ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF ARTIFICIAL INTELLIGENCE

ISSN: 2692-5206, Impact Factor: 12,23

**American Academic publishers, volume 05, issue 11,2025**

Journal: https://www.academicpublishers.org/journals/index.php/ijai

# METFORMIN AND WEIGHT REDUCTION: A NARRATIVE REVIEW OF CONTEMPORARY EVIDENCE (2024–2025)

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**Abstract: Background:**
Metformin, the cornerstone therapy for type 2 diabetes mellitus (T2DM), has demonstrated consistent weight-modulating properties beyond its glucose-lowering effects. Recent research (2024–2025) has expanded understanding of its metabolic and hormonal mechanisms influencing adiposity and insulin resistance.

**Objective:**
This review synthesizes recent randomized controlled trials (RCTs) and meta-analyses examining the efficacy, mechanisms, and safety of metformin in weight reduction among diabetic, prediabetic, and non-diabetic populations.

**Methods:**
A narrative synthesis was performed using systematic literature searches across PubMed, Scopus, ScienceDirect, and SpringerLink from January 2024 to November 2025. Studies were included if they were peer-reviewed RCTs or quasi-experimental trials evaluating metformin monotherapy or combination therapy for ≥12 weeks, with quantitative outcomes on body weight, BMI, or metabolic parameters. Fifteen studies, encompassing more than 2,000 participants, met inclusion criteria.

**Results:**
Metformin monotherapy achieved an average weight reduction of 3–5% (≈3.4 kg), while combination therapy with GLP-1 or SGLT2 inhibitors yielded superior outcomes (≈5–7 kg). Mechanistically, metformin activates AMPK, modulates gut microbiota—particularly Akkermansia muciniphila—and influences hypothalamic GLP-1 signaling to enhance satiety and lipid metabolism. The therapy was well tolerated, with gastrointestinal symptoms as the most frequent mild adverse event.

**Conclusion:**
Metformin remains a safe, cost-effective, and multi-mechanistic pharmacologic option for managing obesity and metabolic disorders. Its synergistic efficacy in combination regimens underscores its evolving role in modern metabolic and precision medicine.

**Keywords:** Metformin; Weight loss; Obesity; Type 2 diabetes mellitus; PCOS; GLP-1 receptor agonist; SGLT2 inhibitor; AMPK; Gut microbiota; Metabolic regulation.

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## Introduction

Obesity has emerged as one of the most critical global health challenges of the 21st century, with the World Health Organization (WHO) estimating that over 1 billion adults are currently obese, a figure projected to rise by more than 40% by 2035 (1). Excess adiposity is strongly associated with insulin resistance, dyslipidemia, and chronic inflammation, leading to the development of type 2 diabetes mellitus (T2DM), cardiovascular disease, and certain cancers (2). Consequently, weight management remains a central therapeutic objective in metabolic and endocrine medicine.

Metformin, a biguanide derivative derived from Galega officinalis, has served as the first-line pharmacologic therapy for T2DM for more than six decades. Its principal mechanism involves the activation of AMP-activated protein kinase (AMPK), resulting in inhibition of hepatic gluconeogenesis, increased peripheral glucose uptake, and enhanced fatty acid oxidation (3,4). In addition to its well-established glycemic effects, accumulating evidence has revealed metformin's potential to promote modest but sustained weight loss in both diabetic and non-diabetic populations (5–7).

Unlike other antidiabetic agents such as sulfonylureas and insulin, which often contribute to weight gain, metformin has consistently demonstrated neutral or negative weight effects across numerous trials (8). This unique metabolic profile has stimulated growing interest in its off-label application for obesity management, particularly in individuals with insulin resistance, prediabetes, and polycystic ovary syndrome (PCOS).

Recent research between 2024 and 2025 has significantly expanded understanding of metformin's multisystem mechanisms contributing to weight modulation. Emerging data from randomized controlled trials and meta-analyses suggest that metformin may exert its effects via both peripheral metabolic and central neuroendocrine pathways. Mechanistic studies have demonstrated its role in gut microbiota regulation, particularly the proliferation of Akkermansia muciniphila, which enhances mucosal integrity and modulates inflammatory responses (9). Moreover, metformin appears to influence hypothalamic appetite signaling through modulation of GLP-1 secretion and gut–brain axis pathways (10).

The clinical translation of these findings is reflected in recent intervention studies. For instance, Sharif et al. (2025) reported significant weight reduction and hormonal improvement in women with PCOS treated with metformin compared to placebo (11). Similarly, Hassan et al. (2025) demonstrated that combining lifestyle modification with metformin led to a 4.7% mean reduction in body weight among prediabetic adults in a Caribbean cohort (12). In diabetic populations, metformin's combination with SGLT2 inhibitors or GLP-1 receptor agonists—such as canagliflozin and semaglutide—yielded synergistic weight and glycemic benefits, as shown in the CANNA Trial (Jun et al., 2025) and the DREAMS-3 Study (Luo et al., 2025) (13,14).

These recent findings collectively underscore metformin's pleiotropic metabolic effects that extend beyond glucose control, including improvements in lipid metabolism, body composition, and inflammatory markers. Importantly, its cost-effectiveness, safety, and tolerability further justify its consideration as a cornerstone agent in integrated weight management protocols.

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Therefore, this review aims to synthesize and critically evaluate the most recent (2024–2025) evidence on metformin's efficacy for weight reduction, its underlying biological mechanisms, and clinical applicability across diverse metabolic conditions. Through a narrative analysis of contemporary randomized trials and systematic reviews, this paper seeks to contextualize metformin's evolving role as both a therapeutic and preventive tool in modern obesity and metabolic care.

## Methods

This narrative review was conducted using systematic principles of data synthesis. A comprehensive literature search was performed in PubMed, Scopus, ScienceDirect, and SpringerLink databases covering publications from January 2024 to November 2025. The search terms included "metformin," "weight loss," "randomized controlled trial," "obesity," "PCOS," and "glycemic control." Eligible studies were peer-reviewed randomized controlled or quasi-experimental trials that investigated metformin as monotherapy or in combination with other agents for a minimum duration of 12 weeks, and that reported quantitative outcomes such as body weight, body mass index (BMI), or metabolic parameters. After screening and eligibility assessment, fifteen studies meeting the inclusion criteria were identified, encompassing a combined sample of over 2,000 participants representing diverse demographic and clinical populations.

## Results and Synthesis

### Weight Loss and Metabolic Outcomes

Recent randomized studies have confirmed the reproducibility of metformin's modest but meaningful weight-lowering effect. In a double-blind RCT involving 120 women with polycystic ovary syndrome (PCOS), a 4.8 kg mean reduction in body weight was observed after 16 weeks of metformin 500 mg twice daily, accompanied by significant improvements in insulin sensitivity and free androgen index [15]. Similarly, combination therapy studies have shown that adding semaglutide (1 mg weekly) to metformin enhances mean weight loss from 3.9 kg to 7.1 kg, highlighting the synergistic benefits of GLP-1 receptor agonism [16].

Among diabetic populations, adults receiving canagliflozin with metformin lost 4.1 kg compared to 1.8 kg in the placebo–metformin group after 24 weeks, with additional reductions in HbA1c and waist circumference, reinforcing metformin's adjunctive potential [17]. In non-diabetic obese adults, a community-based intervention demonstrated a 4.7% mean body weight reduction following 12 months of metformin escalation combined with lifestyle modification [18].

A meta-analysis synthesizing these outcomes quantified metformin's pooled weight effect at approximately –3.5 kg (95% CI: –2.1 to –4.8) across heterogeneous populations, confirming its statistically significant though modest anti-obesity action [19].

### Mechanistic Insights

Translational research has refined the biological understanding of metformin's weight-regulating mechanisms. The AMP-activated protein kinase (AMPK) pathway remains the central driver, leading to reduced hepatic gluconeogenesis, enhanced fatty acid oxidation, and inhibition of lipogenesis [16]. Additionally, metformin modulates gut microbiota composition,

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particularly increasing Akkermansia muciniphila and Bifidobacterium species associated with improved insulin sensitivity and reduced adiposity [20].

Emerging evidence also implicates central neuroendocrine regulation, suggesting metformin's interactions with hypothalamic GLP-1 signaling pathways may suppress appetite and enhance satiety [21]. Together, these metabolic and neurohormonal pathways contribute to its sustained weight and fat mass reduction

**Subgroup Responses**

Subgroup analyses demonstrate differential efficacy across populations.
In PCOS, metformin reduced body weight by 4–6% and improved menstrual regularity [15,22]. In type 2 diabetes, combination therapy with SGLT2 inhibitors such as canagliflozin or dapagliflozin yielded 4–5 kg mean reductions over 6 months [17,19]. Among non-diabetic obese adults, lifestyle interventions enhanced metformin's effect, as seen in the LIME trial [18].

Furthermore, in adolescents receiving antipsychotics, metformin 850 mg twice daily significantly mitigated medication-induced weight gain, reinforcing its neuroendocrine regulatory role [23].

**Discussion**

The collective findings from 2024–2025 reinforce metformin's position as a weight-modulating agent with a favorable safety profile. Although the degree of weight loss is less dramatic than with GLP-1 analogues, its accessibility, cost-effectiveness, and metabolic versatility render it a cornerstone for obesity-related metabolic management.

Mechanistically, metformin's pleiotropic effects — including AMPK activation, gut microbiota modulation, and appetite regulation — distinguish it from other oral antihyperglycemics. The growing body of combination therapy research indicates a synergistic metabolic advantage when paired with GLP-1 or SGLT2 agents, resulting in enhanced adiposity reduction and cardiometabolic protection [16–18,24].

Personalized medicine represents a critical next step in optimizing metformin's efficacy. Genetic polymorphisms (e.g., SLC22A1 variants) influence drug transport and response variability, while microbiome composition and diet modulate metabolic outcomes [24]. Future large-scale, multiethnic RCTs should integrate genomic and metabolomic profiling to tailor metformin-based regimens.

Safety and Tolerability

Across all reviewed studies, metformin demonstrated excellent safety and tolerability. The most frequent adverse events were mild gastrointestinal disturbances—nausea, diarrhea, and abdominal discomfort—reported in approximately 10–15% of participants [15–19,23]. No serious hypoglycemia or lactic acidosis occurred. Average adherence rates exceeded 80%, confirming its suitability for long-term clinical use.

**Conclusion**

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Metformin remains a foundational therapy for metabolic disorders and demonstrates consistent, modest efficacy in reducing body weight. Between 2024 and 2025, emerging evidence consolidated its status as a safe, affordable, and multi-mechanistic agent for obesity management, particularly in individuals with insulin resistance or PCOS.

The drug's future role will likely expand through combination therapies and precision-medicine approaches, leveraging its AMPK, mitochondrial, and microbiome-mediated mechanisms to optimize patient outcomes in metabolic care.

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