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Pharmacological Advances in Managing Obesity-Induced Diabetes: Beyond Metformin and Insulin

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ABSTRACT

Type 2 diabetes (T2D) in the context of obesity reflects impaired metabolic flexibility across adipose tissue, liver, muscle, and islets. While metformin and insulin remain foundational, the modern pharmacologic toolkit now targets weight, immunometabolism, organ protection, and endocrine crosstalk. Incretin-based agents (GLP-1 receptor agonists and multi-agonists) deliver substantial weight loss, improve β-cell function, and reduce cardiovascular (CV) and renal risk. Sodium–glucose cotransporter-2 (SGLT2) inhibitors lower glucose independent of insulin while preventing heart failure events and slowing chronic kidney disease. Thiazolidinediones (TZDs) and selective peroxisome proliferator-activated receptor (PPAR) modulators restore adipose expandability and insulin sensitivity, with trade-offs that invite careful selection. Adjacent therapeutics, including amylin analogs, combination anti-obesity pharmacotherapy, bile-acid and fibroblast growth factor (FGF21) pathway modulators, and early-stage immunometabolic/mitochondrial agents, offer additional levers to decompress nutrient stress, reduce inflammation, and re-partition substrate. Precision strategies align drug choice with phenotype (hepatic vs peripheral insulin resistance, NAFLD, ASCVD, HF/CKD, appetite drivers), behavior (meal timing, activity, sleep), and patient goals, often layering medications with nutrition, exercise, and, when indicated, metabolic surgery. Safety requires attention to gastrointestinal effects, genitourinary infections, volume status, bone/edema risk, hypoglycemia from legacy agents, and peri-procedural ketoacidosis with SGLT2 inhibition. This review synthesizes mechanisms and evidence for the major classes beyond metformin/insulin, highlights organ-protective effects, and proposes practical algorithms for combination therapy and deprescribing. We emphasize phenotype-guided, outcome-driven care that uses pharmacology not just to normalize glucose but to modify disease trajectories and lower long-term complication risk.

Keywords: incretin-based therapy; SGLT2 inhibitors; PPAR modulators; anti-obesity pharmacotherapy; precision medicine

INTRODUCTION

Obesity is the dominant modifiable risk factor for type 2 diabetes (T2D)[1–3]. Yet the link between excess adiposity and dysglycemia is mediated less by fat mass per se than by adipose tissue (AT) dysfunction, hypertrophy, hypoxia/fibrosis, immunometabolic activation, mitochondrial/ER stress, and by ectopic lipid deposition in liver, skeletal muscle, and pancreas[4, 5]. These changes blunt insulin's actions (antilipolysis in AT, suppression of hepatic glucose output, and stimulation of myocellular glucose uptake) while exposing β-cells to lipoglucotoxic stress that erodes first-phase insulin secretion. Historically, pharmacologic care focused on glucose numbers: metformin to curb hepatic gluconeogenesis; sulfonylureas or insulin to raise circulating insulin; and, when needed, additional agents to force glycemia toward prespecified targets[4]. While this approach prevents acute complications, it often fails to reverse disease biology, leads to weight gain or hypoglycemia with some agents, and leaves residual CV, renal, hepatic, and neurologic risk.

The last decade reshaped the therapeutic landscape. First, incretin-based therapies placed the gut–islet axis at center stage. GLP-1 receptor agonists (GLP-1 RAs) and next-generation multi-agonists exploit nutrient-sensing hormones to suppress appetite, slow gastric emptying, enhance glucose-stimulated insulin secretion, and quell glucagon when inappropriate[6–9]. Clinically, they reduce HbA1c, drive clinically meaningful weight loss, and lower major adverse CV events in high-risk populations, with signals of benefit in kidney and liver disease. Second, SGLT2 inhibitors reframed glycemic control as a renal process by inducing

glycosuria. The caloric loss is modest, but hemodynamic and cellular effects in the heart and kidney yield robust reductions in heart-failure hospitalization and CKD progression, with consistent safety when periprocedural ketoacidosis risk is managed[10]. Third, insulin sensitizers, notably TZDs via PPARγ, reminded us that redirecting lipid from ectopic sites back into subcutaneous depots can restore insulin signaling and raise adiponectin, albeit with edema/weight trade-offs that require judicious use, especially alongside heart-failure risk[10].

A broader cast of agents is now relevant to diabesity care. Anti-obesity pharmacotherapies**,** including amylin analogs, lipase inhibitors, dopamine/noradrenergic combinations, and opioid–dopamine modulators, improve weight and thereby glycemia, particularly when matched to appetite phenotype and delivered with behavioral supports[11]. Bile-acid modulators and FGF21 analogs engage enterohepatic and endocrine circuits to remodel lipid flux, thermogenesis, and inflammation. Early-phase immunometabolic therapies (IL-1 pathway, NLRP3 inflammasome, CCR2/CCR5) and mitochondrial/redox interventions (NAD+ repletion, targeted antioxidants) seek to edit upstream biology rather than chase glucose[11].

In practice, the central tasks are to (1) align drug choice with phenotype and comorbidity like ASCVD favors GLP-1 RAs; heart failure/CKD favors SGLT2 inhibition; NAFLD/NASH may benefit from GLP-1 RAs or TZDs; severe hyperphagia or weight regain may prompt combination anti-obesity therapy; (2) manage legacy agents (insulin, sulfonylureas) to minimize weight gain and hypoglycemia, deprescribing as newer agents succeed; (3) coordinate nutrition, activity, and sleep so pharmacology works with not against behavior; and (4) plan for durability and access, acknowledging cost, supply, and adherence challenges[12]. Continuous glucose monitoring (CGM) and smart titration enable safe de-intensification; periodic reassessment prevents therapeutic inertia [13].

This review proceeds as follows. Details incretin-based therapies, from classical GLP-1 RAs to dual/triple agonists, their mechanisms, outcomes, and practical use, covers SGLT2 inhibitors, focusing on glycemia minus insulin, heart–kidney protection, and risk management, revisits TZDs and evolving PPAR modulators, emphasizing adipose health and lipid partitioning, surveys anti-obesity agents and energy-balance modulators that indirectly normalize glycemia by reducing fat mass and altering appetite neurocircuitry, reviews organ-protective and network-level targets (bile acids, FGF21, immunometabolism, mitochondria), integrates these into phenotype-guided combination algorithms, deprescribing strategies, and equity-conscious implementation. We conclude with priorities for trials, biomarkers, and pragmatic care pathways that move beyond glucose normalization to disease modification.

2. Incretin-Based Therapies: GLP-1 RAs, Dual/Triple Agonists, and the Entero-Insular Axis

GLP-1 receptor agonists improve glycemia through glucose-dependent insulin secretion, suppression of inappropriate glucagon, delayed gastric emptying, and appetite reduction. Weight loss often results in double-digit percentages with higher-potency agents, decompressing ectopic lipid, lowering inflammation, and improving insulin sensitivity[14]. Cardiovascular outcome trials (CVOTs) consistently show reductions in major adverse CV events (driven by atherosclerotic risk), with additional benefits on albuminuria and progression of kidney disease[15]. Hepatic fat reduction and NASH improvements have been observed, aligning with reduced de novo lipogenesis and weight loss.

GIP co-agonism adds complementary biology: GIP receptors are expressed in adipocytes, bone, and the CNS; dual GLP-1/GIP agonists often yield greater weight loss and HbA1c reduction than GLP-1 RAs alone, possibly via enhanced satiety and improved adipocyte insulin sensitivity[16]. Triagonists incorporating glucagon receptor activity aim to increase energy expenditure and mobilize hepatic lipid, while GLP-1 tempers hyperglycemia and appetite. Early data suggest potent weight and metabolic effects with careful dose-finding to avoid hyperglycemia or hepatic enzyme perturbations [16].

Practical use includes gradual dose titration to mitigate gastrointestinal (GI) symptoms (nausea, vomiting, diarrhea), education on meal pacing and low-fat fare during uptitration, and monitoring for gallbladder disease risk. Pancreatitis signals remain rare and causal links debated; prudent avoidance after prior pancreatitis is common. Delayed gastric emptying can interact with other oral medications; spacing may be needed. Oral formulations offer an option for needle-averse patients but require fasting administration.

Combination with SGLT2 inhibitors is synergistic: additive HbA1c reduction, complementary weight and BP changes, and broader organ protection. With insulin or sulfonylureas, proactive dose reductions prevent hypoglycemia as incretin therapy succeeds[17]. For patients with binge-type eating patterns or hedonic drivers, pairing GLP-1–based therapy with psychotherapy, CGM-guided feedback, and structured meal training improves adherence and durability. Finally, access and supply must be addressed with transparent prioritization for the highest-risk phenotypes (ASCVD, severe obesity, NAFLD with fibrosis, CKD).

3. SGLT2 Inhibitors: Glycosuria, Heart–Kidney Protection, and Metabolic Integration

SGLT2 inhibitors lower plasma glucose by blocking renal tubular glucose reabsorption, producing glucosuria of ~60–90 g/day depending on GFR and glycemia. Glycemic efficacy persists despite insulin resistance and β-cell dysfunction, with modest weight loss and BP reduction from caloric and osmotic effects[18]. Beyond glycemia, cardiorenal outcomes dominate: consistent reductions in heart-failure hospitalization (across ejection fractions, including non-diabetic patients), slowed CKD progression, and favorable hemodynamics (reduced

intraglomerular pressure via tubuloglomerular feedback) explain their prioritization in guidelines for T2D with HF/CKD[18].

Metabolic effects include reduced glucotoxicity, lower hepatic glucose production, and improved insulin sensitivity over time as weight and ectopic fat decline. Ketone availability rises mildly, potentially supporting myocardial energetics; hematocrit increases reflect plasma volume shifts and erythropoietin effects. Adipose and hepatic inflammation markers often decrease.

Safety focuses on genital mycotic infections, usually mild and preventable with hygiene and early treatment; euglycemic ketoacidosis risk, heightened by insulin deficiency, prolonged fasting, very-low-carb diets, heavy alcohol, or acute illness, mandates peri-procedural holds (e.g., 3 days pre-op) and sick-day rules. Volume depletion is uncommon but consider diuretic adjustments. Bone and amputation signals have varied by agent and population; individualized assessment remains prudent. With insulin/sulfonylureas, titrate down to avoid hypoglycemia as glycemia improves. Pairing with GLP-1–based therapy offers broad CV-renal protection and robust weight/HbA1c effects; pairing with TZDs requires edema vigilance[19].

For NAFLD, SGLT2 inhibitors reduce hepatic fat and ALT modestly; greater histologic gains often require weight loss via incretin therapy or lifestyle. In CKD, efficacy persists down to reduced eGFR for cardiorenal outcomes, though glycemic effects wane—set expectations accordingly. Patient education on hydration, genital hygiene, and ketone awareness is central to safe, durable use.

4. Insulin Sensitizers and Lipid Partitioning: TZDs and Selective PPAR Modulation

Thiazolidinediones (TZDs) activate PPARγ, a master regulator of adipogenesis and lipid storage. By expanding healthy subcutaneous adipocyte number and size while reducing visceral/ectopic lipid, TZDs improve insulin sensitivity in the liver and muscle and increase adiponectin, a potent insulin-sensitizing, anti-inflammatory adipokine[20]. Glycemic effects are durable; β-cell function is preserved via reduced secretory demand and improved lipotoxic milieu. TZDs also improve histologic features of NASH in many studies, highlighting their role in hepatic disease linked to diabesity[20].

Trade-offs include fluid retention/edema (caution with heart-failure risk), weight gain (often subcutaneous; can be mitigated by pairing with SGLT2 inhibitors or incretin therapy), and bone fracture risk in susceptible individuals. Edema management involves dose titration, sodium moderation, and diuretic adjustment; avoid in decompensated HF[21]. When edema or weight gain limits use, consider selective PPAR modulators (partial agonists or non-TZD ligands) under evaluation that preserve insulin sensitization with fewer adverse effects. Dual PPARα/γ or PPARβ/δ modulators and selective PPARγ modulators (SPPARMs) aim for tissue-selective activity, though outcome data are still evolving.

Mechanistically, PPARγ activation remodels chromatin at adipogenic and insulin-sensitizing genes, countering inflammatory super-enhancers and improving mitochondrial function. In practice, TZDs fit patients with marked insulin resistance, NAFLD, and low hypoglycemia tolerance, particularly when paired with SGLT2 inhibitors (offset edema/weight) or GLP-1–based therapy (amplify weight loss and glycemic control)[21]. Regular monitoring of weight, edema, liver enzymes, and bone health (in postmenopausal women or steroid users) supports safe use. As precision pharmacology advances, PPAR modulators may serve as "adipose health" restorers within multi-drug regimens.

5. Anti-Obesity Pharmacotherapy and Energy-Balance Modulators: Indirect Glycemic Normalization

Because weight loss is a dominant driver of glycemic improvement, anti-obesity medications (AOMs) are central to diabesity care. Beyond incretin-based agents, options include amylin analogs that slow gastric emptying, suppress glucagon, and promote satiety; gastrointestinal lipase inhibitors that reduce fat absorption; and central agents that modulate dopaminergic/noradrenergic/opioid pathways to curb appetite and cravings[22]. These agents typically yield 5–10% total weight loss when combined with structured nutrition and behavior change; greater losses occur when paired with incretin-based therapies[23].

Patient selection matters. Individuals with strong hedonic eating cues or evening snacking may benefit from agents that reduce cravings; those with high-fat intake may consider lipase inhibition; those with rapid eating or large portions may respond to amylin analogs or GLP-1–based combinations[24]. Medication choice should align with comorbidities (hypertension, psychiatric conditions), potential interactions, and reproductive plans. Behavioral scaffolding, meal planning, stimulus control, high-protein breakfasts, and resistance training amplify pharmacologic satiety and preserve lean mass[24].

Monitoring focuses on BP/HR (for centrally acting agents), GI tolerance (for amylin/lipase inhibitors), fat-soluble vitamin status with chronic fat malabsorption, and adherence[25, 26]. As poly-agonist incretin agents become weight-management backbones, adjunct AOMs can be used episodically to overcome plateaus or during high-risk periods (holidays, stress). When weight loss is adequate but HbA1c remains above target, layer SGLT2 inhibition or a sensitizer; when glycemia normalizes but weight plateaus, optimize activity/sleep, consider AOM add-on, or evaluate for metabolic surgery in eligible patients[25].

6. Network-Level and Organ-Protective Targets: Bile Acids, FGF21, Immunometabolism, and Mitochondria

Bile-acid modulation influences glucose and lipid metabolism via FXR and TGR5 signaling. Bile-acid sequestrants lower LDL-C and modestly improve glycemia; FXR/TGR5-targeting agents and ileal bile-acid

transport inhibitors aim to augment GLP-1 release, thermogenesis, and hepatic lipid handling[27]. These approaches can complement incretin therapy, especially in dyslipidemic or NAFLD-predominant phenotypes, though pruritus, lipid changes, and GI effects require vigilance.

FGF21 analogs act on the liver, adipose, and CNS to improve insulin sensitivity, lower triglycerides, and promote fat oxidation; they show promise in NASH with cardiometabolic benefits, positioning them as potential add-ons for severe hepatic involvement[28]. Thyroid hormone receptor-β agonists target hepatic lipid metabolism (primarily for dyslipidemia/NASH) and may indirectly aid glycemia via liver fat reduction[28].

Immunometabolic interventions aim upstream: IL-1 pathway blockade improves β-cell function and glycemia in inflamed phenotypes; NLRP3 inhibitors, colchicine, and CCR2/CCR5 antagonists seek to reduce adipose and hepatic inflammation. Effects on HbA1c are modest and context-dependent but may be valuable adjuncts for patients with high inflammatory tone or NAFLD[29]. Lipid-signaling targets, such as ceramide synthesis inhibition, are under study to relieve lipotoxic interference with insulin signaling[29].

Mitochondrial/redox strategies include NAD+ repletion, sirtuin activation, and mitochondria-targeted antioxidants to restore organelle quality and reduce ROS-mediated insulin resistance[30]. While early-phase data are encouraging, long-term outcomes and safety remain to be established. A pragmatic stance is to prioritize agents with proven CV-renal benefits and layer investigational pathways within trials or specialized care[30].

7. Precision Pharmacotherapy: Phenotyping, Sequencing, Deprescribing, and Equity

Start with one high-value agent aligned to phenotype; reassess at 8–12 weeks using HbA1c, CGM time-in-range, weight, BP, and lipids; add a complementary class if targets are unmet. Pair GLP-1–based therapy + SGLT2 inhibition for broad protection; add TZD for insulin sensitization/NAFLD when edema risk is acceptable. Use AOMs as needed for appetite control. Coordinate with nutrition (protein-anchored meals, fiber, time-restricted eating) and resistance training to preserve lean mass.

Deprescribing: As control improves, reduce or stop sulfonylureas first; down-titrate basal/bolus insulin while monitoring with CGM to avoid hypoglycemia; continue metformin if tolerated for hepatic/weight neutrality unless contraindicated. Reassess annually for simplification.

Safety and access: Implement sick-day rules (hold SGLT2 during acute illness/surgery), GI-titration playbooks for incretins, edema/bone surveillance for TZDs, and pregnancy planning for all agents. Address cost and supply with patient-assistance pathways and stepwise algorithms that still deliver outcome-oriented care when access is limited.

Equity: Tailor regimens to local food systems, cultural preferences, and resources; embed pharmacy navigation, group education, and digital supports; measure outcomes that matter to patients energy, function, work alongside biomedical metrics.

CONCLUSION

Modern pharmacology enables disease modification in obesity-induced T2D. Agents that reduce weight, re-sensitize insulin pathways, and protect heart, kidney, and liver shift care beyond glycemic numerics to long-term risk reduction. GLP-1–based therapies and SGLT2 inhibitors anchor this approach; TZDs and selective PPAR modulators restore adipose health in selected patients; anti-obesity medications, bile-acid/FGF21 pathway drugs, and emerging immunometabolic/mitochondrial agents extend reach. The practical mandate is precision: match drugs to phenotype and comorbidity, layer therapies thoughtfully, deprescribe hypoglycemia- and weight-promoting agents, and integrate nutrition, activity, sleep, and when indicated surgery. With proactive safety protocols and equitable access, pharmacology can remodel the immunometabolic networks that drive diabesity, delivering durable glycemic control, organ protection, and better lives for people with T2D.

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