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METFORMIN'S IMPACT ON BODY WEIGHT IN TYPE 2 DIABETES: A NARRATIVE REVIEW OF MECHANISMS, CLINICAL EVIDENCE, AND COMPARATIVE EFFICACY

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ABSTRACT

Background: Metformin remains one of the most widely prescribed first-line therapies for type 2 diabetes, yet its role as a weight-modifying agent remains debated.
Aim: This review evaluates the mechanistic basis, clinical evidence, comparative efficacy, and safety profile of metformin with respect to body weight outcomes in type 2 diabetes.
Material and Methods: A narrative review was conducted using PubMed, encompassing publications from 1995 to 2026. Eligible study types included randomised controlled trials, observational studies, systematic reviews, and meta-analyses reporting weight-related or mechanistic outcomes relevant to metformin therapy.
Results: Metformin reduces body weight through AMPK-mediated inhibition of hepatic lipogenesis, appetite suppression via incretin pathways, and gut microbiota modulation. Pooled clinical evidence demonstrates a modest but consistent weight reduction of approximately 1.5 to 2.5 kg versus placebo, with durability reported over long-term follow-up. This effect is substantially inferior to GLP-1 receptor agonists and tirzepatide, which produce reductions of 10–20% in major trials. Metformin's safety profile is characterised by manageable gastrointestinal adverse effects, negligible hypoglycaemic risk, and a clinically important association with vitamin B12 depletion on long-term use.
Conclusions: Metformin should not be regarded as a primary weight loss agent but retains meaningful value as a globally accessible and well-tolerated component of metabolic management in type 2 diabetes.

KEYWORDS

Metformin, Body Weight, Weight Loss, Type 2 Diabetes, GLP-1 Receptor Agonists, SGLT-2 Inhibitors

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1. Methods

This narrative review was conducted using the PubMed database. The search encompassed publications from 1995 to 2026, covering the period from metformin's FDA approval through to the most recent available evidence. Search terms included combinations of: "metformin," "body weight," "weight loss," "obesity," "type 2 diabetes," "randomised controlled trial," "meta-analysis," "systematic review," "GLP-1 receptor agonist," "SGLT-2 inhibitor," "gut microbiota," "AMPK," and "vitamin B12."

Inclusion criteria were as follows: English-language publications involving human subjects; study designs comprising randomised controlled trials, observational studies, systematic reviews, and meta-analyses; and studies reporting weight-related outcomes or mechanistic data relevant to metformin's effects on body weight or metabolic parameters. Animal and in vitro studies were included only where cited to support the mechanistic discussion in the absence of adequate human data.

Exclusion criteria comprised non-English publications, studies not involving metformin as an active intervention or comparator, and publications for which full-text access could not be obtained.

Study selection was conducted in two stages. In the first stage, titles and abstracts were screened to exclude publications that did not meet the inclusion criteria. In the second stage, full-text assessment of eligible publications was performed to confirm relevance. Studies were ultimately included if they examined the magnitude, consistency, durability, or mechanisms of metformin's effects on body weight across any eligible study design. Given the narrative nature of this review, no formal meta-analytic pooling of effect sizes was performed. Quality and risk of bias were considered qualitatively during the review process, with methodological limitations of individual studies noted where relevant throughout the text.

2. Introduction

Metformin remains a widely used first-line pharmacological therapy for patients with type 2 diabetes ("Global Guideline for Type 2 Diabetes: recommendations for standard, comprehensive, and minimal care," 2006; Jabłonowska M, 2025; "Standards of Medical Care in Diabetes-2019 Abridged for Primary Care Providers," 2019). Even though metformin has been used widely for many years, its pharmacological characteristics and mechanisms of action continue to be refined through accumulating experimental and clinical evidence. Primarily, metformin was introduced for its glucose-lowering effects stemming mainly from suppression of hepatic glucose production, with additional contributions from intestinal and peripheral mechanisms. Now, it is understood that metformin is a multifaceted drug with metabolic actions surpassing glycemic control (Foretz et al., 2023; R. V. Sivaprakash, 2026; Zapasek D, 2024). Patients with type 2 diabetes present with a plethora of symptoms and complications, many of which include metabolic disorders and obesity. It has been observed that weight reduction and better control of metabolic factors can significantly impact the course of type 2 diabetes, and even lead to partial or full remission (Kanbour et al., 2025; Ko & Kim, 2022). In recent years, newer pharmacological agents — particularly GLP-1 receptor agonists and SGLT-2 inhibitors — have become preferred options in patients with obesity or established cardiovascular disease, given their superior weight loss and cardiorenal benefits ("8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: Standards of Care in Diabetes-2024," 2024; Committee, 2024b; Marx et al., 2023). Nevertheless, metformin retains considerable clinical value due to its favorable metabolic profile, global accessibility, long safety record, and low cost. This review aims to summarize and critically evaluate the current evidence on metformin's effects on body weight, exploring the underlying mechanisms, clinical outcomes, and its role relative to emerging pharmacological alternatives.

3. Metformin’s Characteristics and Mechanism Of Action

Metformin continues to be a subject of numerous studies focusing on its pharmacokinetics and metabolic actions that lead to lowering glucose levels. Administered orally, around 50-60% of the dose is absorbed mainly from the small intestine and is later excreted in an unchanged form in urine (Graham et al., 2011; Rena et al., 2017). Peak plasma concentrations are usually achieved within two to three hours for the intake of immediate-release formulations. The drug is widely distributed in body tissues, particularly the liver, kidneys, and gastrointestinal tract, with relevant accumulation in muscles (Gormsen et al., 2016; Rena et al., 2017).

Its primary site of action is represented by the liver, where it inhibits hepatic gluconeogenesis, thereby leading to reduced endogenous glucose production (Gormsen et al., 2016). This effect is mediated through inhibition of mitochondrial respiratory chain complex I, which results in decreased ATP production and increased intracellular AMP levels. Elevated AMP activates adenosine monophosphate-activated protein kinase (AMPK), a key regulatory enzyme involved in cellular energy homeostasis (Foretz et al., 2023; R. V. Sivaprakash, 2026). AMPK activation enhances insulin sensitivity, increases glucose uptake in peripheral tissues such as skeletal muscle, and reduces lipogenesis, the latter being of particular relevance to metformin's effects on body weight and fat mass (R. V. Sivaprakash, 2026).

The gastrointestinal tract, especially the intestines, has been identified as an important point of metformin’s metabolic activity. The drug's high intestinal concentrations and common gastrointestinal effects have been observed for many years, including alterations in intestinal motility, changes in bile salt metabolism, increased intestinal glucose turnover and modulation of the gut microbiota (Bouchoucha et al., 2011).

One of the probable mechanisms of metformin’s metabolic function is the gut-brain axis. Metformin is known to increase the secretion of glucagon-like peptide 1 (GLP-1), an incretin that suppresses hunger and promotes weight loss (R. A. DeFronzo et al., 2016; Mulherin et al., 2011; Napolitano et al., 2014). Additionally, metformin induces the production of peptide YY (PYY), an anorexic neuropeptide shown to act as a signal of post-meal fullness that decreases appetite (R. A. DeFronzo et al., 2016).

Metformin can also inhibit hunger by an additional local action on the gastrointestinal tract, namely an alteration of bile acid absorption through interaction with farnesoid X receptor (Kuhre et al., 2018; Lien et al., 2014; Napolitano et al., 2014). Bile acids stimulate secretion of the incretin hormones, glucose-dependent insulinotropic peptide (GIP), and GLP-1, which results in suppression of appetite (Kuhre et al., 2018).

The gut microbiota has been increasingly highlighted as a potential mediator of metformin's metabolic benefits. Among proposed mechanisms, metformin has been associated with a reduction in *Bacteroides fragilis* abundance, which may consequently elevate glycoursodeoxycholic acid (GUDCA) levels and contribute to improved glycemic signaling (Cherney & Lam, 2018; Sun et al., 2018). Additionally, increased abundance of *Akkermansia muciniphila* — a finding reported more consistently across independent studies — has been

linked to enhanced gut barrier function and improved metabolic parameters (de la Cuesta-Zuluaga et al., 2017; Ke et al., 2021; Shin et al., 2014). These microbiota-mediated pathways represent active areas of investigation, and the relative contribution of each mechanism to metformin's overall metabolic effect remains to be fully established.

Metformin can additionally improve peripheral insulin sensitivity, although this effect is considered secondary to its hepatic and gut-mediated actions (Hundal et al., 2000).

4. Metformin's Impact on Weight Loss

The mechanistic pathways described above — hepatic AMPK activation, reduced lipogenesis, and gut microbiota modulation — collectively suggest a biological basis for weight reduction with metformin therapy. However, the extent to which these mechanisms translate into clinically meaningful weight loss in patients with type 2 diabetes has been a subject of considerable debate.

The clinical investigation of metformin's effects on body weight emerged as a secondary observation within trials primarily designed to evaluate glycemic outcomes. Among the earliest and most influential of these was the UK Prospective Diabetes Study (UKPDS), a large multicentre randomised controlled trial enrolling 1,704 overweight patients with newly diagnosed type 2 diabetes across 15 centres in the United Kingdom, with a median follow-up of 10.7 years. UKPDS 34 demonstrated that intensive blood-glucose control with metformin was associated with less weight gain and fewer hypoglycaemic episodes than treatment with insulin or sulphonylureas, and based on these findings, it was proposed as the first-line pharmacological therapy of choice in overweight patients with type 2 diabetes ("Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group," 1998; "United Kingdom Prospective Diabetes Study (UKPDS). 13: Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years," 1995). Crucial observation was that while patients assigned to chlorpropamide, glibenclamide, and insulin gained between 3.5 and 4.8 kg over the study period, obese participants treated with metformin demonstrated no significant change in mean body weight ("United Kingdom Prospective Diabetes Study (UKPDS). 13: Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years," 1995). This weight-neutral to modestly weight-reducing profile distinguished metformin meaningfully within the pharmacological landscape of its era, and its cardiovascular and mortality benefits were found to persist in a 10-year post-trial monitoring analysis, reinforcing its clinical value in overweight patients with type 2 diabetes.

A second pivotal contribution came from the Diabetes Prevention Program (DPP), a randomised, double-blind, placebo-controlled trial enrolling 3,234 adults at high risk of developing type 2 diabetes — defined by elevated fasting glucose, impaired glucose tolerance, and a mean BMI of 34.0 kg/m². Participants were assigned to one of three arms: placebo, metformin 850 mg twice daily, or an intensive lifestyle intervention. After a mean follow-up of 2.8 years, average weight losses observed were 0.1 kg, 2.1 kg, and 5.6 kg in the placebo, metformin, and lifestyle intervention groups, respectively, with metformin reducing the incidence of type 2 diabetes by 31% relative to placebo (Yerevanian & Soukas, 2019). Although the lifestyle intervention achieved substantially greater weight reduction, the modest but statistically significant weight loss observed in the metformin group was notable given that weight loss was not a primary endpoint of the trial and that the drug was administered without structured dietary support.

Long-term follow-up of DPP participants in the Diabetes Prevention Program Outcomes Study (DPPOS) further strengthened the case for the durability of metformin's weight-related effects. Throughout the follow-up period, weight loss remained significantly greater in the metformin group than in the placebo group (2.0% vs. 0.2%, $P < 0.001$), and the magnitude of this effect was directly related to adherence to metformin therapy (Knowler et al., 2009; "Long-term safety, tolerability, and weight loss associated with metformin in the Diabetes Prevention Program Outcomes Study," 2012; Yerevanian & Soukas, 2019). This finding of durable, adherence-dependent weight loss over a decade of follow-up remains among the most robust long-term weight data available for metformin in a non-diabetic at-risk population.

The dose-dependency of metformin's weight-reducing effects has been a recurring observation across RCTs, with higher daily doses — particularly those at or exceeding 1,500–2,000 mg per day — associated with greater reductions in body weight. A prospective, multicentre, phase IV open-labelled study in 324 newly diagnosed Chinese patients with type 2 diabetes receiving extended-release metformin monotherapy demonstrated a gradual, progressive weight reduction across each assessment interval, with an average weight

loss of approximately 2 kg achieved at 16 weeks, and the magnitude of this loss was found to be independently associated with BMI at baseline (Zhou et al., 2017).

In patients with established type 2 diabetes, a meta-analysis of randomised controlled trials assessing the effect of metformin versus placebo on body weight and lipid parameters reported a pooled reduction in mean body weight of −1.66 kg (95% CI −1.88 to −1.44, $p < 0.001$) in favour of metformin, with no significant heterogeneity detected for this outcome variable across the six included studies (Gillani et al., 2021).

In non-diabetic populations at elevated risk for type 2 diabetes, a pooled analysis of 31 trials encompassing 4,570 participants followed for a total of 8,267 patient-years demonstrated that metformin was associated with a 5.3% reduction in BMI (95% CI −6.7 to −4.0), alongside improvements in fasting glucose, fasting insulin, calculated insulin resistance, and lipid parameters compared with placebo or no treatment (Salpeter et al., 2008).

5. Comparison to Other Antidiabetic Agents

To fully appreciate the clinical relevance of metformin's weight effects, it is necessary to situate them within the broader pharmacological landscape that has emerged over the past decade. The introduction and widespread adoption of SGLT-2 inhibitors and GLP-1 receptor agonists has fundamentally altered the hierarchy of weight management in type 2 diabetes, and a comparative perspective reveals both the limitations of metformin's weight-related efficacy and the distinct advantages that continue to support its clinical utility. An important methodological limitation must be stated at the outset of this section: no large randomised controlled trial has yet been designed to compare metformin monotherapy directly against a GLP-1 receptor agonist or SGLT-2 inhibitor with body weight reduction as the primary endpoint. The comparative evidence reviewed below is therefore drawn from three sources: trials in which newer agents have been evaluated as add-on therapy to metformin, where the active comparator arm is metformin alone; head-to-head trials between newer agents conducted against a shared metformin background; and network meta-analyses providing indirect cross-class estimates. Each source carries distinct methodological limitations that should be borne in mind when interpreting the magnitude of reported differences.

SGLT-2 inhibitors produce weight loss primarily through sustained urinary glucose excretion, generating a caloric deficit that is partly offset by compensatory increases in appetite and caloric intake — a counter-regulatory response that limits the weight reduction achievable with this mechanism alone. Across network meta-analyses of randomised controlled trials in patients with type 2 diabetes, weight reductions attributable to SGLT-2 inhibitor therapy compared with placebo have consistently fallen in the range of approximately 1.5 to 2 kg, with dose-dependent effects observed and clinical data extending up to four years suggesting these reductions are maintained over time (Cai et al., 2018; Pereira & Eriksson, 2019; Zaccardi et al., 2016). When compared directly with metformin in the context of add-on therapy, SGLT-2 inhibitors offer broadly comparable or marginally superior weight effects, alongside cardiorenal protective benefits that have increasingly positioned them preferentially over metformin in patients with established cardiovascular disease or chronic kidney disease, independent of their weight effects (Chang et al., 2024; Milder et al., 2019)

The most relevant available evidence for a direct weight comparison between metformin and a GLP-1 receptor agonist comes from trials and meta-analyses evaluating the incremental benefit of adding a GLP-1 receptor agonist to ongoing metformin therapy, where the control arm receives metformin alone. A 2024 systematic review and meta-analysis of ten randomised controlled trials, all using oral semaglutide in overweight or obese patients with type 2 diabetes, compared semaglutide combined with metformin against metformin monotherapy. The pooled analysis demonstrated that the semaglutide-metformin combination produced significantly greater reductions in HbA1c, fasting plasma glucose, BMI, and lipid profiles compared with metformin alone, suggesting that the addition of a GLP-1 receptor agonist substantially augments the metabolic and weight-related benefits achievable with metformin as monotherapy. Although this comparison reflects add-on rather than substitution therapy, it directly quantifies the weight gap between metformin alone and semaglutide-containing regimens in a clinically realistic setting (Li et al., 2024).

While no trial has placed metformin in a direct weight comparison against tirzepatide or high-dose semaglutide, the head-to-head evidence between these newer agents clarifies the upper boundary of pharmacological weight loss now achievable — a benchmark against which metformin's modest effect must be contextualised. The SURPASS-2 trial randomised patients with type 2 diabetes — the majority receiving metformin as background therapy — to once-weekly tirzepatide at three doses or once-weekly semaglutide 1 mg. Tirzepatide at all three doses produced greater reductions in both HbA1c and body weight than semaglutide, with the 15 mg dose achieving a mean body weight reduction of approximately 11.2 kg compared

with 5.7 kg with semaglutide at 40 weeks, representing a difference of more than 5 kg between the two active agents alone (Frías et al., 2021). Subsequently, the SURMOUNT-5 trial provided the first direct head-to-head comparison of weight-approved doses of these agents in adults with obesity but without type 2 diabetes. At 72 weeks, the mean percentage change in body weight was −20.2% with tirzepatide and −13.7% with semaglutide, equating to absolute weight losses of approximately 22.8 kg and 15.0 kg, respectively, with tirzepatide demonstrating superiority across all pre-specified weight endpoints (Aronne et al., 2025).

6. Adverse Effects of Metformin Treatment

Metformin's safety profile, established over six decades of clinical use, is one of its most clinically important attributes. In the context of weight management, tolerability is directly relevant — the drug's real-world effect on body weight depends substantially on patients' ability to maintain adequate doses over time.

6.1 Gastrointestinal Adverse Effects

Gastrointestinal disturbance is the most common safety concern with metformin and the primary driver of dose reduction or discontinuation in clinical practice. A systematic review and meta-analysis of randomised controlled trials found the incidence of individual symptoms to be: diarrhoea 12.94%, bloating 9.15%, abdominal pain 6.54%, nausea 6.45%, vomiting 3.76%, and constipation 2.27%, with the overall risk of abdominal pain approximately 50% higher in metformin-treated patients than in controls (Nabrdalik et al., 2022). Symptoms are predominantly dose-dependent, tend to emerge at treatment initiation, and diminish over time in most patients. Gradual dose titration, administration with food, and substitution with the extended-release formulation are effective mitigation strategies — meta-analytic evidence confirms that extended-release metformin is associated with significantly lower rates of diarrhoea and bloating compared with the immediate-release preparation (Nabrdalik et al., 2022; Siavash et al., 2017). Approximately 5% of patients discontinue treatment due to gastrointestinal intolerance, which carries direct implications for adherence-dependent weight outcomes (Nabrdalik et al., 2022).

6.2 Lactic Acidosis

Metformin-associated lactic acidosis (MALA) is the most serious but rarest safety concern. Metformin elevates plasma lactate in a concentration-dependent manner through hepatic mitochondrial inhibition, and accumulation in the setting of severe renal impairment or acute tissue hypoperfusion can theoretically precipitate frank acidosis. When MALA does occur, mortality approaches 50%. However, the reported incidence in clinical practice is fewer than 10 cases per 100,000 patient-years, with most cases occurring in patients with significant renal dysfunction, hepatic failure, or acute conditions such as sepsis or cardiogenic shock rather than in appropriately selected patients receiving standard doses (R. DeFronzo et al., 2016).

6.3 Vitamin B12 Deficiency

Long-term metformin use is associated with a clinically relevant reduction in vitamin B12 concentrations, primarily through interference with ileal absorption of the intrinsic factor–B12 complex. A meta-analysis of 26 studies demonstrated a mean reduction in serum B12 of approximately 57 pmol/L in metformin-treated patients compared with controls, sufficient to produce frank deficiency or borderline status in a meaningful proportion of users (Chapman et al., 2016). Long-term Diabetes Prevention Program Outcomes Study data confirmed that at 13 years of follow-up, metformin-treated participants had significantly higher rates of B12 deficiency than the placebo group, with preliminary associations observed with peripheral neuropathy (Knowler et al., 2009). Risk is amplified by higher doses, longer treatment duration, older age, and concomitant proton pump inhibitor use (Jung et al., 2025). Periodic monitoring of B12 levels is recommended by the American Diabetes Association for patients on long-term metformin, and supplementation should be considered proactively in at-risk individuals (Committee, 2024a).

6.4 Hypoglycaemia and other adverse effects

A clinically important advantage of metformin monotherapy is its negligible hypoglycaemia risk (Jabłonowska M, 2025). Because it acts through insulin-sensitising rather than insulin-secreting mechanisms, it does not lower glucose below physiological thresholds in the absence of concurrent secretagogue therapy, fasting, or caloric restriction — a meaningful benefit in elderly patients and those undertaking physical activity as part of a weight management programme (Bailey, 2024).

Metformin should be avoided in severe hepatic impairment, given the liver's central role in lactate clearance, and alcohol intake should be limited, given its potentiation of metformin's effects on lactate metabolism (Yamagishi et al., 2024).

Its primary long-term risks — gastrointestinal intolerance and B12 depletion — are both identifiable and manageable with appropriate clinical monitoring.

7. Discussion

The mechanistic case for metformin-induced weight reduction is well-grounded. Through AMPK-mediated inhibition of hepatic lipogenesis, reduction in endogenous glucose production, appetite-modulating effects on hypothalamic signalling pathways, and modulation of the gut microbiota — including effects on short-chain fatty acid-producing bacteria and proposed interactions with microbial metabolites such as glycoursodeoxycholic acid — metformin engages multiple complementary pathways that are highly probable drivers of reduced body weight (Foretz et al., 2023; R. V. Sivaprakash, 2026). However, as documented throughout this review, the translation of these mechanisms into clinically measurable weight outcomes is modest in absolute terms, and the relative contribution of each mechanistic pathway to the drug's overall weight effect in humans remains incompletely characterised.

Clinically, the evidence from landmark trials including UKPDS 34 and the DPP/DPPOS cohort, supplemented by meta-analytic data across multiple populations, converges on a consistent finding: metformin produces a statistically significant but clinically modest reduction in body weight of approximately 1.5 to 2.5 kg (Knowler et al., 2009; "Long-term safety, tolerability, and weight loss associated with metformin in the Diabetes Prevention Program Outcomes Study," 2012; "United Kingdom Prospective Diabetes Study (UKPDS). 13: Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years," 1995). This weight effect, while substantially inferior to that achievable with GLP-1 receptor agonists or tirzepatide, is still vitally meaningful in the context of metformin's cost, accessibility and safety record.

The safety and tolerability profile is one of the most important aspects of metformin's clinical value. Its negligible hypoglycaemic risk, absence of the cardiorenal adverse effects associated with newer agents, manageable gastrointestinal side effects with appropriate formulation strategies, and well-characterised long-term safety over six decades of use collectively constitute an important counterweight to its modest efficacy in reduction of body mass (Bailey, 2024; Yamagishi et al., 2024). The vitamin B12 depletion risk associated with long-term use requires proactive clinical monitoring as outlined in current ADA guidance and should be factored into the risk-benefit assessment for patients maintained on metformin over extended periods of time (Committee, 2024a; Jung et al., 2025).

The evidence reviewed does not support positioning metformin as a primary pharmacological weight loss agent in patients for whom weight reduction is the central therapeutic objective. In such patients, particularly those with obesity and established cardiovascular disease or high cardiovascular risk, GLP-1 receptor agonists and SGLT-2 inhibitors offer substantially superior weight outcomes alongside proven cardiorenal benefits, and current ADA and ESC guidelines appropriately reflect this prioritisation ("8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: Standards of Care in Diabetes-2024," 2024; Marx et al., 2023). However, dismissing metformin's role in weight management based on this comparison alone would be clinically inadequate. In the substantial proportion of the world's diabetic population for whom newer agents are economically inaccessible or unavailable, metformin remains the most widely prescribed glucose-lowering drug, and its modest but durable weight effect contributes meaningfully to overall metabolic risk reduction (Kanbour et al., 2025). Furthermore, emerging evidence suggests that metformin may offer additive metabolic benefits when combined with GLP-1 receptor agonists —a hypothesis supported by the drug's complementary mechanisms of action — though adequately powered trials specifically examining this combination's impact on weight remain limited.

8. Conclusions

Metformin is not, and should not be positioned as, a weight loss drug in the era of tirzepatide and high-dose semaglutide. Its effects on body weight are real, replicable, and durable, but modest, and they cannot compare to the magnitude of weight reduction now achievable with incretin-based pharmacotherapy. What metformin offers instead is a decades-proven, globally accessible, mechanistically multifaceted agent whose weight-attenuating properties are one component of a broader cardiometabolic profile that continues to justify its central role in diabetes management worldwide. The question for the next decade of research is not whether metformin should be replaced, but how its unique properties, particularly its gut and microbiota-mediated mechanisms and its combination potential, can be used most effectively within a rapidly evolving therapeutic landscape that is now present in type 2 diabetes treatment. Answering that question will require the weight-focused, long-term, head-to-head trial evidence that is not yet available.

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