

ECHO IDAHO

Diabetes and Metabolic Conditions

Managing Insulin Resistance with Behavioral and Pharmacologic Innovations

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Jordin Millward, presenter for this educational event, is employed by Inclusive Care Clinic Pharmacy. All of the relevant financial relationships listed for these individuals have been mitigated.

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Disclosures

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Learning Objectives

- Describe the role of insulin resistance in type 2 diabetes, obesity, and metabolic syndrome.
- Identify evidence-based behavioral interventions that improve insulin sensitivity and patient outcomes.
- Explain how to evaluate and integrate pharmacologic treatment options for managing insulin resistance.

HOW DOES INSULIN WORK?

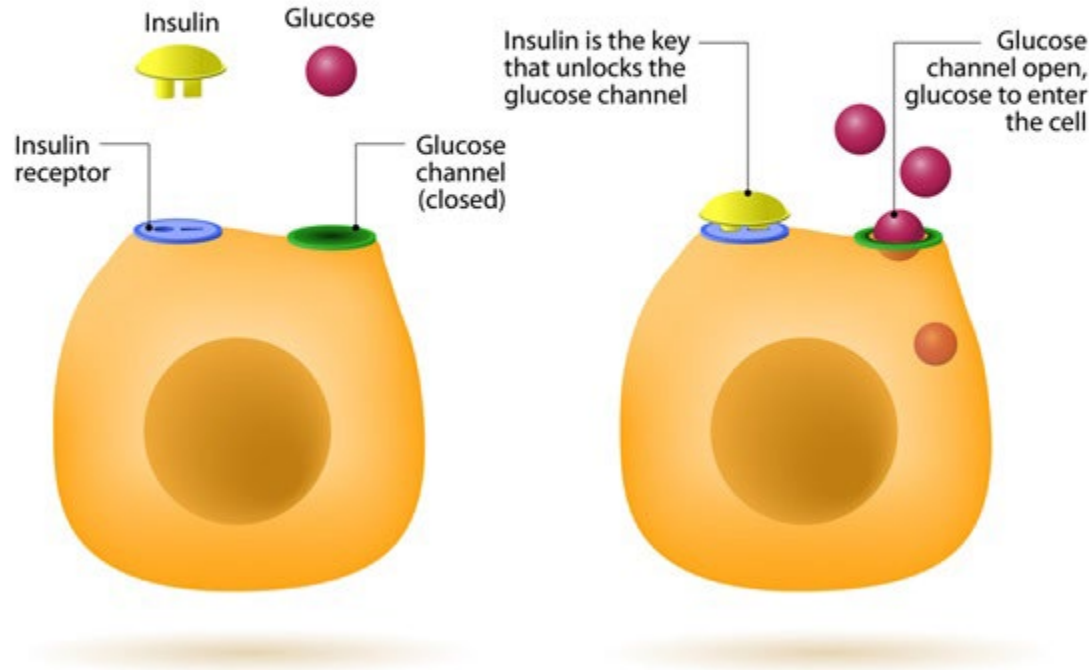
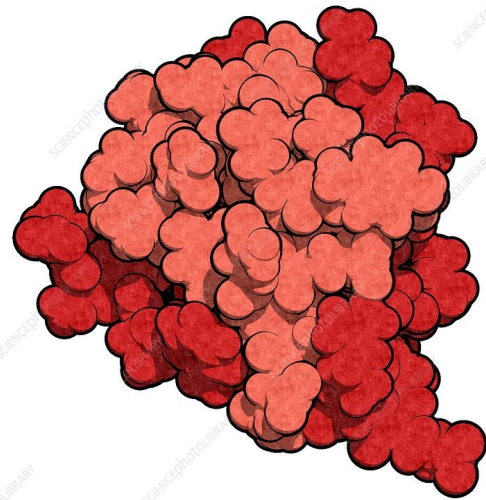
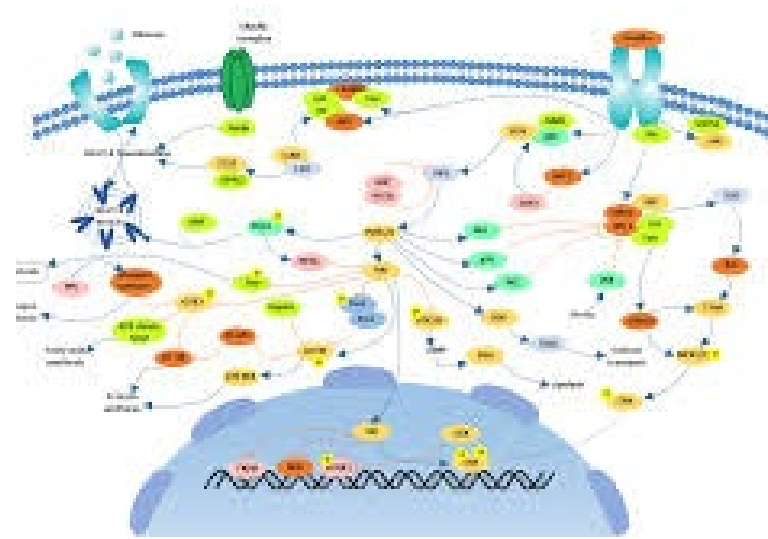


Image Credit: Designua / Shutterstock.com

Insulin Resistance



Decreased insulin
receptor
number/affinity

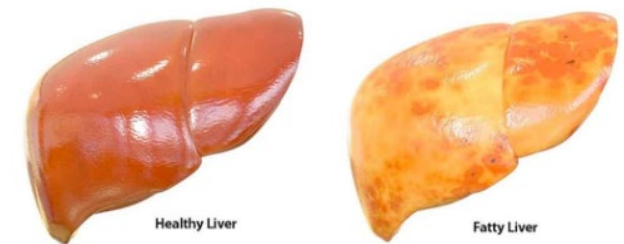
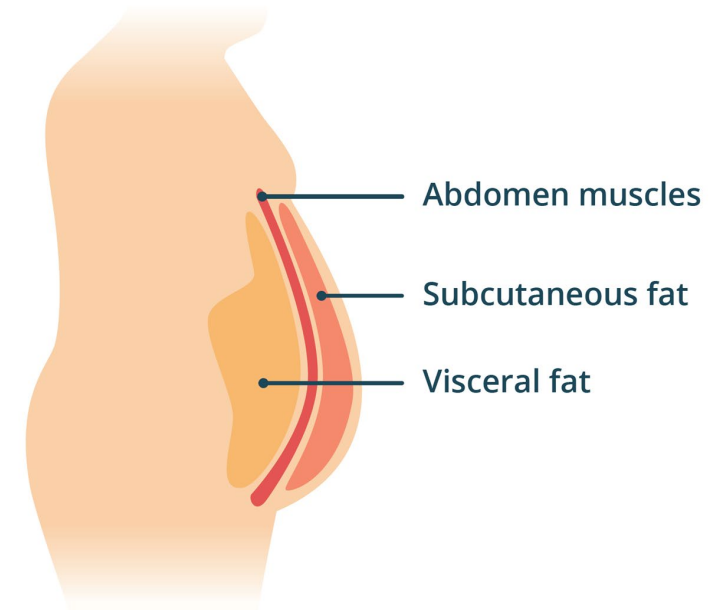


Abnormal signal
transduction

<https://www.cusabio.com/pathway/Insulin-signaling-pathway.html>

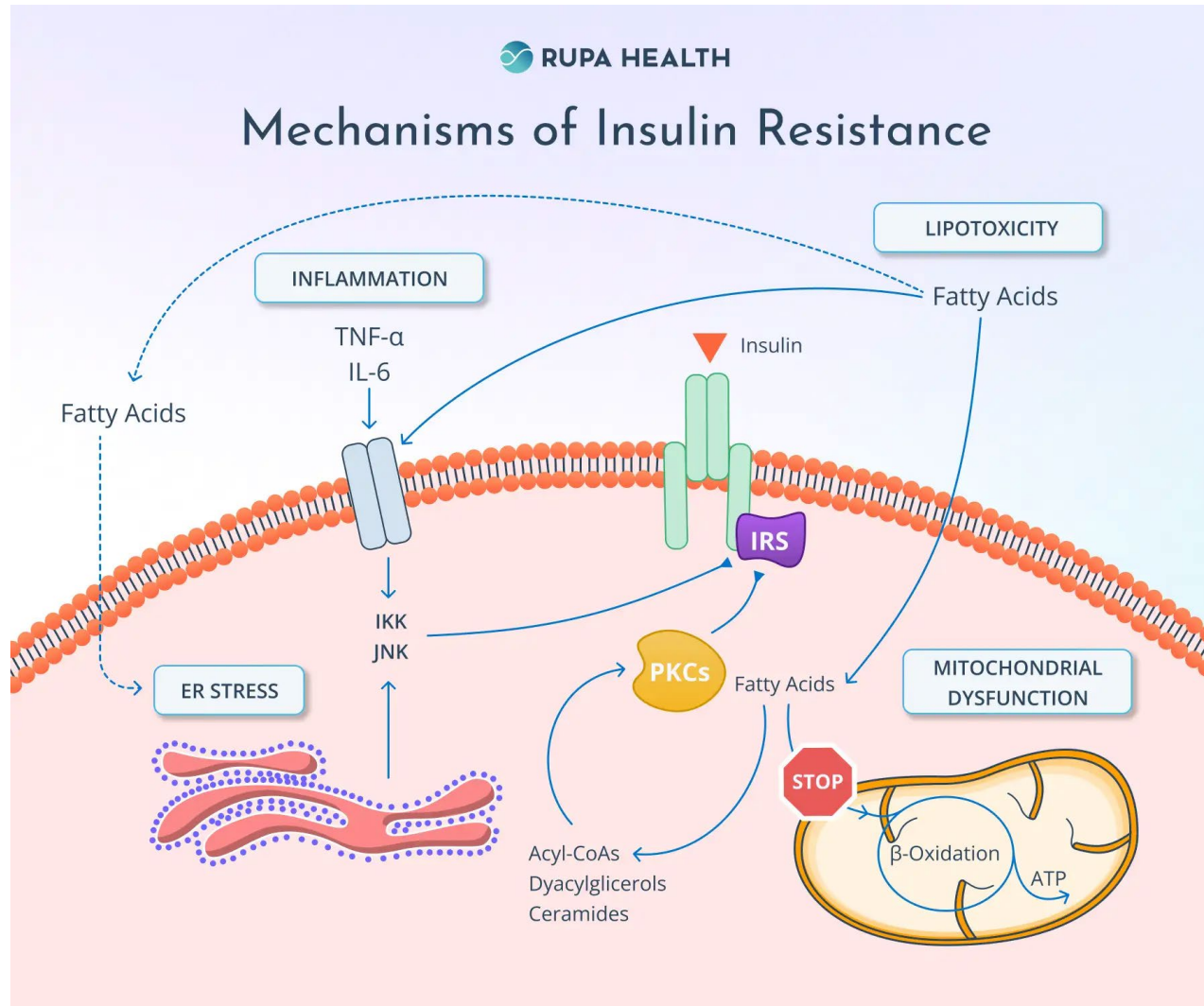
Insulin Resistance Pathophysiology

- **Visceral fat:** surrounds deep internal organs in abdominal cavity
 - More metabolically active than subcutaneous fat
 - More likely to release FFA into circulation
 - Storage of toxic lipid intermediates
 - Release of pro-inflammatory cytokines
 - Less release of anti-inflammatory hormones
 - Individuals may have genetic predisposition towards accumulation of visceral fat
- **Ectopic fat:** fat stored in tissues not meant to store fat (liver, muscle)
 - Can interfere with normal hormonal signaling pathways



<https://www.healthdirect.gov.au/how-to-reduce-excess-internal-body-fat-visceral-fat>
<https://liverfoundation.org/liver-diseases/fatty-liver-disease/nonalcoholic-steatohepatitis-nash/mash-definition-prevalence/>

Insulin Resistance Pathophysiology



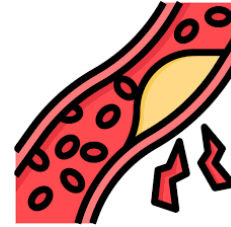
<https://www.rupahealth.com/post/what-is-insulin-resistance-effects>

Metabolic Syndrome via Insulin Resistance



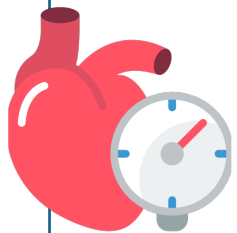
Insulin resistance

- ↓ glucose uptake
- ↑ glucagon secretion (α -cell resistance)
- ↑ gluconeogenesis
- ↑ FFA in circulation



Hyperlipidemia

- ↑ FFA = ↑ hepatic TG synthesis
- ↑ TG = ↑ VLDL production
- ↑ VLDL = ↓ HDL



Hypertension

- ↑ circulating insulin = ↑ Na⁺ retention
- ↓ insulin sensitivity and ↑ FFA = ↓ nitric oxide synthesis = ↑ vasoconstriction
- ↑ cytokines = ↑ endothelial damage



Weight gain

- ↑ insulin = ↑ lipogenesis = ↑ visceral fat and ectopic fat (liver, muscle, pancreas)
- ↓ insulin sensitivity, ↓ leptin sensitivity, ↓ GLP-1 and amylin secretion = ↑ **hunger**

Metabolic Syndrome

- Patients with metabolic syndrome are **5x more likely** to develop T2DM
- Diagnosed when a patient has 3 or more of the following:

High waist
circumference

> 35 in for
women

> 40 in for
men

High blood
pressure

> 130/80
mmHg

Impaired
fasting
glucose

>100
mg/dL

High
triglyceride
levels

>150
mg/dL

Low HDL
levels

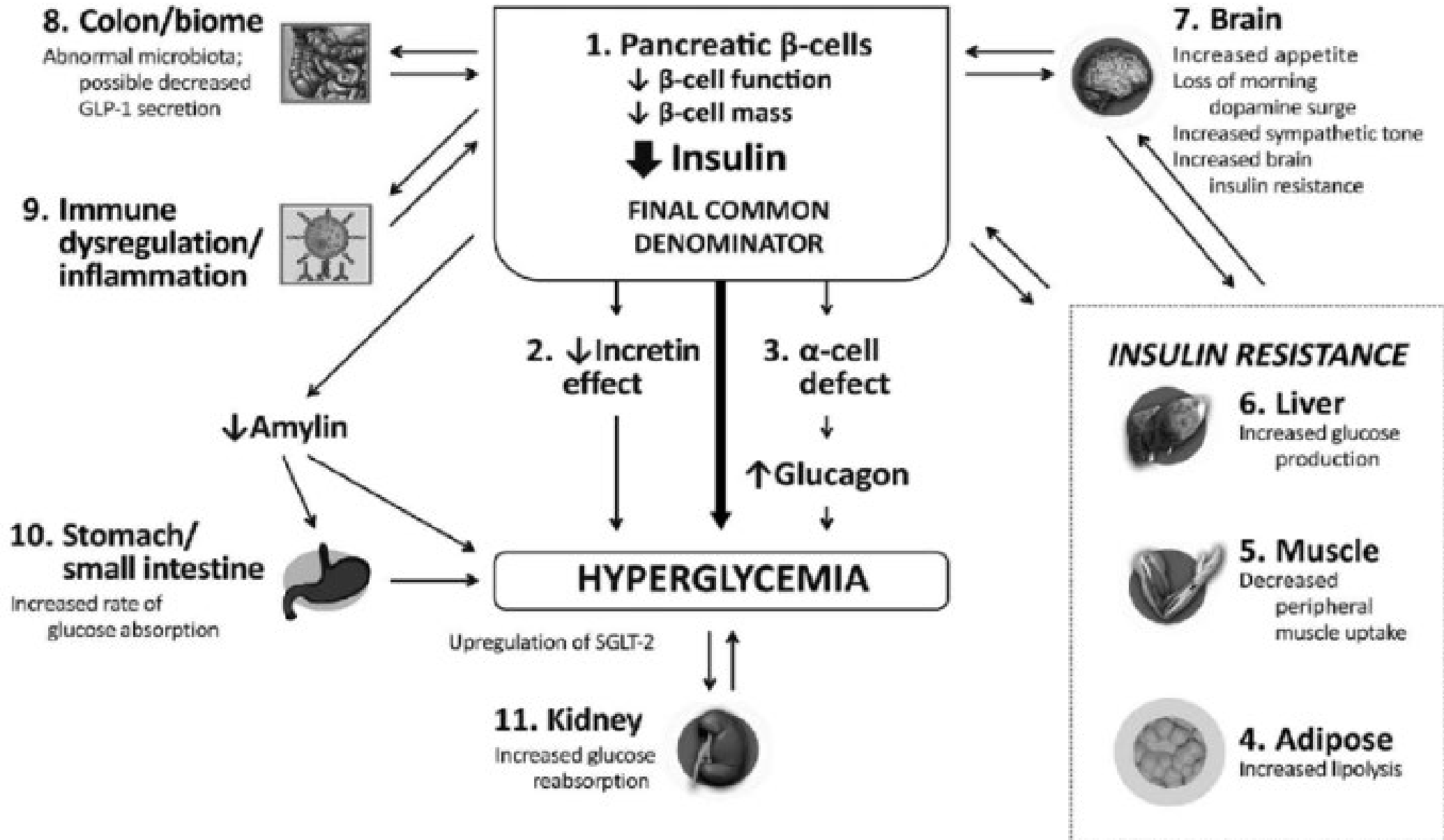
< 40
mg/dL for
men

<50
mg/dL for
women

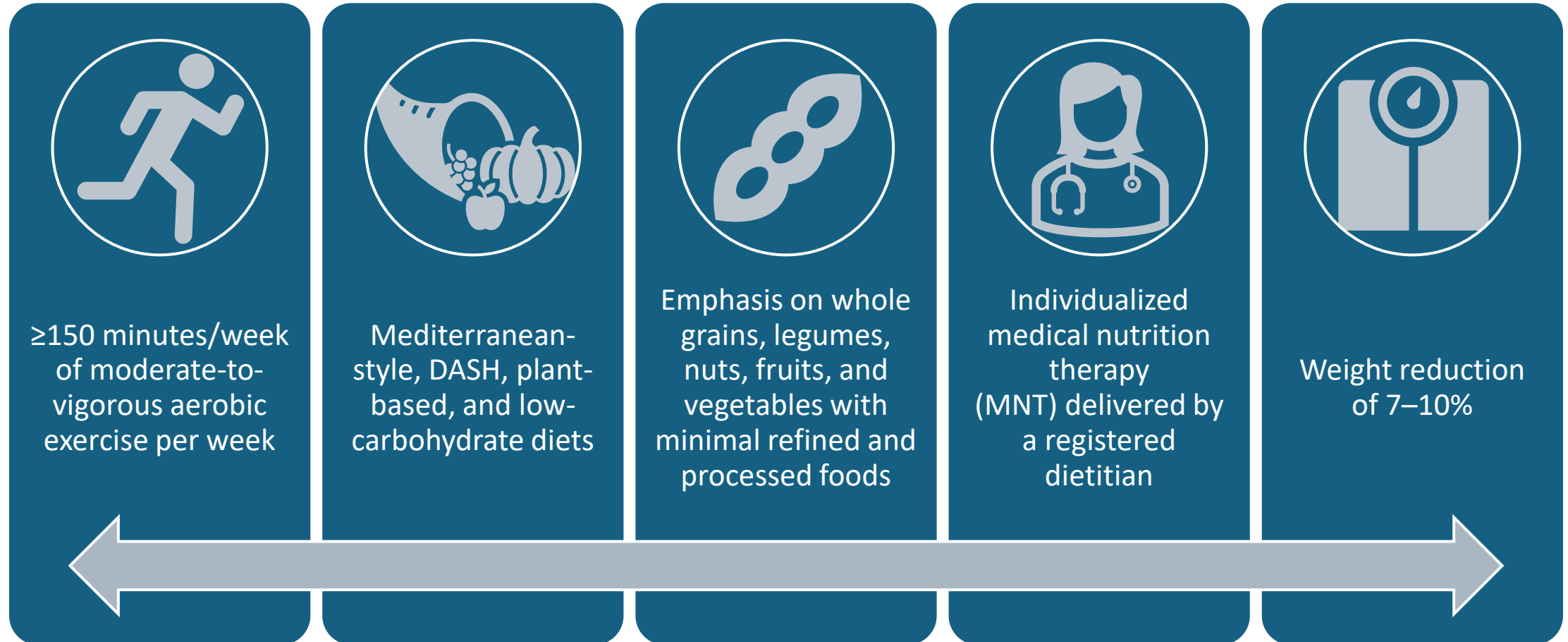
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β -cell-Centric Construct: Egregious Eleven

The β -cell is the FINAL COMMON DENOMINATOR of β -cell Damage



Behavioral Interventions



Pharmacologic Options

Metformin

- Reduces gluconeogenesis
- Improves peripheral glucose uptake
- Enhances insulin sensitivity via AMPK activation

Thiazolidinediones

- PPAR γ activation resulting in direct insulin sensitization in liver, muscle, and adipose tissue
- The most potent insulin sensitizer – with trade-off of weight gain

GLP-1 receptor agonists

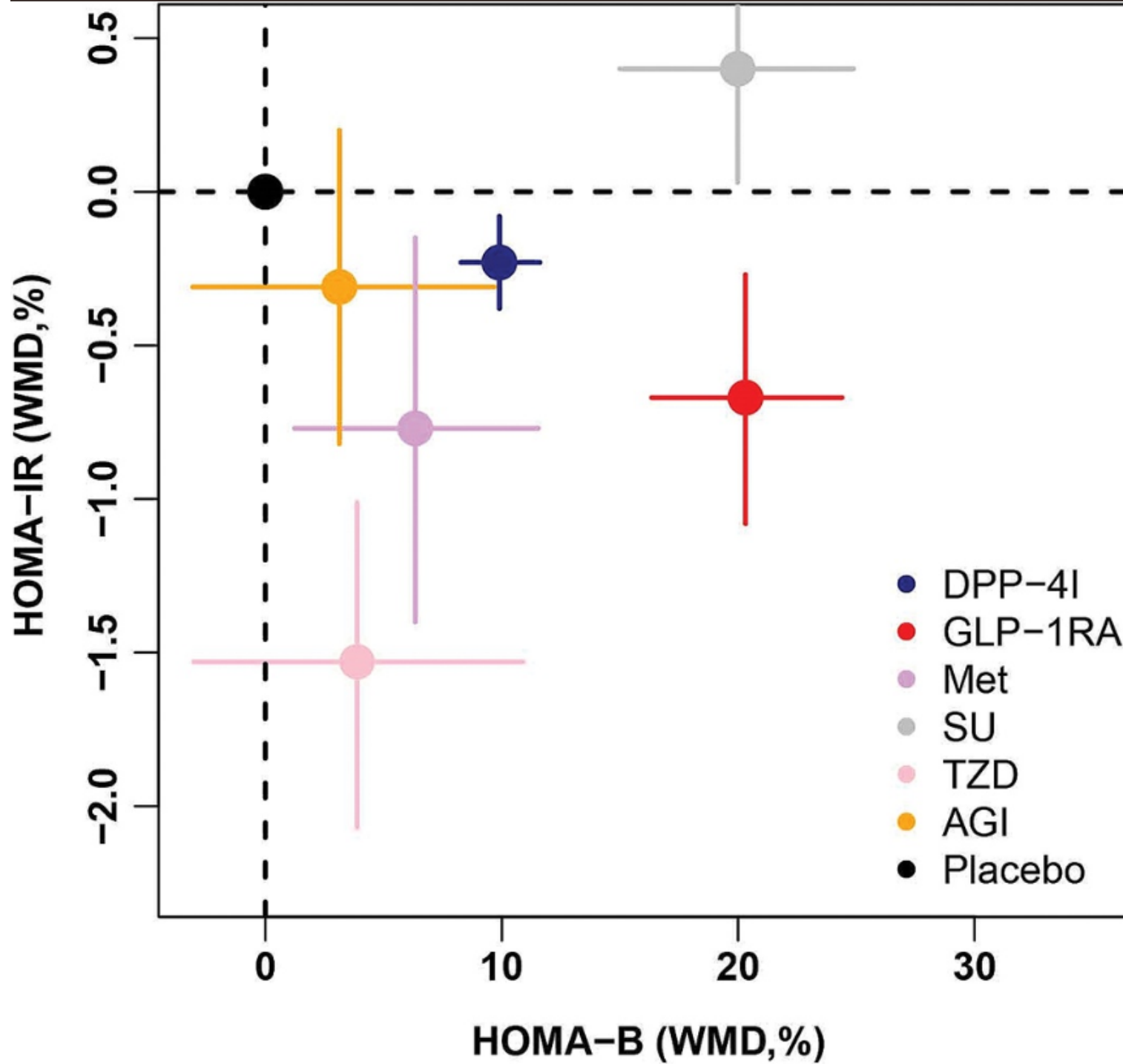
- Weight loss
- Enhanced insulin secretion
- Glucagon suppression
- Slowed gastric emptying
- Significantly improves β -cell function

Dual GIP/GLP-1 receptor agonists

- **Superior** insulin sensitizing effects
- SURPASS-2: tirzepatide (5, 10, 15 mg) reduced HOMA2-IR by **15.5–24.0%** versus only **5.1%** with semaglutide 1 mg
- Improvements only partially attributable to weight loss

SLGT-2 inhibitors

- Indirectly improves insulin resistance
- Reduced glucotoxicity
- Promotes visceral fat reduction



Supplements

Berberine

900-1500
mg/day in
divided doses
ADE: bloating,
diarrhea

CYP3A4 and p-
gp inhibitor

Vitamin D
WITH
documented
deficiency

Chromium

200-1000
µg/day
May increase
hypoglycemia
with insulin

Cinnamon

Ceylon
preferred over
Cassia,
hepatotoxicity
risk
≤2 g/day, in
capsules

Magnesium
WITH
documented
deficiency

Inositol
In PCOS

The ADA does not recommend routine use of herbal supplements due to low- or very-low quality evidence, and supplements should be utilized *adjunctive to* (not in replacement of) established interventions

Behavioral/Pharmacologic Integration

Diabetes Prevention Program

Metformin alone: 31% diabetes incidence reduction

Metformin + lifestyle: 58% diabetes incidence reduction

**2024 Network Meta Analysis:
Type 2 diabetes** (410 RCTs, n = 33,802)

Metformin alone: A1c -0.88%

Metformin + lifestyle: A1c -1.23%

**2024 Network Meta Analysis:
prediabetes** (410 RCTs, n = 33,802)

Metformin alone: -0.23 HOMA-IR

Exercise alone: -0.54 HOMA-IR

2025 Meta Analysis
(33 RCTs, n = 12,028)

GLP-1 RA + lifestyle = additional 7.13 kg of weight loss + improved BP, A1c, FPG, lipids

SURMOUNT-3 Trial

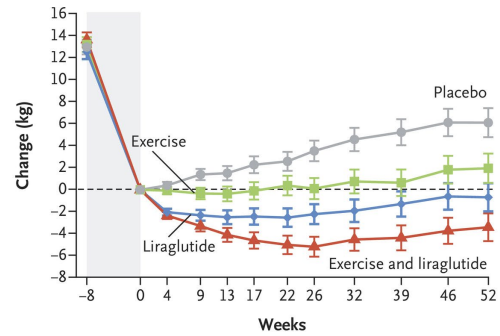
Tirzepatide alone: -20.% body weight

12-week lifestyle lead-in to tirzepatide: -25% body weight

2026 Network Meta Analysis

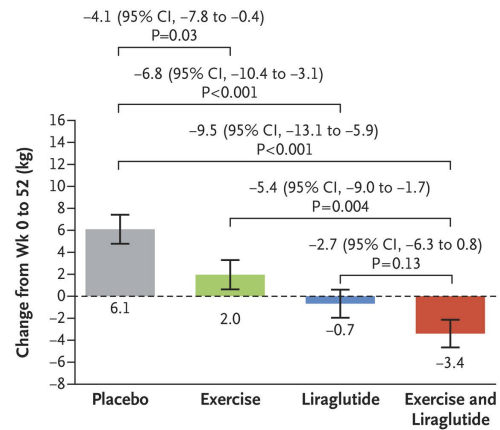
Cognitive behavioral therapy + motivational interviewing + standard behavioral therapy = highest HbA1c reductions over 12-36 months (-1.84%)

A Change in Body Weight

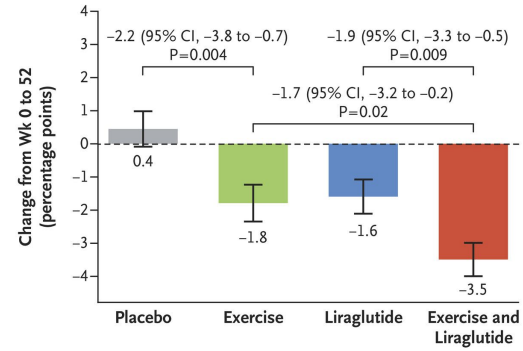
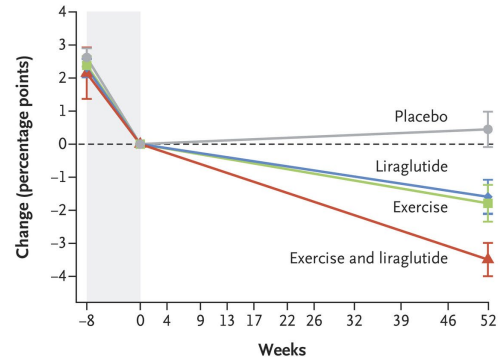


Week	Placebo	Exercise	Liraglutide	Exercise and liraglutide
-8	215	195	187	183
0	181	178	175	171
4	178	175	169	168
9	178	175	168	166
13	178	175	168	166
17	178	175	168	166
22	178	175	168	166
26	178	175	168	166
32	178	175	168	166
39	178	175	168	166
46	178	175	168	166
52	178	175	168	166

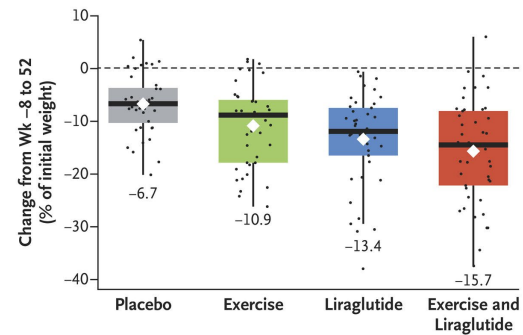
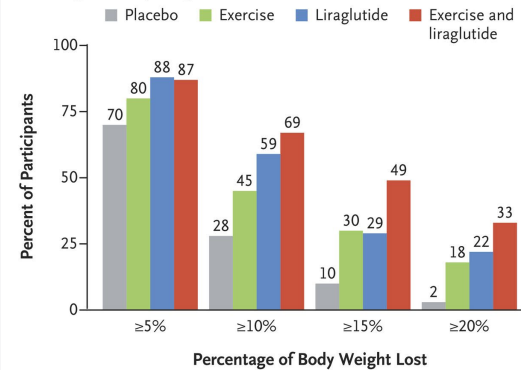
Group	No. Who Underwent Randomization	No. Who Completed Trial
Placebo	49	40
Exercise	48	40
Liraglutide	49	41
Exercise and Liraglutide	49	45



B Change in Body-Fat Percentage



C Change in Body Weight from Wk -8 to Wk 52



Key Points

Insulin resistance drives type 2 diabetes, obesity, and metabolic syndrome through impaired signaling, ectopic fat, and chronic inflammation.

Behavioral interventions are first-line and independently powerful, especially in prediabetes.

Many diabetes medications reduce insulin resistance, but only GLP-1 RAs and GLP-1/GIP RAs both reduce insulin resistance and improve β -cell function.

Selected supplements may provide adjunctive benefit but do not replace established interventions and carry variable evidence quality.

Combination of behavioral and pharmacologic therapy consistently outperforms either alone; sequence and tailor to the individual patient.

References

- American Diabetes Association Professional Practice Committee for Diabetes*. 3. Prevention or Delay of Diabetes and Associated Comorbidities: Standards of Care in Diabetes-2026. *Diabetes Care*. 2026 Jan 1;49(Supplement_1):S50-S60. doi: 10.2337/dc26-S003. PMID: 41358891; PMCID: PMC12690170.
- American Diabetes Association Professional Practice Committee for Diabetes*. 5. Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes: Standards of Care in Diabetes-2026. *Diabetes Care*. 2026 Jan 1;49(Supplement_1):S89-S131. doi: 10.2337/dc26-S005. PMID: 41358898; PMCID: PMC12690188
- American Diabetes Association Professional Practice Committee for Diabetes*. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2026. *Diabetes Care*. 2026 Jan 1;49(Supplement_1):S183-S215. doi: 10.2337/dc26-S009. PMID: 41358900; PMCID: PMC12690185.
- Balkrishna A, Tripathi SK, Singh SK, Verma S, Arya V. A critical appraisal of anti-hyperglycemic mechanisms, matrix-dependent bioavailability, and species-stratified safety of *Cinnamomum* spp. as functional food ingredients. *Food Res Int*. 2026 Aug 1;237:119322. doi: 10.1016/j.foodres.2026.119322. Epub 2026 May 7. PMID: 42169286.
- Chu J, Zhang H, Wu Y, Huang Y, Zhu T, Zhou Z, Wang H. Efficacy of lifestyle modification combined with GLP-1 receptor agonists on body weight and cardiometabolic biomarkers in individuals with overweight or obesity: a systematic review and meta-analysis. *EClinicalMedicine*. 2025 Aug 30;88:103464. doi: 10.1016/j.eclinm.2025.103464. PMID: 40926900; PMCID: PMC12414836.
- Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, Horton ES, Castorino K, Tate DF. Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association. *Diabetes Care*. 2016 Nov;39(11):2065-2079. doi: 10.2337/dc16-1728. PMID: 27926890; PMCID: PMC6908414
- Dankoob V, Shahinfar H, Ostevari A, Norouziasl R, Mohieddin N, Esmaeili F, Rafiei F, Shab-Bidar S. The efficacy of behavioral interventions on cardiovascular risk factors in patients with type 2 diabetes: a systematic review and network meta-analysis of randomized trials. *Diabetes Res Clin Pract*. 2026 Jun;236:113260. doi: 10.1016/j.diabres.2026.113260. Epub 2026 Apr 12. PMID: 41974358.
- de Moura SL, Gomes BGR, Guillarducci MJ, Coelho OGL, Guimarães NS, Gomes JMG. Effects of cinnamon supplementation on metabolic biomarkers in individuals with type 2 diabetes: a systematic review and meta-analysis. *Nutr Rev*. 2025 Feb 1;83(2):249-279. doi: 10.1093/nutrit/nuae058. PMID: 38917435.
- Duan M, Yang M, Li C, Wu X, Yin X, Zhu H. Effects of inositol in women with polycystic ovary syndrome: an umbrella review of meta-analyses from randomized controlled trials. *Front Endocrinol (Lausanne)*. 2026 Feb 11;17:1741509. doi: 10.3389/fendo.2026.1741509. PMID: 41757236; PMCID: PMC12932251.

References

- Frias JP, De Block C, Brown K, Wang H, Thomas MK, Zeytinoglu M, Maldonado JM. Tirzepatide Improved Markers of Islet Cell Function and Insulin Sensitivity in People With T2D (SURPASS-2). *J Clin Endocrinol Metab.* 2024 Jun 17;109(7):1745-1753. doi: 10.1210/clinem/dgae038. PMID: 38252888; PMCID: PMC11180500.
- Haines S. Diabetes Mellitus. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Posey L, eds. *DiPiro's Pharmacotherapy: A Pathophysiologic Approach*, 12th Edition. McGraw Hill; 2023
- Ley SH, Hamdy O, Mohan V, Hu FB. Prevention and management of type 2 diabetes: dietary components and nutritional strategies. *Lancet.* 2014 Jun 7;383(9933):1999-2007. doi: 10.1016/S0140-6736(14)60613-9. PMID: 24910231; PMCID: PMC4751088.
- Lundgren JR, Janus C, Jensen SBK, et al. Healthy Weight Loss Maintenance with Exercise, Liraglutide, or Both Combined. *N Engl J Med.* 2021;384(18):1719-1730. doi: 10.1056/NEJMoa2028198.
- Poon ET, Wong PS, Kong APS, Ali A. Efficacy of exercise-based interventions for prediabetes: an umbrella review of meta-analyses of randomised controlled trials. *EClinicalMedicine.* 2025 Oct 30;90:103606. doi: 10.1016/j.eclinm.2025.103606. PMID: 41245533; PMCID: PMC12613059
- Simental-Mendía LE, Sahebkar A, Rodríguez-Morán M, Guerrero-Romero F. A systematic review and meta-analysis of randomized controlled trials on the effects of magnesium supplementation on insulin sensitivity and glucose control. *Pharmacol Res.* 2016 Sep;111:272-282. doi: 10.1016/j.phrs.2016.06.019. Epub 2016 Jun 18. PMID: 27329332.
- Wang J, Bi C, Xi H, Wei F. Effects of administering berberine alone or in combination on type 2 diabetes mellitus: a systematic review and meta-analysis. *Front Pharmacol.* 2024 Nov 21;15:1455534. doi: 10.3389/fphar.2024.1455534. PMID: 39640489; PMCID: PMC11617981.
- Wu S, Gao L, Cipriani A, et al. The effects of incretin-based therapies on β -cell function and insulin resistance in type 2 diabetes: A systematic review and network meta-analysis combining 360 trials. *Diabetes Obes Metab.* 2019;21:975–983. <https://doi.org/10.1111/dom.13613>
- Xia J, Yu J, Xu H, Zhou Y, Li H, Yin S, Xu D, Wang Y, Xia H, Liao W, Wang S, Sun G. Comparative effects of vitamin and mineral supplements in the management of type 2 diabetes in primary care: A systematic review and network meta-analysis of randomized controlled trials. *Pharmacol Res.* 2023 Feb;188:106647. doi: 10.1016/j.phrs.2023.106647. Epub 2023 Jan 10. PMID: 36638933
- Zhao T, Yang Q, Feuerbacher JF, Yu B, Brinkmann C, Cheng S, Bloch W, Schumann M. Effects of exercise, metformin and their combination on glucose metabolism in individuals with abnormal glycaemic control: a systematic review and network meta-analysis. *Br J Sports Med.* 2024 Dec 2;58(23):1452-1460. doi: 10.1136/bjsports-2024-108127. PMID: 39242178.