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Evidence-based pharmacological investigation of the clinical practice and rational use of metformin in prediabetes mellitus

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ABSTRACT

Prediabetes is a condition where blood glucose levels have deviated from the normal range but have not yet reached the diagnostic criteria for diabetes. It represents a transitional phase between health and diabetes. Currently, there are no global guidelines for managing prediabetes. However, the use of metformin in prediabetes is largely based on clinical experience, and there is a lack of high-quality evidence-based medicine. There are uncertainties regarding its dosage and unknown adverse reactions, and its exact efficacy and safety still require further study. This article systematically reviews the current state of metformin in the treatment of prediabetic, analyzing differences in efficacy across different dosages, the guideline recommendations, clinical application experiences, potential adverse effects and irrational drug use. We aim to provide scientific basis and clinical practice guidance for the rational use of metformin in the management of prediabetes.

Introduction

Evidence-based pharmacy (EBP) is an extension of evidence-based medicine into the field of pharmacy. Clinical pharmacists collect and appraise scientific evidence (such as literature) to assess the role of medications within clinical treatment regimens and make decisions regarding pharmacotherapy.[1] As a scientific practice approach, evidence-based pharmacy emphasizes the integration of the best available evidence, clinical practice experiences, and patients' values and preferences in pharmacological decision-making. Prediabetes refers to a state in which blood glucose levels are elevated above the normal range but have not yet reached the diagnostic threshold for diabetes. It represents an intermediate stage between normal glycemic levels and diabetes and is considered a high-risk condition for developing diabetes. It is also a critical period during which the progression to diabetes may still be reversed. According to the International Classification of Diseases (ICD), prediabetes encompasses impaired fasting glucose (IFG, ICD-11: 5A40.0), impaired glucose tolerance (IGT, ICD-11: 5A40.1), and a combination of both conditions (IFG + IGT).[2] According to the latest data from the International Diabetes Federation (IDF),[3] the global number of individuals with IGT has reached 541 million, with a prevalence of 10.6 %, while 319 million people have IFG, with a prevalence of 6.2 %. Research shows that the prevalence of prediabetes in China has reached 38.1 %, indicating that nearly 40% of adults are at high risk for developing diabetes.[4] Against the backdrop of rising global incidence of both prediabetes and diabetes, it is particularly important to develop effective strategies for the prevention and treatment of prediabetes based on the principles of evidence-based pharmacy.

Metformin, as one of the priority medications for treating type 2 diabetes mellitus (T2DM), has been widely used in clinical

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interventions for prediabetes due to its stable glucose-lowering effect and relatively low risk of hypoglycemia. As early as 20 years ago, the Diabetes Prevention Program (DPP) in the United States demonstrated that metformin can reduce the risk of progression from IGT to diabetes.[5] The American Association of Clinical Endocrinology (AACE) and the American College of Endocrinology (ACE) jointly issued a comprehensive consensus statement on the management of T2DM, explicitly recommending that patients with diabetes should receive both lifestyle interventions and pharmacological treatment.[6] Among available medications, metformin is increasingly emphasized for its significant efficacy, favorable safety profile, and potential cardiovascular benefits[7] in the management of prediabetes. The 2023 American Diabetes Association (ADA) guidelines[8] further pointed out that high-risk individuals with prediabetes—such as those aged 25–59 years, with a body mass index (BMI) $\geq 35\,kg/m^2$, fasting plasma glucose ≥ 6.1 mmol/L, glycated hemoglobin (HbA1c) ≥ 6.0 %, or a history of gestational diabetes mellitus (GDM)—should be considered for metformin use to prevent the onset of type 2 diabetes.[9] Although there is currently no specific guideline in China for the use of metformin in treating prediabetes, several clinical studies have demonstrated its positive effects in lowering blood glucose levels, improving metabolism, and delaying diabetes progression.[10–16]

Here, we compare the effects of different formulations of metformin (e.g., conventional tablets, sustained-release preparations, enteric-coated preparations) on onset time, duration of action, and patient adherence. We incorporate domestic and international expert consensus and clinical guidelines to comprehensively analyze global variations and future trends in the use of metformin for prediabetes treatment. We expect to optimize the therapeutic strategy of metformin in the prevention of prediabetes or diabetes by integrating the current clinical application status, intervention mechanisms, evidence-based evidence, and the status of special populations, so as to provide evidence-based basis for clinical medication.

The current status of clinical application of metformin

Dosage forms, consensus, and guideline recommendations of metformin

At present, the dosage forms of metformin used in clinical practice in China mainly include conventional tablets, enteric-coated tablets (or capsules), and sustained-release tablets (or capsules), with gastrointestinal absorption as the primary route. The differences among various formulations lie in the drug dissolution and release patterns after administration: conventional tablets disintegrate and release in the stomach; enteric-coated tablets and capsules disintegrate and release in the intestines; while sustained-release tablets and capsules slowly dissolve and release the drug throughout the gastrointestinal tract. Compared to conventional tablets, sustained-release formulations release the drug more slowly in the body, resulting in more stable plasma concentrations and reduced dosing frequency. According to the Expert Consensus on Clinical Application of Metformin (2023 edition),[9] when switching from conventional tablets to sustained-release formulations, it is recommended to use the same dosage. The Expert Consensus on Clinical Application of Metformin (2018 edition)[17] indicated that once-daily administration of metformin sustained-release formulations significantly improves gastrointestinal tolerance, thereby enhancing patient medication adherence. A 16-week randomized controlled trial (RCT) demonstrated that once-daily administration of metformin sustained-release tablets was equivalent in efficacy to two or three times daily administration of an equivalent dose of conventional tablets in reducing glycated hemoglobin.[18] Alcohol consumption should be avoided during the use of all metformin formulations to reduce the risk of lactic acidosis. In addition, differences in absorption patterns, dosing time, and frequency among the various formulations may lead to variations in adverse reactions.

The therapeutic intensity of metformin is generally associated with the risk of diabetes and related complications in patients. The Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes (2017 edition) recommend considering pharmacological intervention for prediabetic patients who, after six months of intensive lifestyle intervention, show unsatisfactory results and have additional risk factors.[19] Currently, both guidelines and expert consensus lack specific recommendations regarding the treatment duration of metformin in prediabetes. Moreover, due to variations in individual constitution, disease severity, and drug response, treatment duration may differ among patients. Regarding dosing, there are no specific recommendations for metformin use in prediabetic patients in existing guidelines or consensus documents. However, the Expert Consensus on Clinical Application of Metformin (2023 edition) stated that the hypoglycemic effect of metformin is positively correlated with dose within the range of 500–2000 mg/day.[9] The initial dose is typically 500 mg, taken once or twice daily, and can be gradually increased based on patient tolerance to a maximum tolerated dose (usually 2000 mg/day). For prediabetic patients with abnormal renal function, although the dosage of metformin needs to be adjusted based on the estimated glomerular filtration rate (eGFR), current domestic and international guidelines have not established specific quantitative recommendation criteria for prediabetic populations with abnormal renal function, and there is also a lack of relevant dose-response studies. When the eGFR is below $45\,mL/min/1.73\,m^2$, metformin should be used with caution; when it drops below $30\,mL/min/1.73\,m^2$, metformin should be discontinued. As for indications for discontinuation, for patients whose blood glucose remains within the normal range and is stably controlled over the long term, the medication dose may be gradually reduced under medical supervision until discontinuation is achieved. If the patient experiences severe adverse effects from metformin, such as nausea, vomiting, abdominal pain, or diarrhea, the drug should be stopped immediately. For individuals who remain at high risk for diabetes and persist in a prediabetic state, long-term use of metformin may be necessary, in which case particular attention should be paid to patient adherence.[20]

Personalized treatment is a key principle in achieving rational medication use. For example, in patients with a high BMI, metformin exhibits more pronounced effects on glucose lowering and weight control;[16,40] thus, dosing should be adjusted based on patient weight,[8,9,11,38,39] renal function[8,9,40,41], and other comorbidities. In contrast, for elderly patients, those with hepatic insufficiency, or those with additional cardiovascular risks, dose adjustments and efficacy monitoring are especially important.

Regarding combination therapy, the 2024 American College of Physicians (ACP) guidelines emphasize that metformin combined with lifestyle modifications remains the first-line treatment for T2DM.[21] For patients with inadequate glycemic control, the guidelines recommend adding sodium-glucose cotransporter 2 (SGLT-2) inhibitors or glucagon-like peptide-1 (GLP-1) receptor agonists on top of metformin and lifestyle changes to reduce the risk of all-cause mortality, adverse cardiovascular events, and progression of chronic kidney disease (Table 1). The current guideline trends are also shifting from the past glucose-lowering-centered approach to a patient-centered combination therapy. The Expert Consensus on Clinical Application of Metformin (2023 edition)9 emphasizes that in the absence of strong indications for cardiorenal protection, metformin remains the preferred first-line glucose-lowering agent for T2DM. However, when there are strong indications for cardiorenal protection, GLP-1RA and/or SGLT2i should be prioritized for treatment, with metformin serving as the preferred glucose-lowering agent in combination therapy regimens. This change suggests that in the future, prediabetic patients with cardiorenal diseases should prioritize improving cardiorenal outcomes, and on this basis, combine metformin for glucose-lowering therapy.

Table 1
Metformin formulations, dosage, precautions, combination therapies, and clinical efficacy[22,23].

Factors	Details	Data/Notes
Formulation		
Main formulations	Monotherapy	Conventional tablets (250 mg, 500 mg, 850 mg), sustained-release tablets (500 mg), enteric-coated tablets (250 mg, 500 mg)
	Fixed-dose combinations	Combined with other oral hypoglycemic agents (e.g., sulfonylureas, DPP－4 inhibitors)
Release characteristics		
Conventional tablet	Disintegrate and release in the stomach	Taken with or immediately after meals
Enteric-coated tablet	Disintegrate and release in the intestines	Taken 30 min before meals to reduce gastric retention
Sustained-release tablet/capsule	Slowly dissolve and release throughout the gastrointestinal tract	Taken once daily with or after meals
Dosage		
Dose-efficacy relationship	500–2000 mg/day (glycemic effect increases with dose)	500 mg/day reduces HbA1c by 0.6 %; 2000 mg/day by 2.0 %
	Comparison between 1000 mg/day and 1500 mg/day	No significant difference in gastrointestinal side effects
	500 mg/d	Minimum effective dose
	2 000 mg/d	Optimal effective dose
	2 550 mg/d	Maximum dose for adults (conventional tablet)
	2 000 mg/d	Recommended maximum dose for sustained-release formulations
Adjustment scheme	Administration recommendation	Take with or immediately after meals; Follow “start low, go slow” approach
	Simplified titration	Start with 500 mg twice daily; if tolerated, increase to 500 mg three times daily or 1000 mg twice daily (or maximum tolerated dose)
	Switching recommendation	When switching from immediate-release to extended-release, use the same total daily dose
	Important precautions	All formulations should be avoided with alcohol to reduce the risk of lactic acidosis
	Adverse effects	Differences in absorption may lead to formulation-specific adverse effects (see Table 3)
	Recommendations for high-risk populations	For diabetic patients with high cardiovascular or renal risk, metformin remains the preferred first-line combination agent
Combination therapy		
First-line therapy	Life-style	Metformin and lifestyle modification is first-line for T2DM
	SGLT－2 inhibitors	Reduces all-cause mortality, major adverse cardiovascular events (MACE), CKD progression, and hospitalization for congestive heart failure
For inadequate glycemic control	GLP－1 receptor agonists	Reduce all-cause mortality, MACE, and stroke risk
	DPP－4 inhibitors	Not recommended for reducing incidence or mortality in patients with poor glycemic control
Clinical efficacy		
HbA1c reduction	2018 consensus guideline[17]	1.0 %－2.0 %
	2023 consensus guideline[9]	1.0 %－1.5 %
Discontinuation criteria		
Glycemic control and adverse events	General control	Continue for at least 6–12 months
	Long-term normal and stable blood glucose levels	Gradual dose reduction or discontinuation under physician guidance
	Severe adverse effects	Discontinue immediately
	High-risk individuals for diabetes	Long-term use

Mechanism of metformin as a pharmacological intervention for prediabetes

As the first-line therapeutic agent for T2DM, metformin exerts its hypoglycemic effects through multiple pathways.[24] Primarily acting on the liver, it inhibits hepatic gluconeogenesis, thereby reducing hepatic glucose output. In peripheral tissues (e.g., muscle and adipose), metformin enhances insulin sensitivity, promotes glucose uptake and utilization, accelerates muscle glycogen synthesis, and decreases free fatty acid levels.[9] Concurrently, it modulates intestinal function by inhibiting intestinal glucose absorption, promoting fecal glucose excretion, and potentially augmenting glycemic control through GLP-1 elevation.[9] These integrated mechanisms confer metformin’s efficacy in glycemic control and insulin resistance amelioration. Since metformin does not directly stimulate insulin secretion, it carries a lower hypoglycemia risk, rendering particular advantages for metformin in prediabetes management (Fig. 1). However, current research predominantly focuses on its mechanisms in hyperglycemic states, with insufficient investigation into its actions specifically in prediabetic populations.

(1) Inhibition of hepatic gluconeogenesis

Metformin has been demonstrated to activate AMP-activated protein kinase (AMPK), suppressing the expression of gluconeogenesis-related genes and consequently decreasing hepatic glucose production to stabilize blood glucose levels. It also inhibits ATP synthesis, attenuating glucose-stimulated insulin secretion (GSIS) in β-cells.[24,25] Through AMPK-dependent pathways, metformin promotes GLP-1 release, stimulates insulin secretion, and suppresses glucagon secretion, collectively reducing blood glucose. Furthermore, metformin regulates exogenous pyruvate to induce glucose reduction, further validating its inhibitory effect on hepatic gluconeogenesis. A recent study revealed that metformin ameliorates dysregulated GSIS in prediabetic rat models.[26]

Notably, research indicates that under hyperglycemic conditions, metformin increases intestinal lactate and acetate production, modulates hepatic pyruvate carboxylase, MPC1/2, and FBP1, establishing a gut-liver axis to reduce hepatic glucose generation.[27] Under normoglycemic conditions, metformin-induced enhancement of basolateral glucose uptake is often accompanied by decreased portal vein glucose concentration, which triggers a counter-regulatory mechanism that maintains hepatic glucose production stability.

(2) Enhancing insulin sensitivity in peripheral tissues

In the glucose-lowering effect of metformin, it also achieves this by enhancing insulin sensitivity in peripheral tissues. In skeletal muscle,

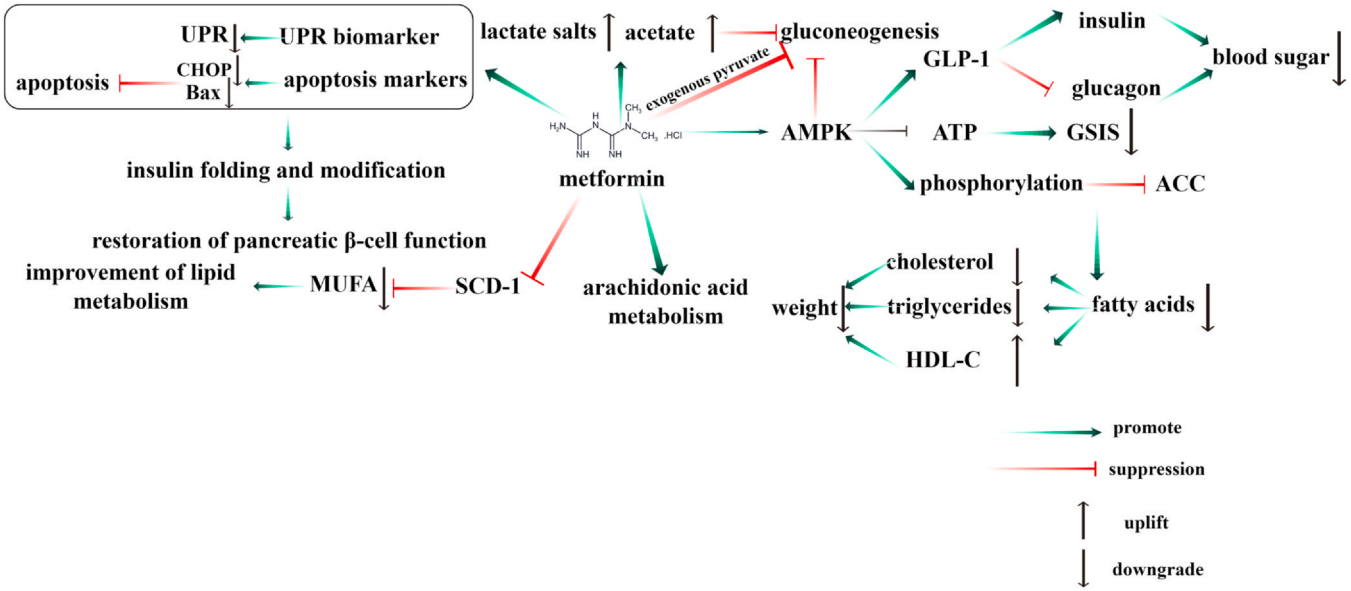

Fig. 1. Mechanisms of metformin action under hyperglycemia (created using Figdraw). Note: UPR: unfolded protein response; CHOP: CCAAT-enhancer-binding protein homologous protein; bax: Bcl-2 associated x protein; MUFA: monounsaturated fatty acids; SCD-1: Stearoyl-CoA Desaturase-1; AMPK: AMP-activated protein kinase; ATP: adenosine triphosphate; ACC: Acetyl-CoA carboxylase; GLP-1: Glucagon-like Peptide-1; GSIS: Glucose-stimulated insulin secretion; HDL-C: High-Density lipoprotein cholesterol. This figure was created using figdraw.

metformin promotes the translocation of Glucose Transporter Type 4 (GLUT4) to the cell membrane by activating AMPK, specifically enhancing insulin-stimulated glucose uptake in oxidative muscle fibers, but has no significant effect on glycolytic muscle fibers.[28] Meanwhile, Metformin regulates lipogenesis and metabolism in prediabetic individuals by modulating stearoyl-CoA desaturase-1 (SCD-1), lipotoxic intermediates, and arachidonic acid metabolism. SCD-1, a pivotal enzyme in lipid metabolism, catalyzes the conversion of saturated fatty acids (SFAs) to monounsaturated fatty acids (MUFAs) such as oleic acid and palmitoleic acid, a process critical for lipogenesis and energy metabolism. Metformin reduces SCD-1 activity, decreasing MUFA production and thereby mitigating lipid accumulation while improving lipid metabolism. Additionally, metformin diminishes the accumulation of lipotoxic intermediates including diacylglycerol (DAG) and lysophosphatidylcholine (LPC), thereby enhancing insulin sensitivity and alleviating cellular lipotoxicity.[29] It also modulates arachidonic acid metabolism to reduce inflammatory metabolites, further optimizing lipid metabolism in prediabetes.[29]

Acetyl-CoA carboxylase (ACC), a rate-limiting enzyme in fatty acid synthesis, catalyzes the conversion of acetyl-CoA to malonyl-CoA, an essential step in fatty acid biosynthesis. Metformin suppresses ACC activity via AMPK signaling, reducing fatty acid synthesis and consequently improving lipid metabolism. This not only lowers blood lipid levels but also ameliorates insulin resistance and metabolic syndrome symptoms. Furthermore, metformin decreases total cholesterol and triglyceride levels while elevating high-density lipoprotein cholesterol, offering comprehensive lipid metabolic benefits.[30,31] Given that prediabetic patients frequently exhibit dyslipidemia and obesity,[29] metformin's dual actions on glycemic control and lipid metabolism make it particularly suitable for obese prediabetic individuals.

(3) Inhibition of pancreatic β-cell apoptosis

In prediabetes, hyperglycemia, oxidative stress, and dyslipidemia exacerbate endoplasmic reticulum (ER) stress and apoptosis in pancreatic β-cells.[32] A study demonstrated that metformin promotes insulin co-localization with ER proteins including PDI and ERp44, which contributes to preserve β-cell functionality.[26] Furthermore, it revealed significant downregulation of unfolded protein response (UPR) markers and apoptotic markers in metformin-treated prediabetic rat islets.[26] These findings indicate that metformin alleviates ER stress, prevents UPR overactivation, and reduces expression of pro-apoptotic genes such as CHOP and Bax, thereby inhibiting β-cell apoptosis.

(4) Improvement of pancreatic β-cell glucose sensitivity

Chronic exposure to hyperglycemia impairs β-cell function, leading to reduced insulin secretion and increased insulin resistance, a phenomenon termed glucotoxicity. Research confirms that metformin at low concentrations (15 μM) effectively blocks glucotoxicity progression, protecting β-cells from hyperglycemic damage.[33] Without metformin, hyperglycemia induces pancreatic β-cell desensitization, leading to diminished responsiveness to glucose stimulation and consequent insulin secretion impairment, a critical event in diabetes pathogenesis. In contrast, metformin treatment preserves glucose-stimulated insulin response even after prior hyperglycemic exposure, confirming its β-cell protective effects and potential diabetes-preventive properties.

Evidence-based evidence of metformin in the treatment of prediabetes

The efficacy of metformin in preventing the onset of diabetes among individuals with prediabetes has been validated by numerous large-scale clinical trials. Metformin intervention not only significantly reduces the incidence of diabetes but also effectively delays its onset. A systematic review including 20 randomized controlled trials and 6774 participants found that, compared to placebo or diet and exercise interventions, metformin reduced or delayed the risk of T2DM in at-risk populations.[34] Results from the U.S. Diabetes Prevention Program (DPP) showed that metformin reduced the cumulative incidence of diabetes by 31 % compared to placebo.[35] According to the DPP, the Diabetes Prevention Program Outcomes Study (DPPOS), and interim studies between the two, metformin demonstrated non-inferiority to lifestyle interventions in preventing increases in fasting glucose and HbA1c levels.[36] In the China Diabetes Prevention Program (CDPP),[37] the combination of lifestyle intervention and metformin was shown to reduce the risk of developing diabetes by 17 % compared to lifestyle intervention alone. Additionally, the incidence of serious or severe adverse events was low and comparable between the lifestyle-only and the combined intervention groups, indicating a favorable safety profile for the combined intervention in diabetes prevention.

In addition to glycemic control, metformin provides cardiovascular benefits and significantly lowers the risk of myocardial infarction. The UK Prospective Diabetes Study (UKPDS),[14] which focused on the long-term follow-up of newly diagnosed diabetes patients, demonstrated that early intensive glycemic control significantly reduced the risks of death and myocardial infarction. Over 24 years of post-trial follow-up, the legacy effect of metformin persisted, with significantly lower risks of death and myocardial infarction in the early metformin group compared to the conventional treatment group and those treated with sulfonylureas or insulin. Overall mortality risk was reduced by 20 %, and the risk of myocardial infarction by 31 %, highlighting a more pronounced legacy effect than other treatments. This study provides important insights into therapeutic strategies and drug choices for prediabetic patients with cardiovascular disease, and underscores the importance of early glycemic control in T2DM management.

Furthermore, metformin therapy is often associated with weight loss. In the DPP study,[38] participants in the metformin group lost an average of 2.5 kg, and this weight loss was sustained over a 10-year follow-up. In the DPPOS,[39] average weight increased in the lifestyle group, whereas the metformin group maintained weight loss. A study involving 112 individuals with prediabetes demonstrated that the combination of metformin and lifestyle intervention significantly increased GDF-15 levels and reduced abdominal fat, further supporting its clinical benefits, particularly in overweight or obese populations.[11] Because the CDPP exclusively enrolled Chinese participants, its findings offer population-specific insights for diabetes prevention in Chinese patients with obesity.

In clinical practice, metformin is often used in combination with other drugs to enhance therapeutic efficacy. For example, studies have shown that combining metformin with acarbose can significantly improve insulin resistance and lipid profiles in prediabetic patients without increasing adverse events.[13] In obese patients, co-administration of liraglutide with metformin can further improve lipid metabolism. A study involving 180 individuals with prediabetes found that both metformin monotherapy and combination therapy with liraglutide improved fasting glucose and glucose tolerance, reducing the risk of progression from prediabetes to diabetes[10] (Table 2).

Application of metformin in prediabetic populations with comorbidities and in special populations

Prediabetes with renal dysfunction

As metformin is primarily excreted through the kidneys, chronic or acute renal impairment may lead to its systemic accumulation, thereby increasing the risk of lactic acidosis. Therefore, in the management of prediabetic patients with renal dysfunction, dosage adjustments should be based on the eGFR to assess renal function staging (Table 3). The Expert Consensus on Clinical Application of Metformin (2023 Edition)[9] recommends regular renal function monitoring to guide metformin dosing, along with suggested monitoring frequencies. Regarding dosage selection, the 2023 ADA guidelines[8] and 2022 KDIGO guidelines[40] provide partially divergent recommendations. Concerning lactic acidosis, the 2022 KDIGO guidelines[40] indicate that metformin use may pose a risk of lactic acidosis, and its dosage should be restricted in high-risk scenarios, with immediate discontinuation if acidosis occurs. In contrast, The Expert Consensus on Clinical Application of Metformin (2023 Edition)[9] maintains that long-term metformin use does not increase lactic acidosis risk when contraindications are well understood and appropriately managed. Thus, for specific prediabetic subgroups, such as malnourished, frail, or elderly patients, current evidence suggests avoiding maximal dosing to mitigate potential risks.[41] Observational studies have demonstrated the feasibility of metformin use in chronic kidney disease (CKD) stage 3b patients, and may even be correlated with reduced all-cause mortality without elevating lactic acidosis risk. However, these findings require further validation through high-quality randomized controlled trials.[9]

Prediabetes during pregnancy or lactation

In managing prediabetes during pregnancy, metformin was previously classified as a pregnancy category B drug by the US Food and Drug Administration (FDA). However, per the latest guidelines from the American College of Obstetricians and Gynecologists (ACOG),[42] insulin remains the first-line therapy. Metformin may serve as an alternative when insulin administration faces patient non-adherence or technical challenges.

Although multiple systematic reviews[43–45] report no significant increase in adverse pregnancy outcomes with metformin versus insulin, long-term follow-up reveals that metformin crosses the placental barrier, potentially affecting offspring growth, development, and long-term weight management.[46–49] Accordingly, The Expert Consensus on Clinical Application of Metformin (2023 Edition)[9] explicitly restricts metformin to prediabetic or T2DM pregnancies where insulin is unfeasible or unsuitable, and contraindicates its use during lactation due to secretion into breast milk, and resumption is permissible after the breastfeeding period. Additionally, metformin is absolutely contraindicated in type 1 diabetes (T1DM), gestational hypertension, preeclampsia, and intrauterine growth restriction.[7] Regarding breastfeeding safety, existing studies suggest that metformin use is generally acceptable when the infant's relative daily exposure remains below 10 mg/kg.[45] However, due to the limited availability of large-scale clinical data, the long-term developmental and health effects of metformin exposure in infants and children born to prediabetic mothers during pregnancy or lactation remain inconclusive.

Prediabetes with hepatic dysfunction

For prediabetic patients with hepatic impairment, metformin should generally be avoided due to potential lactic acidosis risks, particularly in those with serum transaminase levels exceeding the normal upper limit by three times or with severe hepatic insufficiency.[9] However, a cohort study[50] found that non-metformin users had higher risks of variceal bleeding and cirrhotic decompensation compared to metformin users. No significant differences were observed in risks of ascites (aHR 0.99), hepatic encephalopathy (aHR 0.99), or liver failure (aHR 1.07). These findings suggest that metformin's hepatic effects may not be uniformly detrimental, warranting more nuanced and comprehensive investigation.

Prediabetes with cardiovascular diseases

For prediabetic patients with cardiovascular diseases (CVD), the cardiovascular effects of metformin remain controversial. A 21-year follow-up study[51] demonstrated that compared to placebo, metformin did not significantly improve cardiovascular outcomes or prolong the time to first major adverse cardiovascular events. However, other studies suggest that metformin, as an antidiabetic agent, may confer cardiovascular benefits by reducing mortality and myocardial infarction risks.[13] Clinically, metformin is already used in diabetes patients with CVD. Notably, the Expert Consensus on Clinical Application of Metformin (2023 Edition)[9] explicitly contraindicates metformin use in patients with acute or decompensated heart failure. However, for chronic heart failure (CHF) patients, metformin itself does not induce heart failure and is not contraindicated. Some studies even propose combining SGLT2 inhibitors with metformin in prediabetic patients with heart failure to further reduce cardiovascular risks.[52]

Prediabetes with malignancy

For prediabetic patients with malignancies, research indicates that metformin not only lowers blood glucose but also reduces cancer incidence and mortality.[53] The Expert Consensus on Metformin as Adjuvant Therapy for Cancer Patients with Type 2 Diabetes (2022

Table 2
Clinical trial outcomes and limitations of metformin in prediabetes treatment.

Study ID	Study Type	Enrolled population	Sample size (n)	Intervention	Control	Main findings	Study limitations
DPP study[35,38]	Randomized controlled trial (RCT)	Non-diabetic individuals with elevated fasting or postprandial glucose	3234	Metformin	Lifestyle intervention, placebo	Metformin reduced cumulative diabetes incidence by 31 %, significantly delayed disease onset; associated with gastrointestinal side effects and weight loss	Prediabetes was not clearly defined; potential selection bias in enrolled participants
U.S. DPP, DPPOS, and interim studies[36]	RCT and cohort study	Non-diabetic individuals with elevated fasting or postprandial glucose	2766	Metformin	Lifestyle intervention, placebo	Metformin was non-inferior to lifestyle in preventing increases in fasting glucose and HbA1c; 18 % reduction in diabetes incidence and median delay of 2 years (versus placebo); sustained weight loss without rebound (versus lifestyle intervention)	Unclear effects on cancer risk or renal disease incidence in elderly patients
CDPP study[37]	RCT	Patients with impaired glucose regulation (prediabetes)	1678	Metformin and lifestyle intervention	Lifestyle intervention alone	17 % reduction in diabetes incidence; combination therapy more effective than lifestyle alone	Only 14 % of participants had impaired fasting glucose (IFG); selection bias; large-scale studies needed in IFG populations
UKPDS study[14]	RCT	Early-stage T2DM patients	4209	Intensive glycemic control (metformin)	Sulfonylureas or insulin (intensive), diet only (conventional)	Metformin significantly reduced mortality and myocardial infarction; showed greatest legacy effect compared to other therapies	Missing data from surviving participants; absence of key biomarkers (e.g., HbA1c, serum creatinine); missing data on treatment adjustments
Zhang Fang, 2022[11]	RCT	Prediabetic patients	112	Metformin and lifestyle intervention	Lifestyle intervention alone	Greater weight loss in intervention group; increased GDF−15 and reduced abdominal fat; more pronounced in overweight/obese patients	Mechanisms behind metformin's effect on fat distribution unclear; small sample size; potential confounding factors not excluded
Xu Lu, 2021[13]	RCT	Prediabetic patients	100	Metformin and acarbose	Metformin alone	Combination therapy improved insulin resistance, reduced glucose and lipids more effectively	Study only confirmed no new adverse effects; did not quantify difference in adverse event incidence vs. metformin alone; small sample size
Guo Zhihui, 2022[10]	RCT	Prediabetic patients with IFG or IGT	175	Metformin and liraglutide and lifestyle intervention	Lifestyle alone, or lifestyle and metformin	Greater reductions in fasting and 2-hour postprandial glucose and lower progression to T2DM in metformin group (vs. lifestyle alone); combination therapy more effective than metformin alone	Limited domestic data on GLP−1RAs in prediabetes; small sample size

Table 3
Guidelines/consensus recommendations on metformin use in patients with renal impairment.

Glomerular filtration rate (GFR) (mL/min/1.73 m^2)	Metformin Dosing Recommendation	Monitoring Frequency	Additional guideline notes
The Expert Consensus on Clinical Application of Metformin (2023 Edition)			
> 60	No dose adjustment needed	Annually	
45–60	No dose adjustment needed	Every 3–6 months	
30–45	Use with caution or reduce dose	Monitor as clinically indicated	2023 ADA: Reassess risk-benefit; dose reduction may be needed. 2022 KDIGO: Limit to ≤ 1000 mg/day.
< 30	Contraindicated	Continuous GFR monitoring	2023 ADA: Contraindicated; monitor GFR continuously. 2022 KDIGO: No explicit recommendation to discontinue.
KDIGO Guideline (2022 Edition)			
45–59 (at risk of lactic acidosis)	Limit dose to ≤ 1000 mg/day		2023 Expert Consensus: No increased lactic acidosis risk with metformin.

Edition)[54] recommends initiating metformin treatment as early as possible in prediabetic or diabetic cancer patients after excluding contraindications. The primary rationale is that metformin, either as monotherapy or combined with radiotherapy/chemotherapy, can decrease recurrence rates, metastasis, cancer-related mortality, and all-cause mortality while improving survival rates.

Elderly and pediatric prediabetic populations

Metformin is approved as an oral hypoglycemic agent for children and adolescents (aged ≥10 years) with T2DM but is not recommended for those under 10. The 2023 ADA guidelines[55] suggest metformin as initiating therapy for pediatric T2DM patients with normal renal function and HbA1c < 8.5 %. Although guidelines do not explicitly endorse metformin for prediabetes prevention in this population, given the HbA1c range for prediabetes (5.7 %-6.5 %), metformin may be considered for prediabetes management in children and adolescents aged ≥ 10 years.[17]

For elderly patients (> 65 years), metformin should be initiated at lower doses and adjusted based on renal function. In the absence of strong indications for GLP-1 receptor agonists or SGLT2 inhibitors with cardiorenal protective effects, metformin remains the preferred antidiabetic drug. Regular assessments of cardiac and renal function are recommended to guide dosage adjustments in elderly prediabetic patients.

Clinical adverse reactions and precautions of metformin

Metformin treatment is associated with relatively few adverse reactions. The most common adverse effects are gastrointestinal symptoms, with an incidence rate of 20 %-30 %, including nausea, vomiting,[56] and abdominal pain.[57] The mechanisms underlying these symptoms can be categorized into direct and indirect causes. The direct cause is that metformin, being highly water-soluble, rapidly dissolves and releases upon entering the gastrointestinal tract. This results in intense drug stimulation of the gastrointestinal mucosa within a short period, thereby inducing discomfort such as nausea, vomiting, and diarrhea.[58] The indirect cause is that metformin promotes intestinal glucose uptake and lactate production, increases concentrations of GLP-1 and bile acids in the intestine, and alters the gut microbiota and their microenvironment. These changes may affect intestinal digestive, absorptive, and metabolic functions, and potentially trigger intestinal inflammatory responses.[58] To address these gastrointestinal adverse reactions, clinical practice often involves switching from the immediate-release formulation of metformin to a sustained-release form. The gradual disintegration and release of sustained-release formulations in the stomach reduce direct gastrointestinal effects and alleviate metformin-related adverse reactions.

In addition to gastrointestinal reactions, some patients may experience chest discomfort, headache, sweating, hypoglycemia, weakness, and rhinitis while taking metformin.[59] These symptoms may be related to decreased vitamin B12 levels, particularly in patients with anemia or peripheral neuropathy, who should be especially vigilant. Research indicates that metformin may interfere with the calcium-dependent membrane action responsible for vitamin B12-intrinsic factor complex absorption in the terminal ileum, leading to vitamin B12 deficiency. Although vitamin B12 stores in the body can last approximately 2–5 years, long-term metformin users, especially elderly patients presenting with gait instability and frequent falls, should be alert to the possibility of vitamin B12 deficiency. Furthermore, proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) may also affect vitamin B12 absorption. Therefore, patients on long-term metformin therapy are advised to undergo regular vitamin B12 level monitoring.[60]

Another adverse reaction requiring high vigilance is lactic acidosis,[61] a form of metabolic acidosis caused by lactate accumulation in the body that cannot be rapidly cleared. A decrease in blood pH may lead to nonspecific signs and symptoms such as chest discomfort and respiratory distress. Concomitant use of metformin with certain medications may increase the risk of lactic acidosis due to drug interactions. These medications include bupropion, carbonic anhydrase inhibitors, cephalexin, cimetidine, dolutegravir, ethanol, glycopyrrolate, iodinated contrast media, lamotrigine, ranolazine, and topiramate. Additionally, some drug interactions may enhance the hypoglycemic effects of metformin, including androgens, alpha-lipoic acid, salicylates, selective serotonin reuptake inhibitors (SSRIs), quinolones, prothioamine, polyethylene glycol, and other antidiabetic agents[62] (Table 4). Therefore, special attention should be paid to potential drug interactions when using metformin. A thorough evaluation of drug combination safety and monitoring for possible adverse reactions are essential to ensure patient safety and treatment efficacy.

Discussion

Efficacy considerations

As a crucial intervention for prediabetes, metformin improves hyperglycemia through multiple pathways, including inhibition of hepatic gluconeogenesis and enhancement of insulin sensitivity. Extensive clinical studies demonstrate that both monotherapy and combination regimens with metformin effectively reduce fasting blood glucose and IGT, significantly lowering the risk of progression to diabetes. Notably, in overweight or obese individuals, metformin also exhibits modest weight-loss effects, which is closely associated with its positive impact on lipid metabolism. However, metformin application presents certain challenges, such as adverse reaction management and appropriate dose adjustments. Furthermore, in patients with prediabetes, comparative studies on the efficacy of metformin in individuals with IGT versus IFG remain limited. This lack of evidence may affect patient adherence and the sustainability of long-term treatment.

Table 4
Potential adverse reactions and precautions associated with metformin use in diabetes and prediabetes.

Adverse reaction	Cautions
Metformin monotherapy (common)	
Gastrointestinal symptoms	Occur in approximately 20–30 % of patients; include nausea, vomiting, and abdominal pain. Sustained-release formulations may alleviate these symptoms[56]
Vitamin B12 deficiency	May result from impaired absorption in the terminal ileum. Long-term or high-dose use increases risk; regular monitoring and supplementation of vitamin B12 may be required[60]
Lactic acidosis	A form of metabolic acidosis due to lactate accumulation. Risk may be increased by concomitant use of certain drugs that enhance lactate production or impair clearance[61]
Other non-specific symptoms	Include chest discomfort, headache, sweating, hypoglycemia, fatigue, and rhinitis. Long-term use may be linked to reduced B12 levels; caution advised in patients with anemia or neuropathy[59]
Combination therapy	
Increased risk of lactic acidosis	Use with caution when combined with drugs such as bupropion or carbonic anhydrase inhibitors; regimen adjustments may be necessary[62]

Use in special populations

The use of metformin in special populations requires heightened caution. For individuals with high BMI, history of gestational diabetes, or a diagnosis of cancer, more refined management strategies and individualized intervention plans are essential. Dose adjustments should be based on renal function, age, weight, and other factors, alongside regular monitoring of glycemic control and hepatic/renal indices to assess therapeutic efficacy and safety. Additionally, for pregnant or lactating women and patients with gastrointestinal or cardiovascular abnormalities, metformin use warrants careful evaluation. Treatment regimens should be adjusted when necessary, with close monitoring for potential adverse reactions.

Combination therapy issues

Metformin's combination with other agents can further enhance efficacy and improve glycemic/lipid control. However, combination therapy requires vigilance regarding drug-drug interactions and potential side effects. For example, while combining metformin with liraglutide or acarbose significantly improves therapeutic outcomes, it may also increase risks of hypoglycemia and gastrointestinal discomfort. Therefore, combination regimens should be tailored to individual patient profiles, selecting optimal drug combinations and dosages to ensure both efficacy and safety. Concurrently, patient responses to other medications should be closely monitored for timely regimen adjustments.

Safety profile

The efficacy and safety of metformin for prediabetes intervention require further validation. During treatment, patients may experience adverse reactions including headaches, abnormal sweating, hypoglycemic reactions, asthenia, and rhinitis. These symptoms may impair quality of life and compromise treatment adherence/persistence, necessitating deeper investigation into metformin's safety to optimize dosing strategies. Moreover, other health concerns, such as renal dysfunction and gastrointestinal issues, should be monitored during metformin therapy, with appropriate interventions implemented promptly.

Additional effects and benefits

Beyond glycemic control, metformin may reduce cardiovascular risk in prediabetic patients by improving lipid metabolism and attenuating inflammatory responses. Emerging evidence also suggests potential anticancer properties of metformin, indicating value in preventing certain malignancies. These findings provide new perspectives for metformin's role in prediabetes management. Nevertheless, challenges persist in adverse reaction management, dose optimization, and patient adherence. These factors influence both therapeutic outcomes and patient satisfaction. Hence, regimens should be flexibly adjusted based on individual characteristics to ensure personalized and precise care in clinical practice. Enhanced patient education and communication are equally critical to improve adherence and satisfaction.

The insufficiency of localized evidence-based evidence

The insufficiency of localized evidence-based evidenceThe core reason why Chinese guidelines have not recommended metformin for diabetes prevention lies in the insufficiency of localized clinical evidence. Although international studies have confirmed its efficacy in reducing the risk of diabetes progression, long-term follow-up data (over 5 years) with diabetes prevention as the endpoint are lacking in China. Moreover, genetic characteristics and metabolic phenotypes of Chinese populations differ from those in Europe and America, limiting the extrapolation validity of foreign evidence. For special populations such as those with high BMI, history of gestational diabetes, or abnormal liver/kidney function, data on medication dosage, adverse reaction risks, and safety of combination therapy under comorbid conditions are severely lacking, making it difficult to establish risk stratification models and management criteria for Chinese patients. Additionally, the common gastrointestinal reactions of the drug may affect long-term compliance, and the absence of localized adverse reaction management pathways further exacerbates evidence deficiency.Therefore, continuous nationwide multicenter prospective studies should be conducted, including 5+ years of follow-up for Chinese prediabetic populations stratified by IGT/IFG to clarify the optimal timing, dosage, and long-term efficacy of metformin intervention. Secondly, pragmatic RCTs should be designed for special populations and combination therapy scenarios to establish individualized medication guidelines based on renal function and comorbid status, and improve the safety assessment system. Clinically, promoting a medication regimen of low-dose initiation and individualized adjustment can enhance compliance.Metformin's effects in improving insulin resistance and inducing weight loss make it an important supplement to lifestyle interventions, especially for high-risk individuals, significantly reducing the risk of diabetes conversion. Furthermore, its potential cardiovascular protection, anti-inflammatory, and anti-tumor effects can provide multi-faceted therapy for populations with related comorbidities. Therefore, continuous improvement of the evidence chain is necessary to determine the precise efficacy of metformin.

Conclusion

Metformin demonstrates significant clinical value for prediabetes management. However, current understanding of its mechanisms largely extrapolates from diabetes research, while uncertainties remain regarding optimal dosing, efficacy indicators, and special population applicability in prediabetes. Future studies should address these gaps to provide comprehensive and accurate guidance for metformin use in

prediabetes. In clinical practice, the therapeutic plan should be flexibly adjusted according to individualized conditions to ensure precise diagnosis and treatment.

Declarations

Not applicable.

Authors' contributions

D. Liu: Literature collection, chart drawing, and article writing. X. Chen, Q. Wang, X. Pan, X. Wei, B. Wang, Y. Wang, X. Xue: Article revision. C. Lu: Article conceptualization and design, article revision, quality control, and overall project responsibility.

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Availability of data and materials

Not applicable.

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Declarations of Competing interests

The authors declare that they have no competing interests.

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Authors' other information

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Data availability

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