformin or other agent (including combination therapy) that provides adequate efficacy to achieve and maintain glycemic treatment goals. Prioritize avoidance of hypoglycemia in high risk individuals
EFFICACY FOR GLUCOSE LOWERING
Very high: Dulaglutide (high dose), semaglutide, tirzepatide, insulin Combination oral, combination injectable (GLP-1 RA and insulin)
High: GLP-1 RA (not listed above), metformin, pioglitazone, SGLT2i, sulfonylurea
Intermediate: DPP-4i
If glycemia is above goal or significant hypoglycemia or hyperglycemia or barriers to care are identified
Refer to DSMES to support self-efficacy in achievement of treatment goal
Consider technology (e.g., diagnostic or personal CGM) to identify therapeutic gaps and tailor therapy
Identify and address SDOH that affect achievement of treatment goals
ACHIEVEMENT AND MAINTENANCE OF WEIGHT MANAGEMENT GOALS:
Set individualised weight management goals
General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity
Intensive evidence-based structured weight management programme
Consider medication for weight loss
Consider metabolic surgery
WHEN CHOOSING GLUCOSE-LOWERING THERAPIES:
Consider regimen with high-to-very-high dual glucose and weight efficacy
Standards of Care in Diabetes – 2026.
Diabetes Care 2026;49(Suppl. 1):S183-215

28

FIGURE 2: IMPORTANCE OF 24–HOUR PHYSICAL BEHAVIOURS FOR TYPE 2 DIABETES

A whole-day approach—every behaviour matters, every hour counts.

THE TAKEAWAY A balanced 24-hour approach—less sitting, more stepping, regular sweating, strength training and quality sleep—supports better health outcomes in type 2 diabetes.

SITTING STEPPING SWEATING STRENGTHENING SLEEP

Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB. *Diabetes Care* 2022.

29

Medications Associated with Weight Gain

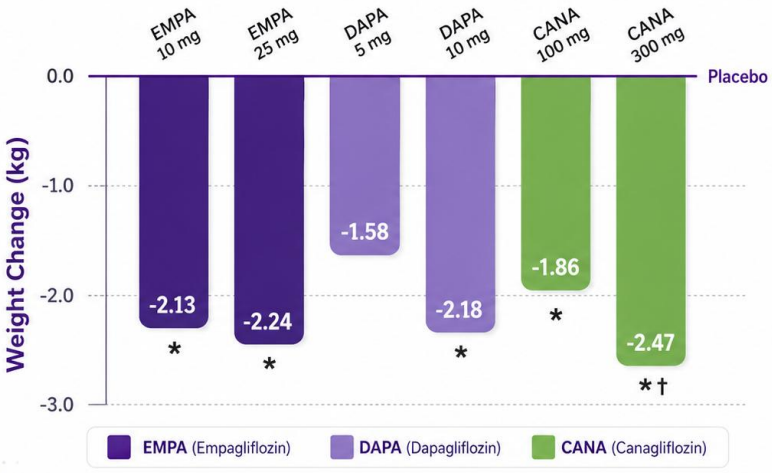
CLASS	MEDICATION EXAMPLES
Insulin & Secretagogues	Insulin; Sulfonylureas (glipizide, glyburide); Meglitinides
Thiazolidinediones (TZDs)	Pioglitazone, Rosiglitazone
Atypical Antipsychotics	Olanzapine, Clozapine, Quetiapine, Risperidone
Corticosteroids	Prednisone, Dexamethasone
Antidepressants	Mirtazapine, Citalopram, Paroxetine, TCAs
Mood Stabilizers	Lithium, Valproate
Beta Blockers	Propranolol, Metoprolol, Atenolol
Antiepileptics	Valproate, Carbamazepine, Gabapentin, Pregabalin
Antihistamines	Diphenhydramine, Cyproheptadine
Hormonal Therapies	Progestins (medroxyprogesterone), Estrogen combinations

Note: Weight gain varies by individual. Consider benefits vs. risks and monitor patients regularly.

30

Effect of SGLT2 Inhibitors on Body Weight

Mean change in body weight (kg) vs. placebo



There have been no head-to-head clinical trials comparing efficacy or safety of SGLT2is.

All doses of DAPA, EMPA and CANA were statistically reduced versus PLACEBO ($p<0.05$)

* Denotes $p<0.05$ versus DAPA 5 mg

† Denotes $p<0.05$ versus CANA 100 mg

Data are reported as mean difference vs. placebo.

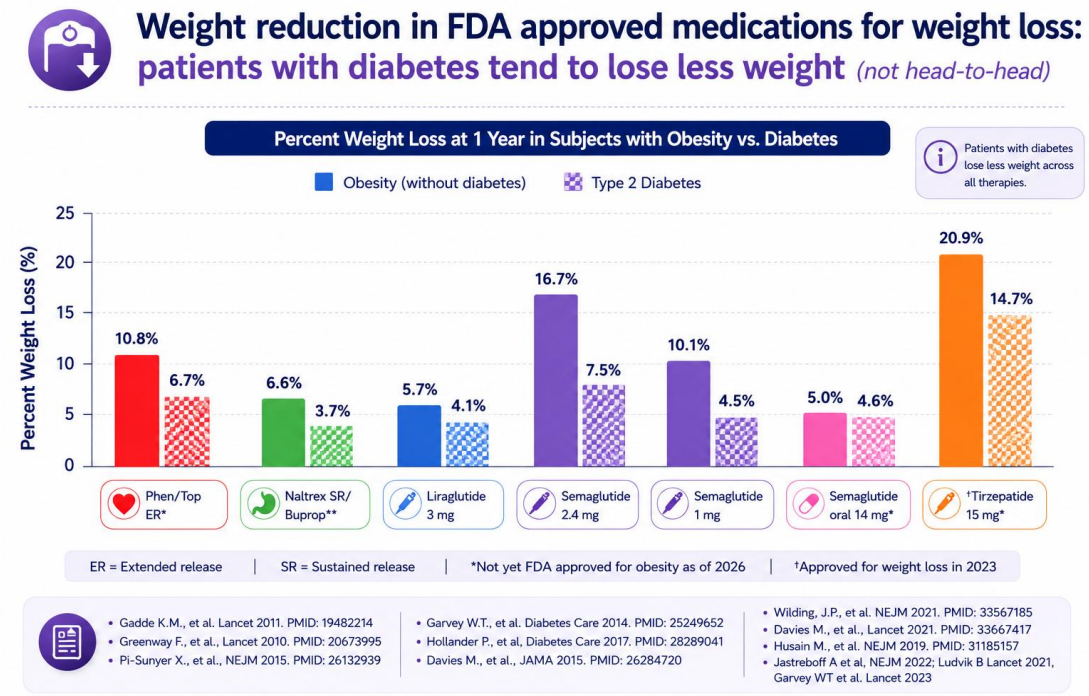
Zaccardi F, et al. *Diabetes Obes Metab.* 2016; 18(8): 783-94.

31

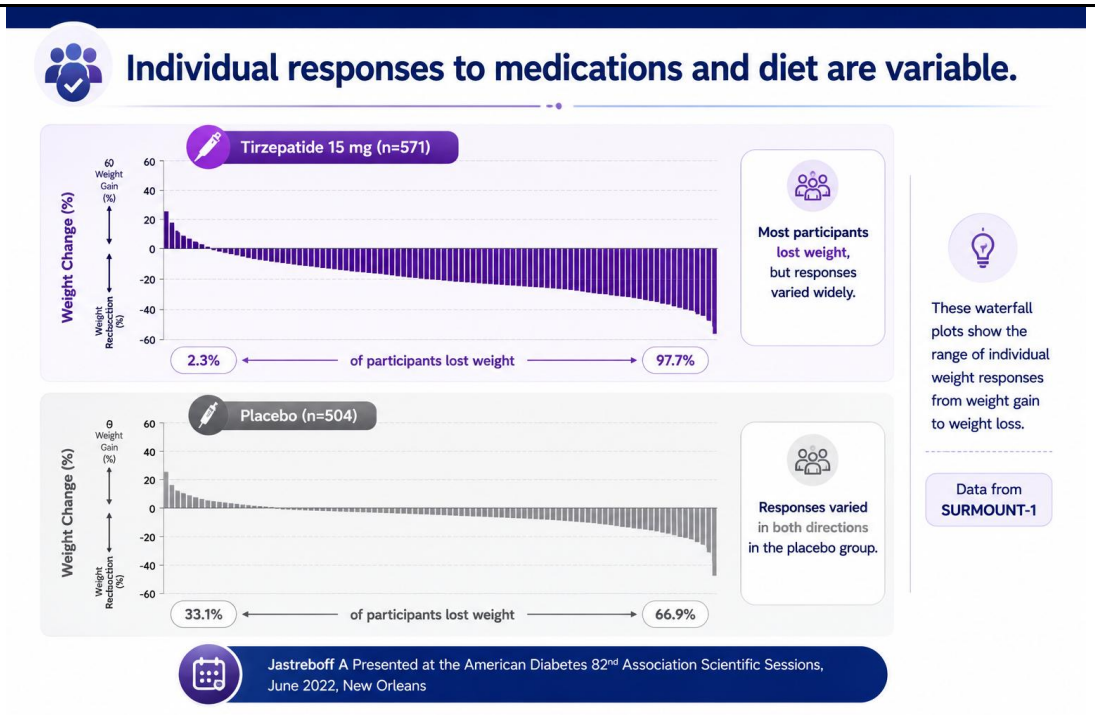
Weight Loss with Incretin Therapies in Type 2 Diabetes

- Nauck M et al. *Lancet* 2026; 407: 892–908
- Frias JP et al. *N Engl J Med.* 2021 (SURPASS-2)
- Ahrén B et al. *Lancet.* 2017 (SUSTAIN-7)
- Marso SP et al. *N Engl J Med.* 2016 (LEADER)
- Dungan KM et al. *Lancet.* 2014 (AWARD)

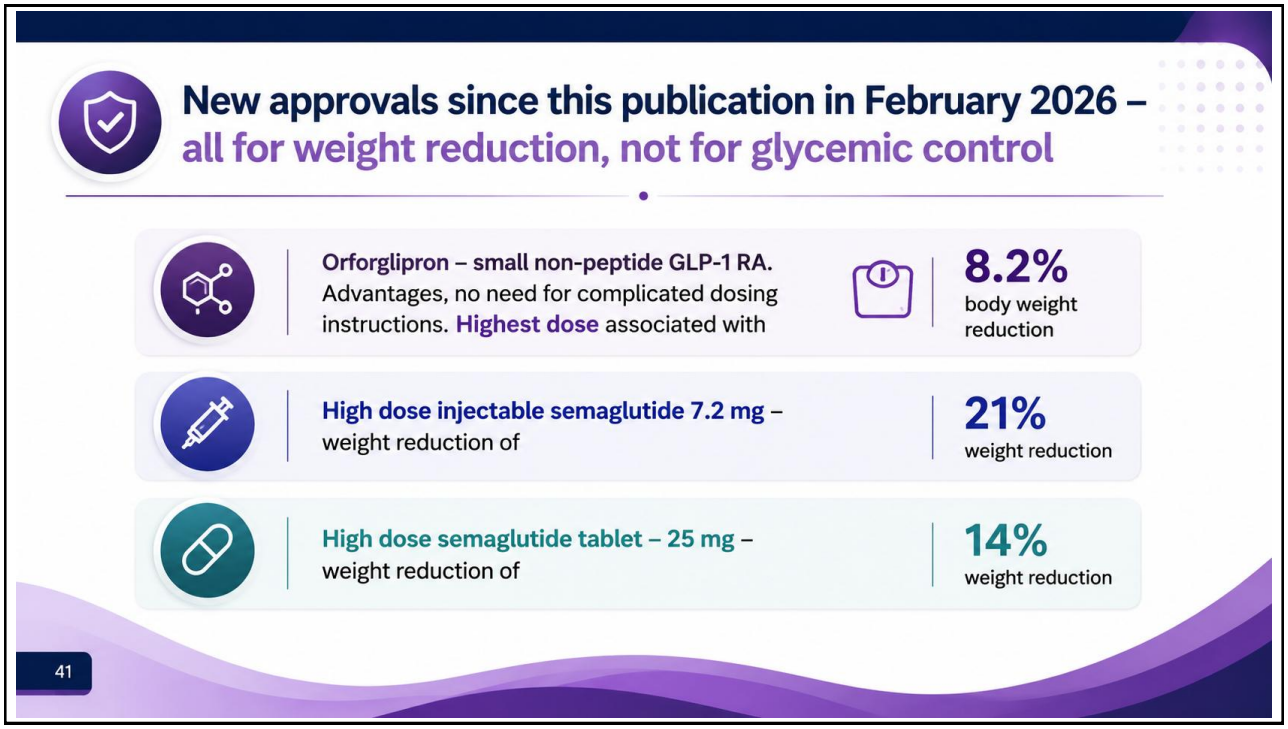
32


Weight reduction in FDA approved medications for weight loss:
patients with diabetes tend to lose less weight (not head-to-head)
Percent Weight Loss at 1 Year in Subjects with Obesity vs. Diabetes
Obesity (without diabetes)
Type 2 Diabetes
Patients with diabetes lose less weight across all therapies.
Percent Weight Loss (%)
25
20
15
10
5
0
10.8%
6.7%
6.6%
3.7%
5.7%
4.1%
16.7%
7.5%
10.1%
4.5%
5.0%
4.6%
20.9%
14.7%
Phen/Top ER*
Naltrex SR/ Buprop**
Liraglutide 3 mg
Semaglutide 2.4 mg
Semaglutide 1 mg
Semaglutide oral 14 mg*
†Tirzepatide 15 mg*
ER = Extended release | SR = Sustained release | *Not yet FDA approved for obesity as of 2026 | †Approved for weight loss in 2023
• Gadde K.M., et al. Lancet 2011. PMID: 19482214
• Greenway F., et al., Lancet 2010. PMID: 20673995
• Pi-Sunyer X., et al., NEJM 2015. PMID: 26132939
• Garvey W.T., et al. Diabetes Care 2014. PMID: 25249652
• Hollander P., et al, Diabetes Care 2017. PMID: 28289041
• Davies M., et al., JAMA 2015. PMID: 26284720
• Wilding, J.P., et al. NEJM 2021. PMID: 33567185
• Davies M., et al., Lancet 2021. PMID: 33667417
• Husain M., et al. NEJM 2019. PMID: 31185157
• Jastreboff A et al, NEJM 2022; Ludvik B Lancet 2021, Garvey WT et al. Lancet 2023

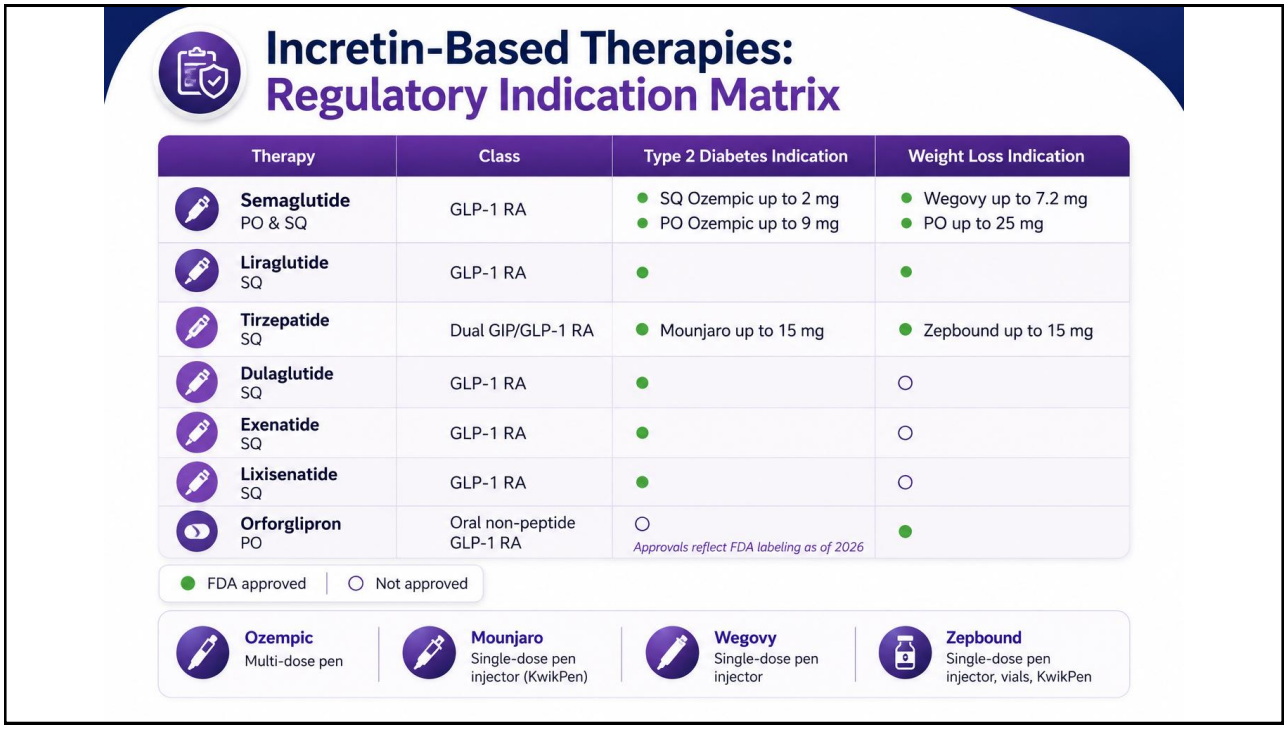
33


Individual responses to medications and diet are variable.
Tirzepatide 15 mg (n=571)
Weight Change (%)
60 Weight Gain (%)
Weight Reduction (%)
60
40
20
0
-20
-40
-60
2.3%
of participants lost weight
97.7%
Most participants lost weight, but responses varied widely.
These waterfall plots show the range of individual weight responses from weight gain to weight loss.
Data from SURMOUNT-1
Placebo (n=504)
Weight Change (%)
0 Weight Gain (%)
Weight Reduction (%)
60
40
20
0
-20
-40
-60
33.1%
of participants lost weight
66.9%
Responses varied in both directions in the placebo group.
Jastreboff A Presented at the American Diabetes 82nd Association Scientific Sessions, June 2022, New Orleans

34


New approvals since this publication in February 2026 –
all for weight reduction, not for glycemic control
Orforglipron – small non-peptide GLP-1 RA. Advantages, no need for complicated dosing instructions. Highest dose associated with
8.2%
body weight reduction
High dose injectable semaglutide 7.2 mg – weight reduction of
21%
weight reduction
High dose semaglutide tablet – 25 mg – weight reduction of
14%
weight reduction
41

35


Incretin-Based Therapies:
Regulatory Indication Matrix
Therapy
Class
Type 2 Diabetes Indication
Weight Loss Indication
Semaglutide PO & SQ
GLP-1 RA
SQ Ozempic up to 2 mg
PO Ozempic up to 9 mg
Wegovy up to 7.2 mg
PO up to 25 mg
Liraglutide SQ
GLP-1 RA
Tirzepatide SQ
Dual GIP/GLP-1 RA
Mounjaro up to 15 mg
Zepbound up to 15 mg
Dulaglutide SQ
GLP-1 RA
Exenatide SQ
GLP-1 RA
Lixisenatide SQ
GLP-1 RA
Orforglipron PO
Oral non-peptide GLP-1 RA
Approvals reflect FDA labeling as of 2026
FDA approved
Not approved
Ozempic Multi-dose pen
Mounjaro Single-dose pen injector (KwikPen)
Wegovy Single-dose pen injector
Zepbound Single-dose pen injector, vials, KwikPen

36

Metabolic surgery versus conventional medical therapy in patients with type 2 diabetes: 10-year follow-up of an open-label, single-centre, randomised controlled trial

Geltrude Mingrone, Simona Panunzi, Andrea De Gaetano, Caterina Guidone, Amerigo Iaconelli, Esmeralda Capristo, Ghassan Chamseddine, Stefan R Bornstein, Francesco Rubino

Lancet 2021; 397: 293–304

AIM

To compare metabolic surgery with medical therapy for the treatment of type 2 diabetes in people with obesity

INCLUSION

30–60 yo + BMI >35 kg/m² + T2DM >5y + HbA1c >7.0%

INTERVENTION

Lifestyle modification and adjustment of T2DM medications with aim HbA1c <7% vs RYGB or BPD

PRIMARY OUTCOME

Rate of diabetes remission at 2 years (fasting glucose level <100 mg/dL and HbA1c <6.5% for >1y without medication)

10-YEAR DURABILITY

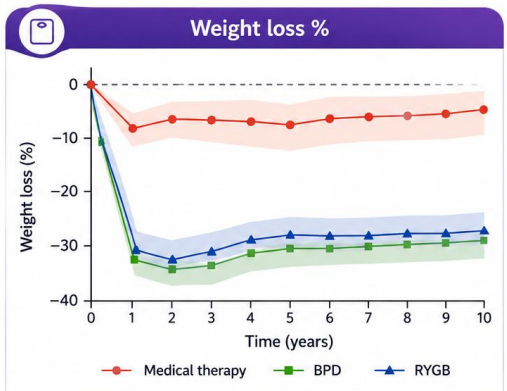
(n=58 of original 60 participants)

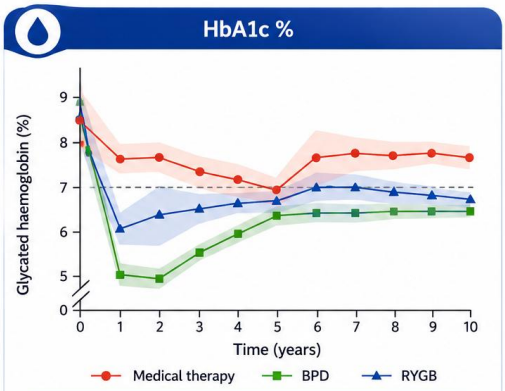
BASELINE CHARACTERISTICS

	RYGB	BPD	Medical
N	20	20	18
% female	60	50	50
Age (y)	44	44	43
Weight (kg)	129	128	137
BMI (kg/m²)	44.2	44.4	44.6
Years with T2DM	6.0	5.5	6.0
HbA1c (%)	8.6	8.9	8.5
Insulin use (%)	45	50	55

37

Greater weight loss with bariatric surgery is associated with greater improvement in glucose control in established T2D





Bariatric surgery (BPD and RYGB) results in ~30–35% weight loss at 10 years vs ~5–7% with medical therapy.

Remission at 10 years: 37% with surgery

Mingrone *Lancet* 2021

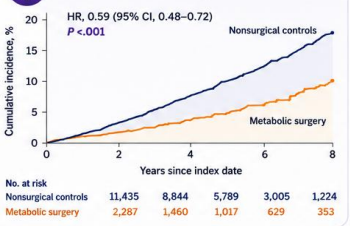
38

Metabolic surgery for T2D – cardiorenal outcomes

(retrospective cohort study)

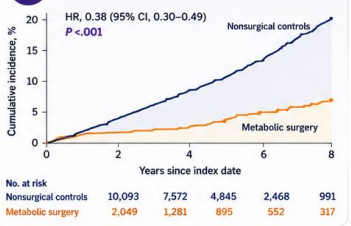
Nonsurgical controls — Metabolic surgery

All-cause mortality



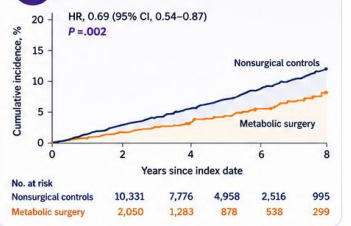
No. at risk					
Nonsurgical controls	11,435	8,844	5,789	3,005	1,224
Metabolic surgery	2,287	1,460	1,017	629	353

Heart failure



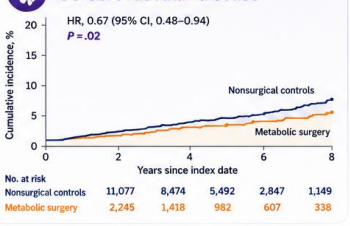
No. at risk					
Nonsurgical controls	10,093	7,572	4,845	2,468	991
Metabolic surgery	2,049	1,281	895	552	317

Coronary artery disease



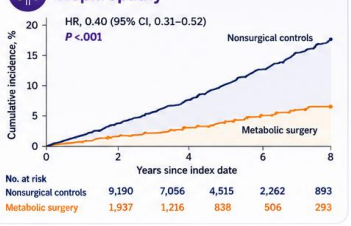
No. at risk					
Nonsurgical controls	10,331	7,776	4,958	2,516	995
Metabolic surgery	2,050	1,283	878	538	299

Cerebrovascular disease



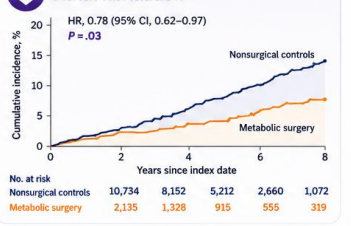
No. at risk					
Nonsurgical controls	11,077	8,474	5,492	2,847	1,149
Metabolic surgery	2,245	1,418	982	607	338

Nephropathy



No. at risk					
Nonsurgical controls	9,190	7,056	4,515	2,262	893
Metabolic surgery	1,937	1,216	838	506	293

Atrial fibrillation



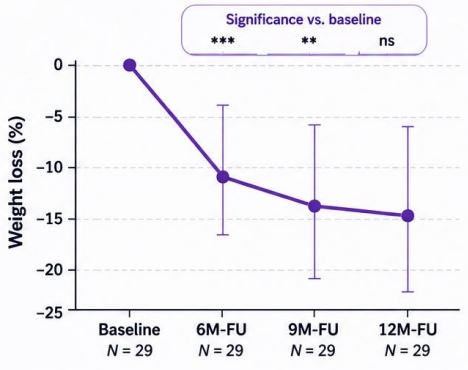
No. at risk					
Nonsurgical controls	10,734	8,152	5,212	2,660	1,072
Metabolic surgery	2,135	1,328	915	555	319

Aminian A et al. *JAMA*. 2019;322:1271–1282

39

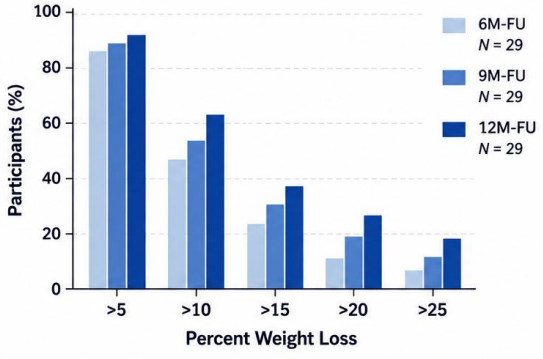
Sustained weight loss with semaglutide in patients without T2D after post-bariatric treatment failure

(A) Mean Weight Loss Over Time



Mean weight loss of ~15% maintained at 12 months

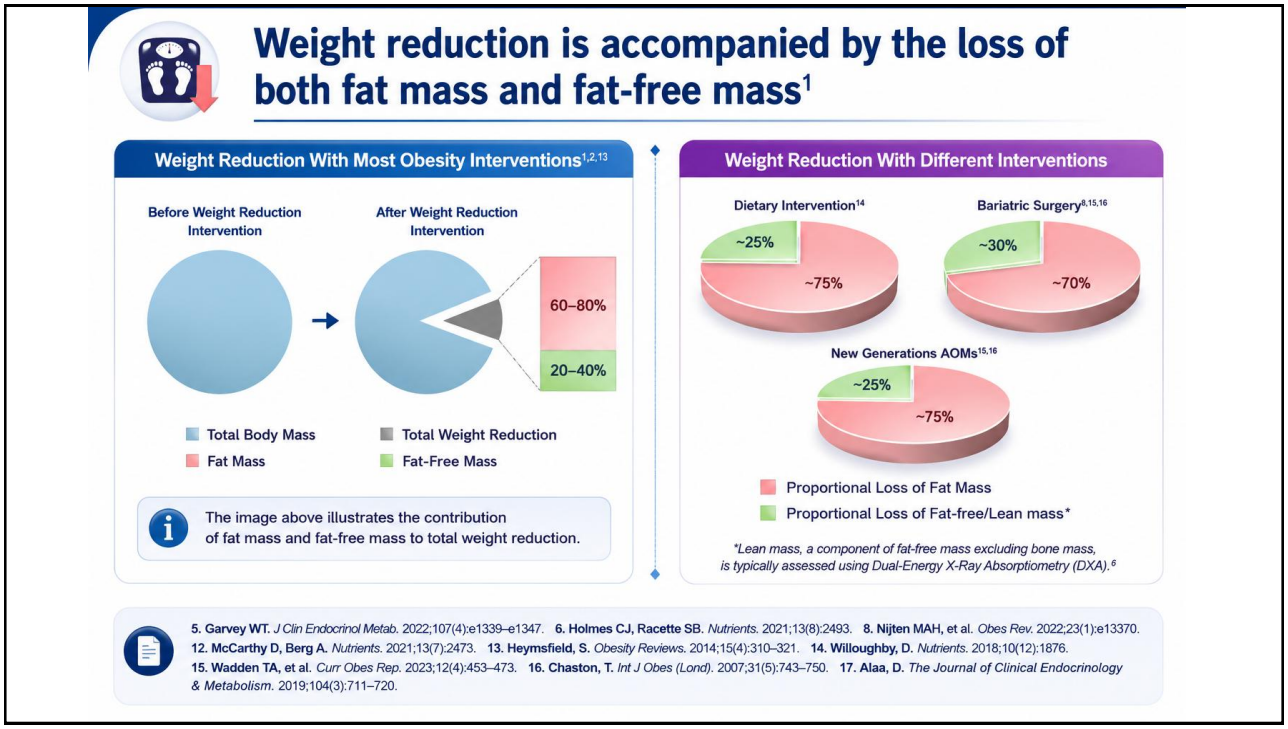
(B) Participants Achieving Weight Loss Thresholds



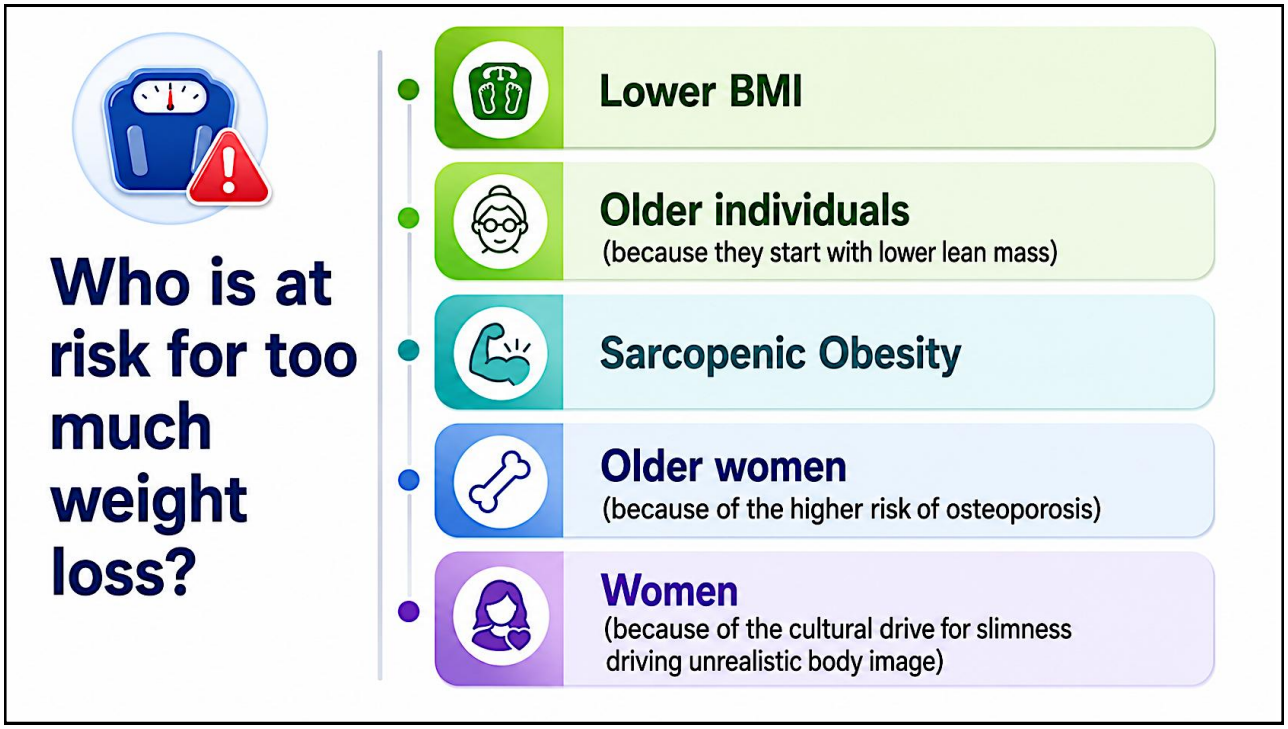
Higher proportions of participants achieve greater weight loss with longer follow-up.

Clinical Obesity, Published online: 26 June 2023, DOI: (10.1111/cob.12593)

40


Weight reduction is accompanied by the loss of both fat mass and fat-free mass[1]
Weight Reduction With Most Obesity Interventions[1,2,13]
Before Weight Reduction Intervention
After Weight Reduction Intervention
60–80%
20–40%
Total Body Mass
Fat Mass
Total Weight Reduction
Fat-Free Mass
The image above illustrates the contribution of fat mass and fat-free mass to total weight reduction.
Weight Reduction With Different Interventions
Dietary Intervention[14]
~25%
~75%
Bariatric Surgery[8,15,16]
~30%
~70%
New Generations AOMs[15,16]
~25%
~75%
Proportional Loss of Fat Mass
Proportional Loss of Fat-free/Lean mass*
*Lean mass, a component of fat-free mass excluding bone mass, is typically assessed using Dual-Energy X-Ray Absorptiometry (DXA).[6]
5. Garvey WT. J Clin Endocrinol Metab. 2022;107(4):e1339–e1347. 6. Holmes CJ, Racette SB. Nutrients. 2021;13(8):2493. 8. Nijten MAH, et al. Obes Rev. 2022;23(1):e13370.
12. McCarthy D, Berg A. Nutrients. 2021;13(7):2473. 13. Heymsfield, S. Obesity Reviews. 2014;15(4):310–321. 14. Willoughby, D. Nutrients. 2018;10(12):1876.
15. Wadden TA, et al. Curr Obes Rep. 2023;12(4):453–473. 16. Chaston, T. Int J Obes (Lond). 2007;31(5):743–750. 17. Alaa, D. The Journal of Clinical Endocrinology & Metabolism. 2019;104(3):711–720.

41

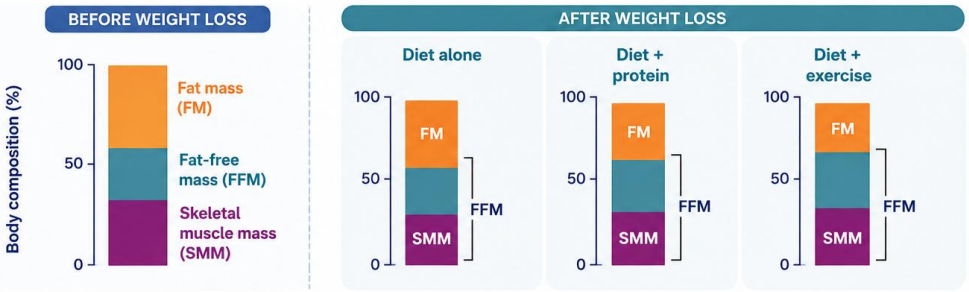

Who is at risk for too much weight loss?
Lower BMI
Older individuals
(because they start with lower lean mass)
Sarcopenic Obesity
Older women
(because of the higher risk of osteoporosis)
Women
(because of the cultural drive for slimness driving unrealistic body image)

42

Weight loss–induced reduction in fat-free mass (FFM) and skeletal muscle mass (SMM) is attenuated through dietary protein and exercise

Figure. Body Composition Before and After Weight Loss

Representation of body composition before and after 25% intentional weight loss



Weight loss reduces both fat mass (FM) and fat-free mass (FFM), including skeletal muscle mass (SMM).

Adequate dietary protein helps preserve FFM during weight loss.

Exercise further attenuates loss of FFM, preserving skeletal muscle mass.

Conte C, et al. *JAMA*. 2024;332(1):9-10

43

Beyond Weight Loss

Before Rx

- Assess risk factors for malnutrition and low muscle mass and function

During WL on Rx

- Prioritize high quality protein intake (1.2–1.5 gm/kg/day, fluids, prevention of nutrient deficiencies and resistance training

Long Term Management on Rx

- Continue nutritional support with meal replacements, sustainable eating plans and individualized physical activity goals

44

Management of GLP-1 Associated Adverse GI Events

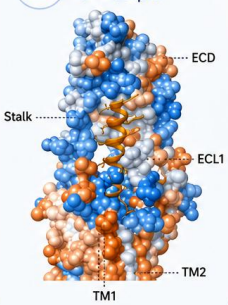
Eat smaller, nutrient-dense meals more frequently	Choose balanced meals rich in protein, fiber, vitamins, and minerals.
Limit high-fat, spicy foods, alcohol, and carbonated beverages	These can worsen GI symptoms such as nausea, bloating, and reflux.
Reduce dose, slow titration, or switch therapy (microdosing)	Adjust treatment to improve tolerability while maintaining benefits.
Use OTC medications for short-term symptom relief if needed	Examples include antacids, H_2 blockers, or antiemetics as appropriate.
Ensure adequate intake of protein, fiber, fluids, and micronutrients	Supports GI health, prevents deficiencies, and promotes overall well-being.
Use short-term supplements if oral intake is inadequate	Consider protein shakes, vitamin or mineral supplements as recommended.

45

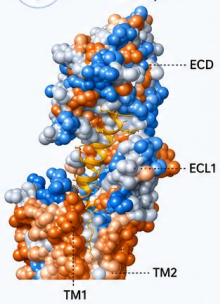
Drugs in Development: Dual and Triple Receptor Agonists

Next-generation incretin and glucagon receptor agonists for obesity treatment

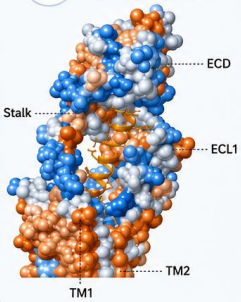
GIPR
GIP Receptor

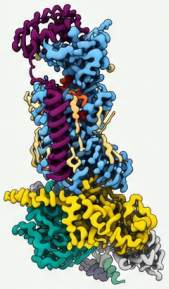


GLP-1R
GLP-1 Receptor



GCGR
Glucagon Receptor





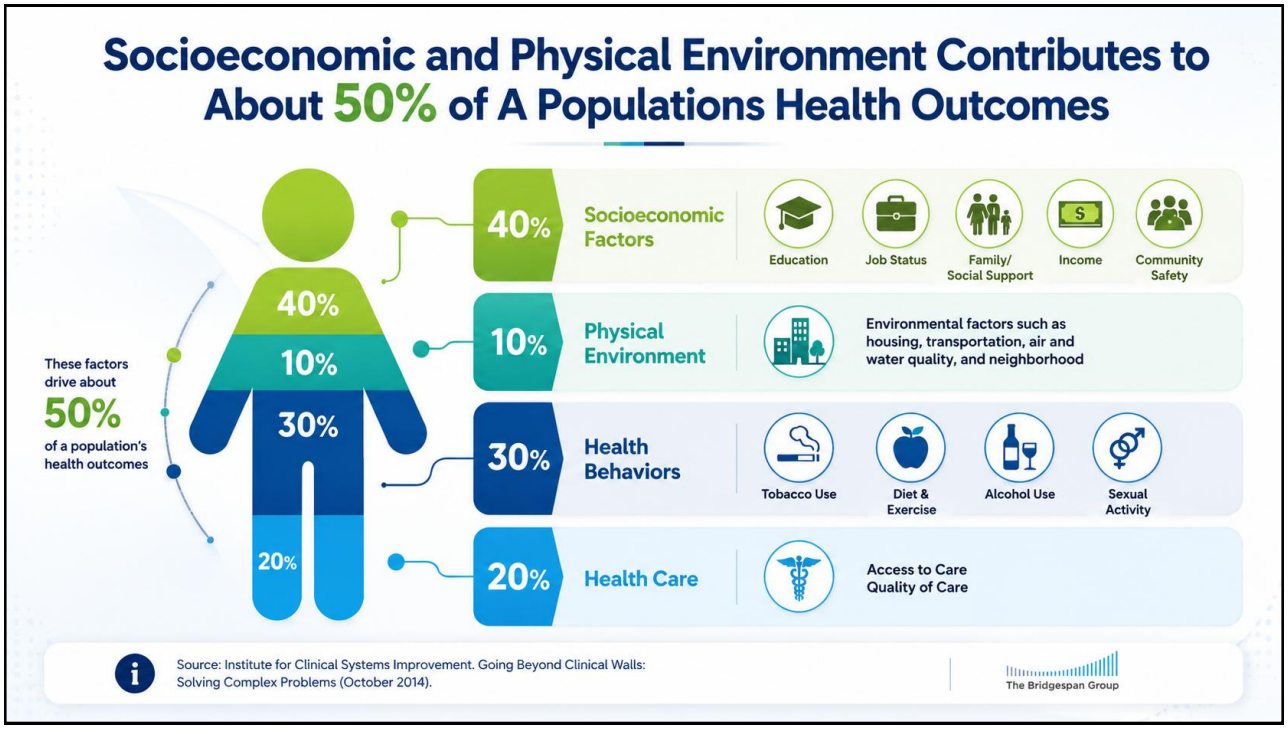
Cagrilintide
(amylin analogue)

Associated with **16%** body weight reduction with dual agonists and **24%** with triple agonists in people without diabetes

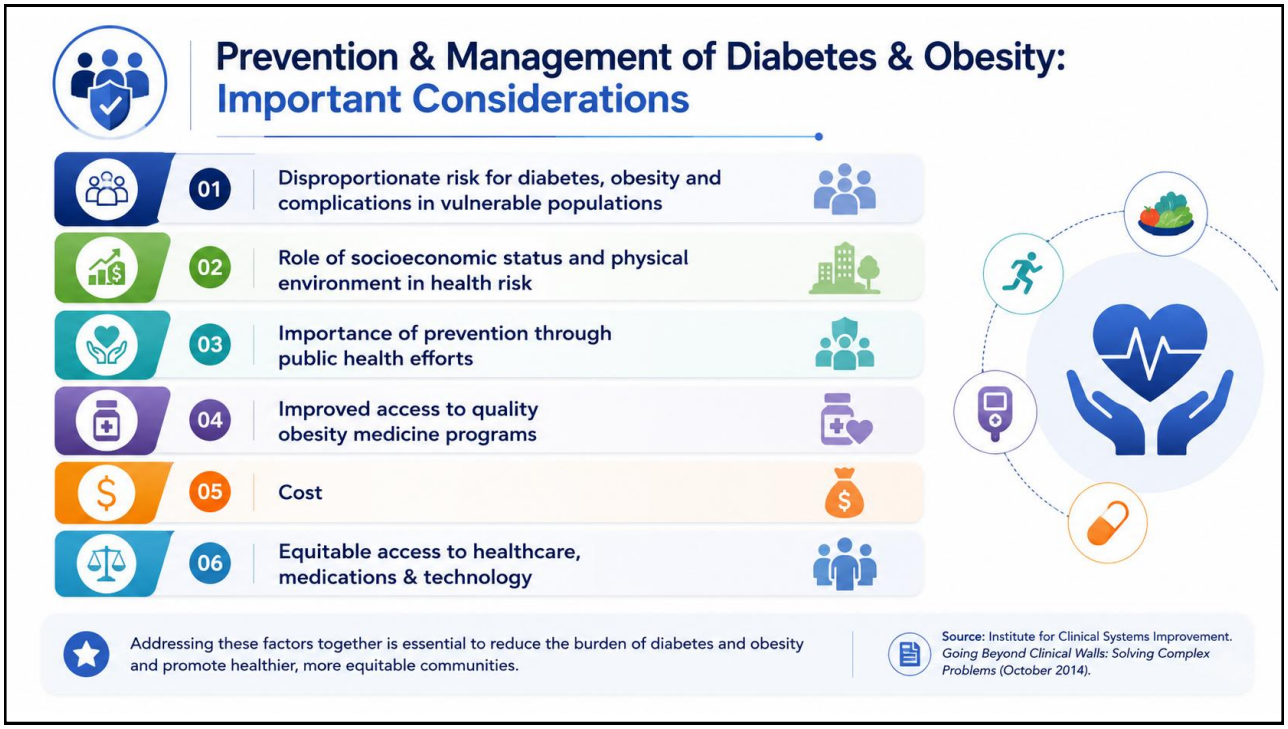
Study population: People without diabetes

Zhao F et al. Structural insights into multiplexed pharmacological actions of tirzepatide and peptide 20 at the GIP, GLP-1 or glucagon receptors. *Nat Comm 2023*

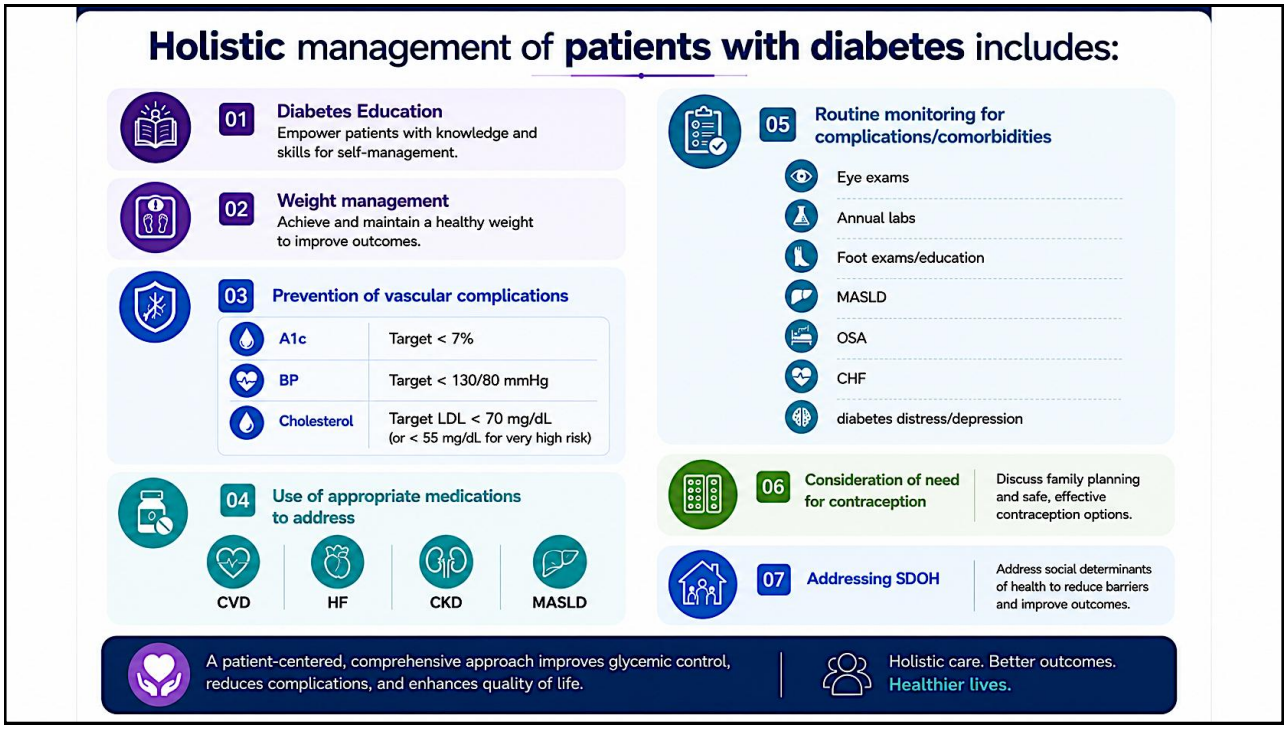
46


Socioeconomic and Physical Environment Contributes to About 50% of A Populations Health Outcomes
These factors drive about 50% of a population's health outcomes
40%
10%
30%
20%
40% Socioeconomic Factors
Education
Job Status
Family/ Social Support
Income
Community Safety
10% Physical Environment
Environmental factors such as housing, transportation, air and water quality, and neighborhood
30% Health Behaviors
Tobacco Use
Diet & Exercise
Alcohol Use
Sexual Activity
20% Health Care
Access to Care
Quality of Care
Source: Institute for Clinical Systems Improvement. Going Beyond Clinical Walls: Solving Complex Problems (October 2014).
The Bridgespan Group

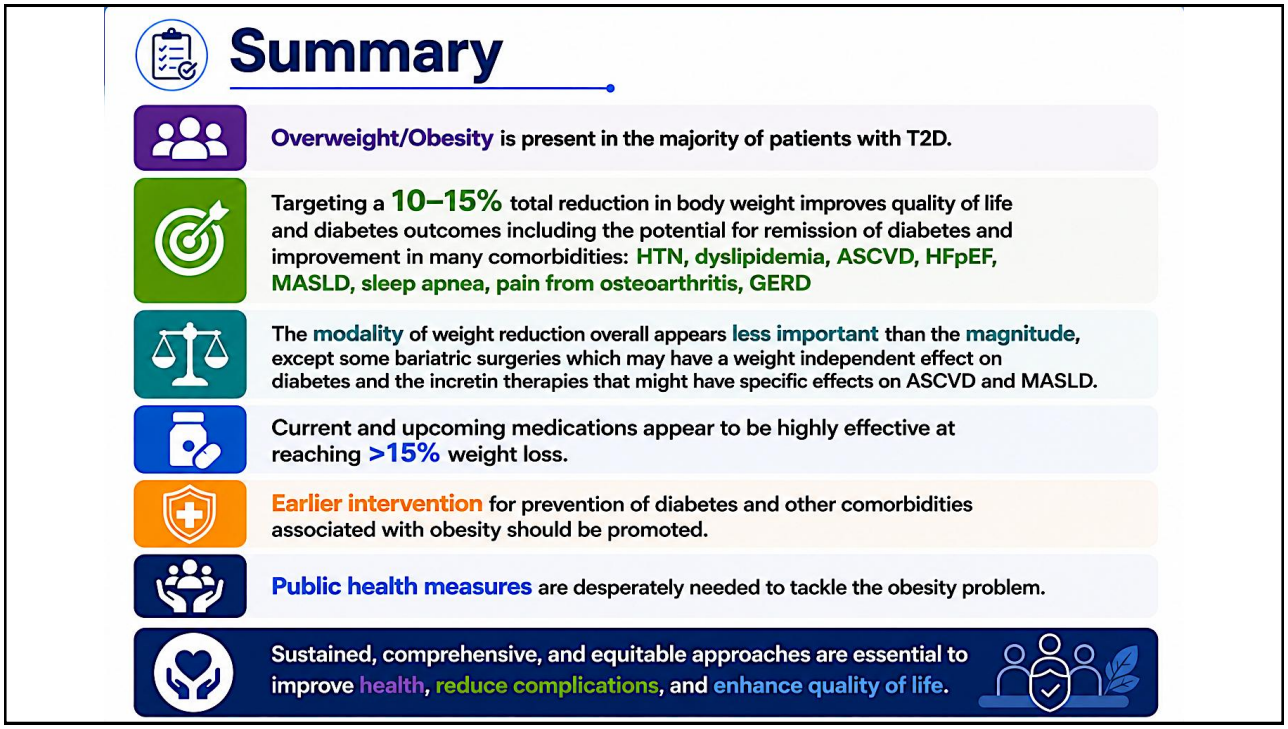
47


Prevention & Management of Diabetes & Obesity:
Important Considerations
01 Disproportionate risk for diabetes, obesity and complications in vulnerable populations
02 Role of socioeconomic status and physical environment in health risk
03 Importance of prevention through public health efforts
04 Improved access to quality obesity medicine programs
05 Cost
06 Equitable access to healthcare, medications & technology
Addressing these factors together is essential to reduce the burden of diabetes and obesity and promote healthier, more equitable communities.
Source: Institute for Clinical Systems Improvement. Going Beyond Clinical Walls: Solving Complex Problems (October 2014).

48


Holistic management of patients with diabetes includes:
01 Diabetes Education
Empower patients with knowledge and skills for self-management.
02 Weight management
Achieve and maintain a healthy weight to improve outcomes.
03 Prevention of vascular complications
A1c Target < 7%
BP Target < 130/80 mmHg
Cholesterol Target LDL < 70 mg/dL (or < 55 mg/dL for very high risk)
04 Use of appropriate medications to address
CVD
HF
CKD
MASLD
05 Routine monitoring for complications/comorbidities
Eye exams
Annual labs
Foot exams/education
MASLD
OSA
CHF
diabetes distress/depression
06 Consideration of need for contraception
Discuss family planning and safe, effective contraception options.
07 Addressing SDOH
Address social determinants of health to reduce barriers and improve outcomes.
A patient-centered, comprehensive approach improves glycemic control, reduces complications, and enhances quality of life.
Holistic care. Better outcomes. Healthier lives.

49


Summary
Overweight/Obesity is present in the majority of patients with T2D.
Targeting a 10–15% total reduction in body weight improves quality of life and diabetes outcomes including the potential for remission of diabetes and improvement in many comorbidities: HTN, dyslipidemia, ASCVD, HFpEF, MASLD, sleep apnea, pain from osteoarthritis, GERD
The modality of weight reduction overall appears less important than the magnitude, except some bariatric surgeries which may have a weight independent effect on diabetes and the incretin therapies that might have specific effects on ASCVD and MASLD.
Current and upcoming medications appear to be highly effective at reaching >15% weight loss.
Earlier intervention for prevention of diabetes and other comorbidities associated with obesity should be promoted.
Public health measures are desperately needed to tackle the obesity problem.
Sustained, comprehensive, and equitable approaches are essential to improve health, reduce complications, and enhance quality of life.

50