OPEN ACCESS

Saudi Journal of Medical and Pharmaceutical Sciences
Abbreviated Key Title: Saudi J Med Pharm Sci
ISSN 2413-4929 (Print) | ISSN 2413-4910 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Review Article **Medicine**

The Outcomes of Metformin Usage in Prediabetic Patients: A Systematic Review

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DOI: https://doi.org/10.36348/sjmps.2025.v11i12.003 | **Received:** 16.10.2025 | **Accepted:** 28.11.2025 | **Published:** 05.12.2025

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Abstract

Objectives: To analyze the existing literature on the outcomes of metformin usage among prediabetic patients. ***Methods:*** A thorough search across four databases identified 914 relevant publications. After removing duplicates using Rayyan QCRI and screening for relevance, 77 full-text articles were reviewed, with 6 studies ultimately meeting the criteria for inclusion. ***Results:*** We included six studies with a total of 295 pre-diabetic patients and 197 (66.8%) were females. Across the included studies, metformin demonstrated consistent benefits in improving insulin sensitivity and lowering fasting glucose and HbA1c levels, particularly when combined with lifestyle interventions such as exercise. Several studies showed delayed or reduced progression to type 2 diabetes (T2D). Metformin was especially effective in individuals with higher baseline fasting plasma glucose or insulin resistance. Adverse effects were minimal and infrequently reported. However, metformin alone was not universally effective in preventing diabetes, emphasizing the importance of combined interventions. ***Conclusion:*** Metformin is a safe and effective adjunct therapy for delaying or preventing T2D in individuals with prediabetes, particularly when used alongside lifestyle changes. Early initiation may offer greater benefits in preserving insulin function and reducing β-cell stress. Future research should explore long-term outcomes and optimal patient selection criteria.

Keywords: Prediabetes, Metformin, Type 2 Diabetes Prevention, Insulin Sensitivity, Lifestyle Intervention, Systematic review.

INTRODUCTION

Prediabetes is an early stage that precedes the onset of diabetes mellitus (DM). While adults with prediabetes typically do not exhibit noticeable symptoms, their blood sugar levels are higher than the normal range of 70 mg/dL to 99 mg/dL. In prediabetic individuals, blood glucose levels usually range from 110 mg/dL to 125 mg/dL. This activity explores the underlying causes and mechanisms of prediabetes and highlights the critical role of a collaborative interprofessional team in its management [1, 2].

The Centers for Disease Control and Prevention reports that approximately 84 million adults in the United States have prediabetes roughly one in three. Alarmingly, around 90% of them are unaware of their condition and the potential risks it brings. Globally, the prevalence of diabetes is increasing at a rapid pace [3].

The primary approach to managing prediabetes involves lifestyle modifications, with a strong emphasis on significant weight loss. The main goal is to achieve a 7% reduction in body weight through a low-fat diet combined with about 30 minutes of daily physical activity [4, 5].

Around 70% of individuals with prediabetes may eventually develop DM, but this progression is not guaranteed. With proper management, the onset of diabetes and the associated risk of cardiovascular disease can be prevented. Some patients, particularly those who are unable to maintain lifestyle changes or are at high risk for developing T2D, may require medication. Metformin and acarbose are the most commonly prescribed drugs for prediabetes; both are well-tolerated, have few side effects, and are effective in reducing the risk of developing diabetes [1].

While lifestyle modification remains the cornerstone of prediabetes management, pharmacological interventions such as metformin have shown potential in delaying or preventing the onset of diabetes. Metformin, widely used for T2D, is increasingly being prescribed for individuals with prediabetes, particularly those at high risk or who fail to achieve adequate results through lifestyle changes alone. Despite its widespread use, the outcomes of metformin treatment in prediabetic populations vary across studies. A systematic review is necessary to consolidate current evidence, evaluate its effectiveness, and guide clinical decision-making.

This systematic review aims to analyze the existing literature on the outcomes of metformin usage among prediabetic patients, focusing on its effectiveness in delaying or preventing progression to T2D, impact on metabolic parameters, and potential side effects or risks associated with its use.

METHODS

The PRISMA and GATHER criteria were met by the systematic review.

Selection Criteria

Inclusion Criteria:

1. Studies involving human subjects diagnosed with prediabetes based on recognized diagnostic criteria.
2. Studies evaluating the use of metformin as a primary intervention for prediabetes.
3. Studies with or without a comparison group (e.g., lifestyle modification, placebo, or no intervention).
4. Studies reporting on at least one of the following outcomes:
    - Progression to T2D
    - Changes in blood glucose levels (e.g., fasting glucose, HbA1c)
    - Weight or BMI changes
    - Insulin sensitivity or resistance
    - Adverse effects or safety profile of metformin
5. Randomized controlled trials (RCTs), cohort studies, case-control studies, and observational studies were included.
6. Articles published in English.

Exclusion Criteria:

1. Studies involving patients already diagnosed with T2D, animal or in vitro studies, and pediatric populations (under 18 years old were excluded.
2. Studies not involving metformin as a treatment.
3. Editorials, commentaries, opinion pieces, conference abstracts without full text, case reports or case series with <10 participants, and uplicate publications.

Search strategy

A thorough search was undertaken to locate relevant studies on the outcomes of metformin usage among prediabetic patients. The reviewers looked at four electronic databases: PubMed, Cochrane, Web of Science, and SCOPUS. We uploaded all of the titles and abstracts identified through electronic searches into Rayyan, removing any duplicates. Studies published between 2010 and 2025 were included. All texts from papers that met the inclusion criteria based on title or abstract were collected and thoroughly inspected. Two reviewers independently evaluated the appropriateness of the extracted publications and resolved any contradictions through discussion.

Data extraction

Two unbiased reviewers retrieved data from studies that met the inclusion criteria in a consistent and established format. The following information was retrieved and recorded: (i) First author (ii) Year of publication, (iii) Study design, (iv) Country, (v) Sample size, (vi) Gender, (vii) Age (viii) metformin dosage, (ix) follow-up duration, (x) Main outcomes (effectiveness and safety).

Risk of Bias Assessment

We applied the ROBINS-I tool to assess the risk of bias, as it provides a comprehensive evaluation of confounding an important factor given the frequent presence of bias from unmeasured variables in this area of research. ROBINS-I is specifically designed for non-randomized studies and is well-suited for cohort designs where participants are followed over time based on their exposure to different staffing levels. Two independent reviewers evaluated each study's risk of bias, with any disagreements resolved through group discussion [6].

For randomized controlled trials (RCTs), we used the Cochrane Risk of Bias Tool [7], which examines seven key areas: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias. Each domain was rated as having a low, unclear, or high risk of bias.

RESULTS

The specified search strategy yielded 914 publications (Figure 1). After removing duplicates (n = 444), 470 trials were evaluated based on title and abstract. Of these, 391 failed to satisfy eligibility criteria, leaving just 79 full-text articles for comprehensive review. A total of 6 satisfied the requirements for eligibility with evidence synthesis for analysis.

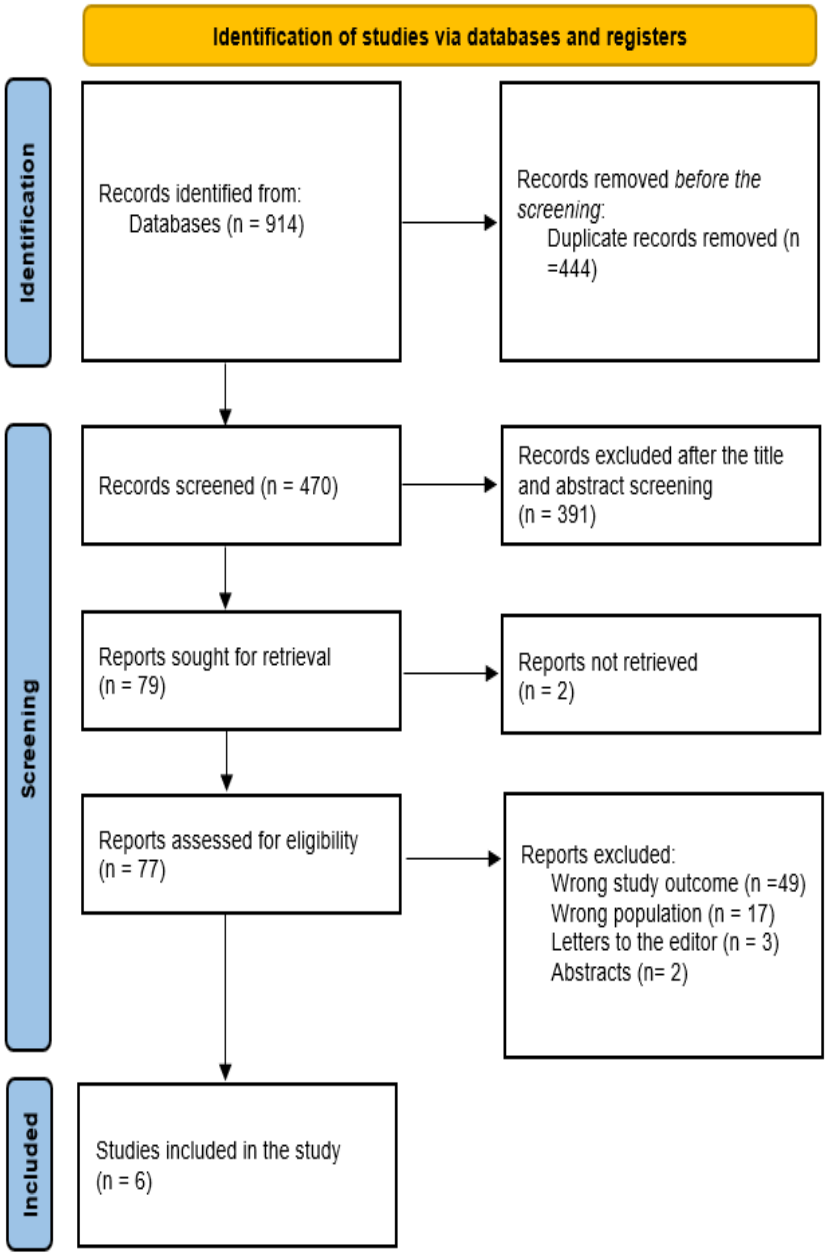

Figure 1: PRISMA flowchart [8]

Sociodemographic and Clinical Outcomes

We included six studies with a total of 295 pre-diabetic patients and 197 (66.8%) were females. Regarding study designs, three were RCTs [12-14], two were case-controls [9, 10], and one was a prospective observational study [11]. The earliest study was conducted in 2012 [10] and the latest in 2024 [14].

Metformin, either alone or in combination with exercise, has been shown to significantly enhance insulin sensitivity and help regulate blood glucose levels. Short-term interventions of around 3 months demonstrated notable improvements in insulin resistance, especially when paired with physical activity [10,13,14]. Additionally, metformin was effective in reducing fasting plasma glucose (FPG), highlighting its potential role in stabilizing glycemic markers in the early stages of metabolic dysfunction [13]. In HIV-positive individuals with prediabetes, metformin contributed to the amelioration of HbA1c and insulin resistance, potentially preventing progression to DM [12].

Another key benefit is its ability to restore glucose tolerance when combined with lifestyle modifications. Participants receiving metformin with moderate exercise interventions achieved better glycemic control than those receiving placebo alone, suggesting a synergistic effect between pharmacologic and behavioral strategies [14]. Furthermore, its usage was associated with a potential normalization of glycemic status among individuals with impaired fasting

glucose (IFG) and impaired glucose tolerance (IGT), though the effect varied by population [11].

On the other hand, the risks and limitations of metformin therapy were also identified. In some studies, metformin alone did not prevent the progression to diabetes in all individuals with prediabetes, especially in the absence of lifestyle modification [11].

Table 1: Outcome measures of the included studies

Study ID	Country	Study design	Sociodemographic	CO rate (%)	Follow-up (months)	Safety and effectiveness
Moreno-Cabañas et al., 2023 [9]	UK	Case-control	Participants: 4 Mean age: 57 Females: 2 (50%)	1,063 ± 425 mg/ day	3	In those with pre-diabetes, metformin and exercise increase insulin sensitivity during an OGTT. The gut-liver impact, which is partially mitigated after exercise, appears to be the mechanism by which metformin lowers blood glucose levels.
Malin et al., 2012 [10]	USA	Case-control	Participants: 8 Mean age: 45 Females: 4 (50%)	The dose increased by 500 mg/day each week to reach 2,000 mg/day by week 4, then stayed at 2,000 mg/day for the remaining 8 weeks.	3	Insulin sensitivity was much higher following 12 weeks of exercise activity and/or metformin in participants with prediabetes.
Khodabandeh et al., 2020 [11]	Iran	Prospective observational study	Participants: 219 Mean age: 43.7 Females: 163 (74.4%)	The dose increased by 500 mg/day each week to reach 2,000 mg/day by week 4, then stayed at 2,000 mg/day for the remaining 8 weeks.	64.32	Patients with IFG and IGT who had not taken metformin were more likely to remain in prediabetes rather than return to normal. In those with prediabetes, metformin did not prevent diabetes.
Nimitphong et al., 2022 [12]	Thailand	RCT	Participants: 37 Mean age: 50.7 Females: 11 (29.7%)	1000 mg/day	12	In HIV-positive individuals with prediabetes, metformin tends to ameliorate HbA1c and insulin resistance and may stop the progression from prediabetes to DM.
Martínez-Abundis et al., 2018 [13]	USA	RCT	Participants: 10 Mean age: 48.3 Females: 5 (50%)	500 mg/day	3	When compared to placebo, pre-diabetic patients receiving three months of metformin treatment demonstrated a substantial drop in FPG.
Umar et al., 2024 [14]	Nigeria	RCT	Participants: 17 Age range: 20-60 Females: 12 (70.5%)	500 mg/day	4	Interventions using metformin and moderate exercise are much more effective than placebo at enhancing glucose tolerance in Nigerians with prediabetes.

Table 2: Risk of bias assessment using ROBINS-I

Study ID	Bias due to confounding	Bias in the selection of participants into	Bias in the classification of interventions	Bias due to deviations from the intended interval	Bias due to missing data	Bias in the measurement of outcomes	Bias in the selection of reported result	Overall bias
Moreno-Cabañas et al., 2023 [9]	Mod	Low	Low	Low	Low	Mod	Low	Low
Malin et al., 2012 [10]	Low	Low	Mod	Low	Low	Low	Mod	Low
Khodabandeh et al., 2020 [11]	Mod	Mod	Mod	Low	Mod	Mod	Low	Moderate

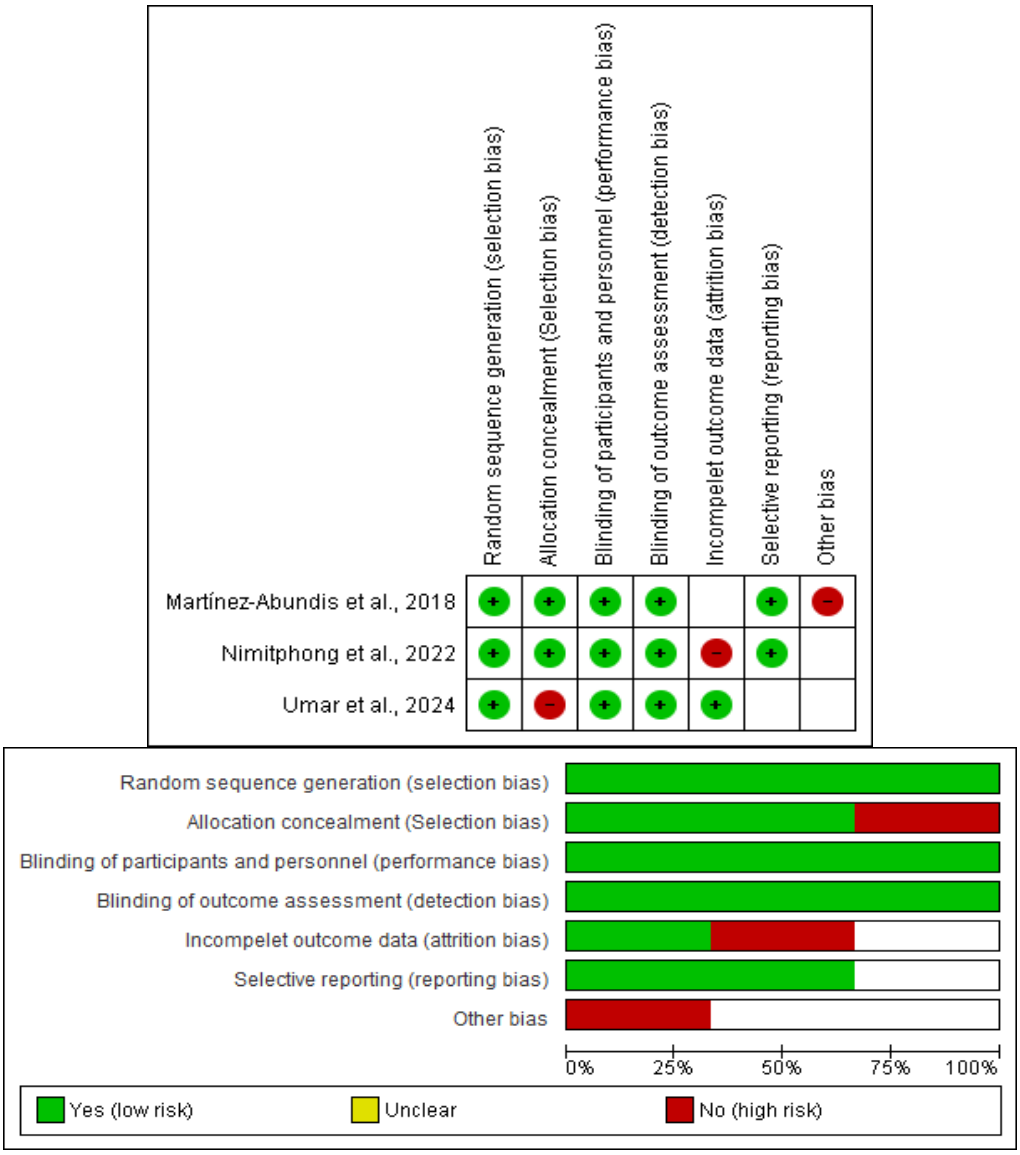

Figure 2: Risk of bias assessment

DISCUSSION

The findings from this systematic review demonstrate that metformin, widely known for its role in managing T2D, also offers notable benefits for individuals with prediabetes. Across multiple studies, metformin usage especially when combined with exercise led to significant improvements in insulin sensitivity, fasting glucose levels, and HbA1c. These metabolic enhancements suggest that metformin can be

a valuable tool in delaying or preventing the progression from prediabetes to DM.

However, the degree of effectiveness varied across studies and populations. While some cohorts showed meaningful improvement or reversal of prediabetic status, others experienced limited preventive benefit. This variation may stem from differences in sample size, adherence to lifestyle recommendations, dosing regimens, or genetic and sociodemographic factors. Notably, metformin alone did not consistently prevent diabetes in all participants, reinforcing the importance of holistic interventions that include physical activity and dietary changes.

Similarly, Warrilow *et al.*, reported that with the exception of one subgroup, metformin consistently maintained insulin sensitivity, which may serve as a more precise predictor of diabetes progression than other markers. In contrast, insulin sensitivity declined across all placebo groups. Notably, participants who began with higher fasting plasma glucose or baseline insulin sensitivity tended to experience the greatest improvements, suggesting that metformin may be most effective when introduced in the early stages of dysglycemia or potentially even prior. Its enhanced efficacy among individuals with marked impaired fasting glucose is consistent with its pharmacologic action [15].

Findings from other studies, including those analyzing Diabetes Prevention Program (DPP) data, indicate that both elevated baseline insulin function and favorable treatment response are linked to reduced rates of diabetes onset. Additionally, metformin's therapeutic effects appear to be additive over time. These insights point to the potential advantage of initiating metformin earlier in the prediabetic trajectory, especially when preserving insulin sensitivity is a clinical priority [15].

Since fasting proinsulin serves as a sensitive marker of β-cell fatigue or dysfunction [16], these findings imply that β-cell depletion may be underway in these specific cohorts. Normally, β-cell mass is carefully regulated through a dynamic equilibrium between β-cell neogenesis and programmed cell death (apoptosis) [17]. However, both obese and non-obese individuals with T2D exhibit a diminished β-cell population relative to their non-diabetic peers matched for age and body weight [18].

The onset and progression of T2D stem largely from the inability of β-cells to adequately compensate for rising insulin resistance, leading to a progressive erosion of β-cell functionality. Persistent hyperglycemia, or glucotoxicity, accelerates β-cell apoptosis [19], while the generation of new β-cells remains relatively static. Over time, this imbalance where cell loss exceeds regeneration results in a net decline in β-cell mass. Theoretically, preventing this several-fold rise in apoptotic activity might create a window for the recovery of β-cell reserves [20].

Also, Hostalek *et al.* reported a significant number of individuals with prediabetes may gain considerable advantage from a combined approach involving both lifestyle modifications and medication to reduce the risk or postpone the development of T2D. Existing research supports the use of metformin as part of a preventive strategy, particularly when paired with guidance aimed at promoting healthier habits and behaviors [21].

From a clinical perspective, metformin presents a low-cost, well-tolerated pharmacologic option for individuals with prediabetes particularly those at high risk of progressing to diabetes or those unable to achieve results through lifestyle changes alone. Its use may be most appropriate in patients with elevated fasting glucose or HbA1c, overweight or obesity, or a strong family history of diabetes.

Healthcare providers should consider incorporating metformin into early intervention plans, but not as a replacement for lifestyle changes. Instead, it should be framed as an adjunct to structured exercise and dietary programs. Furthermore, identifying subpopulations (e.g., HIV-positive patients, as noted in one study) that may benefit uniquely from metformin can help tailor more personalized and effective management strategies.

Strengths

This review included a variety of study designs, including randomized controlled trials and observational studies, offering a broad perspective on real-world effectiveness. The studies spanned diverse populations and geographical regions, enhancing generalizability. A consistent pattern of metabolic improvement supports the reliability of the findings, particularly when lifestyle changes accompanied pharmacologic treatment.

Limitations

Several studies had small sample sizes, which may reduce the statistical power and generalizability of their findings. The duration of follow-up was relatively short in most studies (e.g., 3–4 months), limiting insights into long-term effectiveness and sustainability of metformin's benefits. Limited reporting on adverse effects prevents a complete safety profile analysis. Some studies lacked control groups or randomization, increasing the risk of bias and reducing the level of evidence.

CONCLUSION

Metformin appears to be an effective adjunctive therapy for improving glycemic control and insulin sensitivity in prediabetic patients, particularly when combined with exercise. While it holds promise in delaying the onset of T2D, it should not be considered a

standalone solution. Lifestyle modification remains central to management, and metformin should be viewed as a complementary tool for high-risk individuals or those struggling to implement behavioral changes. Further large-scale, long-term studies are needed to clarify its preventive role and establish clearer clinical guidelines.

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