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## **Metabolic disorders in prediabetes: From mechanisms to therapeutic management**

Prediabetes research and therapeutic management

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### **Abstract**

Diabetes, one of the world's top ten diseases, is known for its high mortality and complication rates and low cure rate. Prediabetes precedes the onset of diabetes, during which effective treatment can reduce diabetes risk. Prediabetes risk factors include high-calorie and high-fat diets, sedentary lifestyles, and stress. Consequences may include considerable damage to vital organs, including the retina, liver, and kidneys. Interventions for treating prediabetes include a healthy lifestyle diet and pharmacological treatments. However, while these options are effective in the short term, they may fail due to the difficulty of long-term implementation. Medications may also be used to treat prediabetes. This review examines prediabetic treatments, particularly metformin, glucagon-like peptide-1 receptor agonists, sodium glucose cotransporter 2 inhibitors, vitamin D, and herbal medicines. Given the remarkable impact of prediabetes on the progression of diabetes mellitus, it is crucial to intervene promptly and effectively to regulate prediabetes. However, the current body of research on prediabetes is limited, and there is considerable confusion surrounding clinically relevant medications. This paper aims to provide a comprehensive summary of the pathogenesis of prediabetes mellitus and its associated therapeutic drugs. The ultimate goal is to facilitate the clinical utilization of medications and achieve efficient and timely control of diabetes mellitus.

**Key Words:** Prediabetes; <sup>1</sup> Glucagon-like peptide (GLP-1) agonists; Sodium-glucose cotransporter 2 (SGLT2) inhibitors; Vitamin D; Chinese herbal medicines

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**Core Tip:** Addressing the global impact of diabetes, this review underscores the pivotal role of pre-diabetes as a precursor and the window of opportunity it offers for reducing diabetes risk. While interventions like lifestyle changes and pharmacological treatments prove effective in the short term, sustained implementation remains challenging. The review delves into the potential of medications, including metformin and other agents, shedding light on the current limitations in research and clinical confusion. By providing a comprehensive overview, the paper aims to enhance understanding, enabling more efficient and timely control of diabetes mellitus.

## **INTRODUCTION**

<sup>12</sup> Prediabetes, also known as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), is a condition that has affected approximately 213,000 young individuals in the United States as of 2017, with an estimated 239,000 individuals projected to be affected by 2060, based on current growth trends<sup>[1]</sup>. Timely management of prediabetes can reduce the incidence of diabetes, particularly type 2 diabetes<sup>[2]</sup>. Prediabetes refers to blood glucose levels that are higher than normal but below the glucose levels detected in patients with diabetes<sup>[3,4]</sup>. Moreover, individuals with prediabetes are in a sub-healthy state, somewhere between being healthy and clinically diabetic. Effective treatment of prediabetes can prevent the development of diabetes and help individuals to return to a healthy state.

Interventional therapy for prediabetes primarily includes lifestyle interventions and pharmacological treatments. Commonly used clinical drugs include metformin,

<sup>1</sup> glucagon-like peptide (GLP-1) agonists, sodium-glucose cotransporter 2 (SGLT2) inhibitors, vitamin D supplements, and Chinese herbal medicines. In this review, we provide an overview of prediabetes and its therapeutic agents. The ultimate aim of this article is to offer insights into prediabetes and contribute to the development of effective treatment strategies.

## **PREDIABETES**

Prediabetic contributory factors may include genetics and diets high in calories and fat<sup>[5]</sup>. Such diets contribute to excess fat accumulation and compensatory lipolysis within the body, resulting in an increased free fatty acid (FFA) content. The FFAs can disrupt cellular homeostasis, hinder cellular insulin response, reduce cellular uptake and utilization, increase the risk of insulin resistance in the liver, and damage muscles and the liver, ultimately leading to the development of diabetes<sup>[6]</sup>.

<sup>3</sup> The criteria for diagnosing prediabetes include a fasting plasma glucose (FPG) level of 100–125 mg/dL (5.6–6.9 mmol/L), a 2-h oral glucose tolerance test (OGTT; 75 g 2 h) result of 140–199 mg/dL (7.8–11.0 mmol/L), and a glycated hemoglobin (HbA1c) level of 5.7–6.4% (39–47 mmol/mol)<sup>[7]</sup>. It is important to note that, among these criteria, the HbA1c test is only applicable to adults. Impaired oral glucose tolerance (IGT) is a key diagnostic criterion for prediabetes; however, HbA1c and fasting blood glucose (FBG) levels are also used in the diagnosis, as shown in Table 1<sup>[8–11]</sup>.

A clinical survey in the United States reported that the prevalence of prediabetes is as high as 30%, indicating that approximately one in three adults has a fasting glycemic index or HbA1c level that meets the criteria for prediabetes<sup>[12]</sup>. Meanwhile, in India, the number of individuals with impaired glucose tolerance reached 25.2 million in 2019 and is expected to reach 35.7 million by 2045<sup>[13]</sup>. The prevalence of prediabetes has notably increased from 15.5% in 2008 to 38.1% in 2018 in China (Table 2)<sup>[14–16]</sup>.

Patients with prediabetes may exhibit characteristics associated with diabetes, including weight and blood glucose abnormalities and systemic insulin resistance. Systemic insulin resistance plays a key role in prediabetes, as it leads to decreased

ability of the body to respond to insulin, resulting in an imbalance in glucose homeostasis which, in turn, leads to insulin resistance. The decreased ability of muscle cells to uptake and process glucose reduces the storage capacity for both glucose and triglycerides, resulting in abnormally elevated levels of free glucose and triglycerides in the blood, ultimately increasing the risk of developing diabetes<sup>[17,18]</sup>.

Most prediabetic states progress to diabetes mellitus, accompanied by complications including microvascular complications, retinopathy, and cardiovascular disease. Insulin resistance affects normal oxidative stress in nerves, leading to mitochondrial dysfunction, which causes retinopathy and drives neurological and vascular pathology. The incidence rate of retinopathy is approximately 8.2–20.9% in prediabetic patients<sup>[19–22]</sup>, while the risk of stroke increases by 0.74% compared to that in patients without diabetes<sup>[23]</sup>. Additionally, the prevalence of metabolic syndrome is approximately 37.6% higher than that of normoglycemic patients, and the vascular risk ratio score is increased by 0.43<sup>[24,25]</sup>. Prediabetes is characterized by hyperglycemia and insulin resistance, partly due to the disruption of glucose homeostasis, primarily caused by the compromised function of pancreatic islet  $\beta$ -cells. AMP-activated protein kinase (AMPK) is an insulin sensitizer that exists in the form of a heterotrimeric complex with major subunits comprising AMPK $\alpha$ , AMPK $\beta$ , and AMPK $\gamma$ . As blood glucose levels transition from fasting to postprandial levels, the decline in phosphorylated AMPK (pAMPK) levels within islets triggers the activation of AMPK phosphorylation, enhancing glucose-stimulated insulin secretion (GSIS). This promoted glucose uptake in muscle tissues while reducing glucose production in the liver to maintain constant blood glucose levels. The activity of AMPK activity is lowest when ATP occupies the subunit site of AMPK $\gamma$  under high-energy conditions. Liver kinase B1 (LKB1) is required to regulate AMPK activity through AMP/ADP or AMPK phosphatase inhibition. LKB1 primarily phosphorylates AMPK $\alpha$  by binding to Thr172, while LKB1 deficiency in  $\beta$ -cells inhibits the phosphorylation of Thr172 and AMPK target proteins. In contrast, the variable binding of the subunit to AMPK $\gamma$ , phosphorylation of the downstream kinase Thr172, and impaired downstream dephosphorylation determine

the degree of AMPK activation. This kinase in pancreatic  $\beta$ -cells may be protein phosphatase 1, which prevents the sustained activation of AMPK in the presence of high glucose, leading to GSIS failure and insulin resistance<sup>[26]</sup>. In damaged pancreatic  $\beta$ -cells, a sustained high-glucose environment results in sustained AMPK phosphorylation in the pancreatic  $\beta$ -cells, inhibiting GSIS and promoting insulin resistance.

Apart from hyperglycemia and insulin resistance, prediabetes also presents elevated endoplasmic reticulum (ER) stress levels and abnormal apoptosis of pancreatic islet  $\beta$ -cells. ER stress induces senescence of pancreatic  $\beta$ -cells due to the over-activation of the mammalian target of rapamycin (mTOR), a serine-threonine kinase, encompassing mTOR1 and mTOR2. mTOR1 is responsible for protein synthesis and ribosome genesis, while mTOR2 activates AKT-serine 473. Protein synthesis occurs in the ER.

8 The unfolded protein response (UPR) is activated when misfolded proteins accumulate in the ER. Over-activation of mTOR1 promotes excessive protein synthesis, increasing the likelihood of misfolded protein synthesis. This, in turn, sustains UPR activation, impairs cellular autophagy mechanism, and leads to pancreatic  $\beta$ -cell death. In patients with prediabetes, prolonged over-activation of the mTOR complex 1 signaling pathway in the  $\beta$  islets results in increased pancreatic  $\beta$ -cell numbers and inhibition of the  $\beta$ -cell autophagy protection mechanism, increasing the likelihood of apoptosis<sup>[27]</sup>.

Insulin resistance and pancreatic islet  $\beta$ -cell apoptosis due to insufficient insulin secretion impedes the normal glucose-lowering effect. Reduced insulin target cell receptor sensitivity leads to diminished insulin signaling, thereby decreasing glucose uptake and increasing extracellular free glucose. Furthermore, the body's negative feedback leads to more insulin release, causing hyperinsulinemia and creating a vicious cycle. The resulting insulin resistance promotes the development of prediabetes. Additionally, excessive free extracellular glucose promotes glucose uptake by the cells, leading to an imbalance in blood glucose homeostasis<sup>[27]</sup>.

The primary preventive measures for prediabetes include lifestyle interventions and pharmacotherapy (Table 3). These interventions primarily aim to reduce glycemic weight, improve insulin resistance, reduce pancreatic  $\beta$ -cell apoptosis, and reduce oxidative stress, thereby reducing islet resistance. Additionally, lifestyle interventions are intended to assist patients with prediabetes in improving unhealthy **lifestyles** and dietary habits, among others, while naturally reversing the imbalance in blood glucose homeostasis. An advantage of lifestyle interventions is their rapid effectiveness; however, lifestyle regulation is time-consuming<sup>[28-30]</sup>. Dietary and lifestyle changes can considerably improve the weight and blood glucose levels of individuals who have followed high-fat and-calorie diets over a long time. However, sustained improvement in blood glucose with weight loss may be minimal<sup>[30]</sup>. Additionally, maintaining a healthy diet over the long term may be challenging for individuals in the contemporary context. Pharmacological management is another form of prediabetes intervention that is remarkably more effective in controlling weight and blood glucose than dietary control. It is also adaptable to modern, high-stress, fast-paced lifestyles<sup>[31-36]</sup>. The main available drugs include metformin, GLP-1 receptor agonists (GLP-1RAS), SGLT2 inhibitors, vitamin D supplements, and Chinese herbal medicine, among others.

## **DRUGS FOR PREDIABETES TREATMENT**

### ***Metformin***

Metformin is a primary hypoglycemic agent that can lower glucose levels by impeding glucose production and enhancing its uptake and utilization<sup>[37-39]</sup>. Metformin stimulates AMPK, considerably ameliorating abnormalities in glycolipid metabolism<sup>[40]</sup>. Metformin can promote AMPK phosphorylation, reduce oxidative stress in skeletal muscle, and reverse glucose intolerance, leading to a hypoglycemic effect on the body<sup>[41]</sup>. Ma *et al*<sup>[42]</sup> explored the relationship between metformin, presenilin enhancer 2 (PEN2), and AMPK by knocking down the *PEN2* gene or reintroducing the *PEN1* mutant gene into *Cryptobacterium*. They reported that metformin can bind PEN2,



activate ATP6AP1 and AMPK, and initiate glucose metabolism-related signaling pathways, exerting its hypoglycemic effect<sup>[42]</sup>.

AMPK acts as a cellular energy sensor<sup>[43,44]</sup> and is closely related to the body's activity level. ATP decreases with strenuous exercise, and the ATP/ADP and ATP/AMP ratios subsequently decrease. The concomitant activation of the closely related AMPK positively regulates pathways that replenish the cellular ATP supply, including increasing glucose uptake, activating cellular autophagy, and promoting fatty acid oxidation, negatively regulating biosynthetic processes that consume ATP, including gluconeogenesis<sup>[45,46]</sup>, cholesterol synthesis, protein synthesis, and fatty acid synthesis (Figure 1)<sup>[47]</sup>.

Indeed, metformin effectively reduces the risk of developing diabetes during the prediabetic stage<sup>[2,48]</sup>. The American Diabetes Association (ADA) states that metformin is the most effective drug for diabetes prevention and recommends its use for prediabetes intervention<sup>[2]</sup>. Long-term metformin administration results in marked weight loss in a few patients, with minimal gastrointestinal upset. Therefore, it is considered safe, effective, and well-tolerated for the treatment of patients with prediabetes and abnormally elevated fasting glucose and IGT levels<sup>[49]</sup>.

Metformin is clinically prescribed at a starting dose of 500 mg, which can be increased to 1,000 mg twice daily. The dosage varies according to the individualized requirements of the patient. Reported doses used during prediabetic interventions are listed in Table 4. In previous safety trials, patients exhibited symptoms of anemia after long-term use of metformin due to the diminished concentrations of vitamin B12<sup>[50]</sup>. Therefore, the Diabetes Prevention Program (DPP) recommends that long-term metformin users should be tested for vitamin B12 Levels, with B12 supplementation.

Metformin use has certain shortcomings, including gastrointestinal symptoms, such as abdominal pain and diarrhea, which occur in 30% of users. The incidence of such symptoms increases with the duration of use<sup>[49]</sup>. Metformin use may also cause lactic acidosis or even death <sup>5</sup> in patients with severe renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73 m). Additionally, metformin is a biologically active



molecule with a low environmental decomposition capacity and may cause aquatic environmental contamination<sup>[56]</sup>.

### **Glucagon-like peptide receptor agonists**

GLP-1, a large peptide hormone comprising 30 or 31 amino acids, is primarily secreted by distal enteroendocrine L cells, pancreatic  $\alpha$ -cells, and the central nervous system. GLP-1 participates in regulating glucose homeostasis by acting on the GLP-1 receptor (GLP-1R). GLP-1R agonists (GLP-1RAS) approved for marketing in China primarily include the six types listed in Table 5.

GLP-1 is a type of entero-insulin, a hormone-stimulated and secreted by intestinal food and endothelial cells, respectively, that acts *via* GLP-1R on pancreatic  $\beta$ -cells to generate more intracellular cyclic AMP and ATP, thereby promoting insulin release from pancreatic  $\beta$ -cells. Additionally, GLP-1 can inhibit abnormal secretion of glucagon from pancreatic  $\alpha$ -cells<sup>[58]</sup>. It regulates glucose abnormalities by lowering HbA1c concentration, promoting insulin secretion from pancreatic  $\beta$ -cells, reducing body weight, contributing to postprandial glucose regulation<sup>[59]</sup>, and reducing glucagon secretion from pancreatic  $\alpha$ -cells in a glucose concentration-dependent manner. This inhibitory function is achieved *via* the paracrine effect of the islets<sup>[60]</sup>. However, GLP-1 glucose regulation is limited due to its short half-life in plasma. Hence, GLP-1RAS was developed to achieve longer-lasting glucose regulation by extending the half-life.

GLP-1RAS promotes the uptake and utilization of glucose *via* several mechanisms<sup>[61]</sup>. GLP-1RAS can activate pancreatic  $\beta$ -cell GLP-1R by increasing the affinity of GLP-1 to GLP-1R or by binding directly to GLP-1R, promoting insulin secretion by facilitating the conversion of glucose to ATP, enhancing calcium ions inflow and inhibiting K<sup>+</sup> outflow from cells (Figure 2)<sup>[62]</sup>. GLP-1RAS can inhibit glucagon secretion while promoting glucose-dependent insulin secretion owing to its high affinity and similarity to the natural GLP-1RAS and GLP-1, respectively, counteracting the increase in blood glucose caused by diet. The effect of maintaining blood glucose levels in a normal state is known as the entero-insulin effect<sup>[63]</sup>.

Glucose metabolism is significantly improved after 68 wk of treatment with semaglutide<sup>[64]</sup>. Oral semaglutide therapy causes HbA1c levels and weight reduction<sup>[65]</sup>. Meanwhile, tirzepatide upregulates insulin sensitivity in the body and restores islet  $\beta$ -cell function<sup>[66]</sup>; tirzepatide and semaglutide reduce HbA1c levels<sup>[67]</sup>. Thus, GLP-1RAS notably aids the restoration of glucose homeostasis, improves islet function, enhances insulin sensitivity, and controls body weight.

Currently, the main adverse reactions associated with GLP-1RAS include nausea, vomiting, and gastrointestinal discomfort<sup>[68]</sup>. GLP-1RAS is a biomolecular formulation that can only be administered *via* dermal injection. Therefore, it lacks the portability and comfort of small-molecule drugs that can be orally administered.

### **Sodium-glucose cotransporter 2 inhibitors**

SGLT 1 and SGLT2 play a prominent role in the reabsorption of filtered glucose by the glomerulus. SGLT2 inhibitors reduce SGLT2 activity and the efficiency of glucose uptake in the proximal tubules of the kidney, which increases the urinary glucose concentration and reduces blood glucose. The main SGLT2 inhibitors currently on the market are listed in Table 6<sup>[69-71]</sup>.

SGLT2 is an important member of the cotransport protein family. SGLT2 is mainly expressed in the proximal renal tubule, where it facilitates the reabsorption of glucose in the primary filtrate and converts it into ATP or glycogen (Figure 3)<sup>[72]</sup>. Under normal circumstances, the amount of glycosuria produced by the body after consuming a large quantity of carbohydrates is extremely small, mainly attributed to the filtering and reabsorption ability of SGLT2. SGLT2 inhibitors are a class of hypoglycemic drugs that inhibit the activity of sodium-glucose transport proteins on the luminal surface of the proximal tubule of the kidney, preventing glucose and Na<sup>+</sup> from normally entering the cells in the proximal tubule. In addition to lowering blood glucose and body weight, SGLT2 inhibitors improve insulin sensitivity and enhance pancreatic  $\beta$ -cell function, among other effects<sup>[39,73-75]</sup>.

Dapagliflozin and empagliflozin reduce HbA1c by an average of 0.66%<sup>[76]</sup>. SGLT2 inhibitors delayed the development of diabetes in four randomized trials involving 5,655 patients with prediabetes<sup>[77]</sup>. Moreover, dapagliflozin administration to obese and overweight individuals resulted in weight loss and marked reductions in blood lipids and glucose, including associated OGTTs<sup>[78]</sup>. These findings show that SGLT2 inhibitors are highly effective in preventing diabetes.

However, the increased glycosuria level caused by SGLT2 inhibitors increases the risk of fungal infections. In eight clinical trials, 3.5% of SGLT2 inhibitor users experienced ketoacidosis. SGLT2 inhibitors may also accelerate the loss of minerals from bone, thereby increasing the risk of fracture. Additionally, SGLT2 inhibitors facilitate Na<sup>+</sup> excretion and may cause adverse effects, such as acute kidney injury and renal function impairment<sup>[79,80]</sup>.

#### **10** *Characteristics of metformin, Glucagon-like peptide -1 receptor agonists, and sodium-glucose cotransporter 2 inhibitors use*

Prediabetes is treated with medications similar to those used for treating diabetes. Table 7 summarizes the dosages, main results, and related conclusions of the use of metformin, GLP-1 agonists, and SGLT2 inhibitors in individuals with prediabetes, non-diabetic individuals, and individuals with obesity.

#### ***Vitamin D***

Vitamin D plays an important role in maintaining Ca<sup>2+</sup> and phosphorus homeostasis, enhancing bone strength<sup>[83]</sup>, increasing bone growth<sup>[84]</sup>, reducing body weight<sup>[85]</sup>, participating in cell differentiation<sup>[86]</sup>, supporting immune function<sup>[87]</sup> (Figure 4), and delaying the progression of diabetes by lowering blood glucose and maintaining glucose metabolism homeostasis<sup>[88,89]</sup>. Randomized double-blind and placebo human trials have found that increasing and maintaining serum vitamin D levels reduce the risk of diabetes<sup>[90,91]</sup>.

Recent research indicates that vitamin D reduces the risk of diabetes and its related conditions *via* various mechanisms<sup>[92,93]</sup>. First, vitamin D promotes insulin synthesis and secretion by improving the function of pancreatic  $\beta$ -cells<sup>[94]</sup>. Second, vitamin D reduces insulin resistance and improves sensitivity by modulating insulin's target sites (liver, muscle, and adipose tissue)<sup>[95]</sup>.

Research indicates a marked reduction in the insulin resistance index (HOMA-IR) in a vitamin intervention group compared with a placebo group<sup>[96]</sup>. Additionally, a considerable improvement was found in the glycemic index with dosages of vitamin D >2,000 IU/day.

A study of baseline serum vitamin D concentrations in more than 6,000 patients with abnormal blood glucose levels found that individuals with high levels of serum vitamin D have a considerably reduced prevalence of elevated blood glucose and associated complications compared with those with serum vitamin < 25 nmol/L<sup>[97]</sup>. Another study in 2,423 individuals with prediabetes identified the lowest risk of diabetes in individuals with serum vitamin D levels of  $\geq 125$  nmol/L; serum vitamin D levels of 100–124 nmol/L reduced the risk of developing diabetes in some individuals<sup>[98]</sup>. Furthermore, 43 randomized controlled trials have reported that high doses of vitamin D ( $\geq 1,000$  IU/day) markedly reduced the risk of developing diabetes in 55,936 individuals with prediabetes<sup>[99]</sup>. Four trials, including 896 participants, have found that vitamin D supplementation effectively reduces the risk of prediabetes progressing to diabetes<sup>[91,100]</sup>.

Vitamin D use for therapeutic interventions may cause hypercalcemia<sup>[101]</sup>. Vitamin D is present in the body mainly as vitamins D<sub>2</sub> or D<sub>3</sub>, which are not biologically active. The inactive forms are catabolized and metabolized in the liver to 25-hydroxyvitamin D (ossified diol) and the kidney to 1,25-dihydroxy vitamin D (ossified triol), with both metabolites being biologically active<sup>[102]</sup>. Osteotriol is the main metabolite of vitamin D in the body and mediates Ca<sup>2+</sup> and phosphorus uptake. Excessively elevated osteotriol levels can lead to hypercalcemia and hyperphosphatemia, which increases the risk of

vascular calcification. Therefore, phosphate levels should be strictly monitored with vitamin D intervention.

Patients may also include vitamin D-enriched foods in their daily dietary regimen, such as those listed in Table 8<sup>[103]</sup>.

### *Chinese herbal medicine*

The use of herbal medicine for treating diabetes and prediabetes dates back to the Qin Dynasty (approximately 221 BC). Currently, herbal medicines are considered useful for preventing and treating diabetes and its complications <sup>[104]</sup>. The herbs used for diabetes and prediabetes generally have multiple effects, including counteracting hypoglycemia, reducing insulin resistance, reducing oxidative stress, lowering lipids, and regulating intestinal flora. Numerous Chinese herbal medicines are currently used for treating prediabetes, including Huang Lian, qingqianliu, mulberry leaf, *Astragalus*, guajia, lady's mantle, dendrobium, dry lotus, ginseng, wolfberry, pentaphyllum, and sanguisorba <sup>[105]</sup>. The functions and mechanisms of action of the herbs, including berberine, safranin, cyanotis, mulberry leaf, and *Astragalus*, in alleviating diabetes and prediabetic symptoms are briefly discussed here.

Berberine, a main active ingredient in Huanglian used in treating diabetes and prediabetes, plays crucial roles in treating hypoglycemia and other aspects. It positively affects mucin increase and promotes the improvement of intestinal mucosal morphology. Additionally, berberine can down-regulate <sup>9</sup> the expression of Toll-like receptor 4, nuclear factor kappa B (NF- $\kappa$ B), and tumor necrosis factor- $\alpha$ , alleviating the chronic inflammation caused by diabetes. Furthermore, it counteracts the reduction of intestinal microbial diversity caused by IGT; reduces FBG and HOMA-IR; improves liver and kidney function; reduces cholesterol, blood lipid, and high-density fatty acid levels; and increases the number of cupped cells and villi length in IGT rats <sup>[106,107]</sup>. Berberine induces accelerated closure of KCNH6 K<sup>+</sup> channels, decreases KCNH6 currents, prolongs glucose-dependent cell membrane depolarization, and promotes insulin secretion <sup>[108]</sup>. However, it exhibits an IC<sub>50</sub> of 713.57 mg/kg in acute toxicity tests



in rats [109]. Therefore, the use of berberine as an alkaloidal constituent of *Coptis chinensis* should be approached with due consideration of its toxicity.

Phellodendrin (PAL) is an active constituent of *Phellodendron* that improves blood glucose and insulin resistance levels in rats with IGT. Furthermore, PAL ameliorates the defective insulin secretion in insulinoma cells induced by chondroitin (PA) *via* the c-Jun N-terminal kinase signaling pathway. It also extensively inhibits PA-induced cell-induced  $\beta$ -cell apoptosis[110]. However, PAL elicits toxic effects with an IC<sub>50</sub> of 1,533.68 mg/kg in acute toxicity tests in rats[109]. Accordingly, attention to dosage is required in PAL use for prediabetes prophylaxis[111].

Cycads have various therapeutic properties, including hypoglycemic, hypolipidemic, hypotensive, anticancer, anti-fatigue, and antioxidant effects[112,113]. *Cyanus* was used in ancient times to treat diabetes[114–116]. Cyanidin improves insulin secretion by reducing apoptosis of pancreatic  $\beta$ -cells, reducing excessive oxidative stress in the pancreas, and maintaining the balance of glucose and lipid metabolism in the liver, thereby regulating blood glucose and lipid regulatory homeostasis[119]. *Cryptococcus* can also relieve hyperglycemic symptoms by modulating the intestinal microflora[120,121]. *Cyclocarya paliurus* is a traditional medicinal plant with various active effects; however, its safety issues should not be overlooked. Rats have shown good tolerance in acute toxicity studies; however, adverse changes in hematology, serum chemistry, urinalysis parameters, organ weights, and histopathology occur. Currently, *C. paliurus* is regarded as safe for use in the treatment of prediabetes[122].

Mulberry (*Morus alba*) is an Asian medicinal plant with roots, fruits, and seeds used to lower glucose levels, reduce liver damage, and improve oxidative stress[123,124]. Flavonoids, polysaccharides, and alkaloids are key active components in mulberry leaves that alleviate symptoms of hyperglycemia. Mulberry leaf extract intervention in mice with IGT reduces insulin resistance and IGT while improving glucose uptake in a hepatocyte islet resistance model[125]. *Morus alba* extract considerably improves glucose lipid levels, islet function, and insulin resistance index. It also substantially inhibits PA-induced apoptosis and markedly activates the AMPK/mTOR signaling pathway,



inducing islet cell autophagy and improving the functional utilization of islet cells<sup>[125,126]</sup>. The aqueous extract of *M. alba* downregulates the expression levels of relevant inflammatory factors, ameliorating chronic inflammation. Additionally, *M. alba* eliminates oxidative stress caused by IGT by modulating the advanced glycation end-products (AGEs)/receptor of advanced glycation end-products (RAGE)/ NADPH oxidase 4 (Nox4)/nuclear factor kappa-B (NF-κB) signaling pathway<sup>[127]</sup>. Importantly, ensuring the safety of mulberry leaves is crucial due to the abundance of biologically active phytochemicals and their many beneficial components. Acute toxicity, subacute toxicity, and genotoxicity studies in rats have shown no mortality or abnormal behavioral changes; no parameter changes in blood, biochemistry, or histopathology; and no mutagenic activity in the Ames assay. These findings weaken the claim that the aqueous extract of mulberry leaves may induce chromosomal aberrations or sperm abnormalities<sup>[128]</sup>. Therefore, the medicinal use of the aqueous extract of mulberry leaves is considered safe.

*Astragalus membranaceus* has a long history of medical applications in China, including tonifying qi, lowering lipid and blood pressure levels, nurturing the heart, and regulating blood glucose<sup>[129,130]</sup>. Moreover, flavonoids of *A. membranaceus* regulate intestinal microflora, reduce FBG, and improve brain damage caused by IGT<sup>[131]</sup>. Water-soluble *A. membranaceus* polysaccharides considerably reduce blood glucose levels and the insulin resistance index. They enhance glucose intolerance; improve insulin resistance in mice; and reduce oxidative stress, inflammation, and liver injury, while increasing the concentration of short-chain fatty acids in the intestinal flora. Notably, they augment the levels of *Allobaculum*, *Lactobacillus*, *Akkermansia*, *Faecia*, *Akkermansia*, and *Faecalibaculum* in the intestinal flora of mice with IGT<sup>[132,133]</sup>. These functions have positive implications for alleviating symptoms associated with diabetes<sup>[134]</sup>. Unfortunately, studies on the toxicity of *A. membranaceus* are limited, and toxicology tests are required before considering it as an intervention for prediabetes.

## **BEHAVIORAL INTERVENTION**

In addressing prediabetes, obesity is a key factor. To delay diabetes onset, increasing exercise intensity and duration is crucial. For prediabetic patients, a weekly increase of 150 minutes in exercise or 30 minutes daily can significantly lower the fasting glycemic index<sup>[135]</sup>. Six months of high-intensity exercise effectively improves oral glucose tolerance<sup>[136]</sup>, and 20 wk of sustained exercise normalizes blood glucose levels<sup>[137]</sup>. A Meta-analysis confirms that both aerobic and resistance training, individually or combined, benefit insulin resistance and glycemic control in prediabetic patients<sup>[138]</sup>.

Enhancing behavioral interventions requires a comprehensive, adaptable strategy that accounts for patient preferences, risks, and comorbidities, ensuring long-term adherence. This strategy should include building supportive relationships that encourage healthy behaviors, timely plan adjustments based on patient progress, and incorporating incentives for sustained motivation and adherence<sup>[139]</sup>.

### **DIETARY INTERVENTION**

A high-calorie diet contributes to prediabetes development. Epidemiologic evidence supports increasing intake of non-starchy vegetables, fruits, and whole grains<sup>[140]</sup>, while limiting added sugars to effectively reduce glycated hemoglobin, fasting glycemic index, serum insulin, insulin resistance, cholesterol levels, body weight, and BMI<sup>[141]</sup>. This approach also lowers type 2 diabetes risk<sup>[142]</sup>. Early time-restricted feeding (eTRF), involving a 6-hour eating window ending by 3 p.m., improves insulin sensitivity,  $\beta$ -cell responsiveness, blood pressure, oxidative stress, and appetite within 5 wk, aiding diabetes prevention<sup>[143]</sup>. This study aims to concisely highlight the importance of dietary protein and fiber in mitigating prediabetes.

### **PHARMACOLOGICAL AND LIFESTYLE INTERVENTIONS**

Pharmacologic and lifestyle interventions can be combined for the prevention of diabetes. Metformin is the most commonly used drug in combination with lifestyle interventions. The administration of metformin (500–2,000 mg/day) combined with

exercise has improved insulin sensitivity in prediabetic patients<sup>[54]</sup>. However, this combination does not offer an advantage<sup>[144]</sup> and may even diminish the glucose-lowering effects of exercise<sup>[145]</sup> compared with metformin alone (1,000 mg twice daily) and exercise training alone.

## **DISCUSSION**

Diabetes has a high incidence with a low reversal rate. Prediabetes, a common precursor often accompanied by microvascular complications like retinopathy, cardiovascular disease, and other issues, underscores the importance of effective intervention and management to slow or even prevent the development of diabetes.

Unhealthy lifestyles play a pivotal role in prediabetes development. Achieving complete remission of prediabetes necessitates the long-term maintenance of a healthy lifestyle. A combination of a nutritious diet and increased physical activity plays a crucial role in preventing or delaying the onset of diabetes and its complications. While lifestyle interventions are effective in the short term, their long-term efficacy is limited. Therefore, pharmacological interventions become necessary. These interventions can correct glucose homeostasis dysregulation, delay diabetes progression, and control glucose and lipid metabolism disorders. Common pharmacological interventions for prediabetes include metformin, GLP-1R agonists, SGLT2 inhibitors, vitamin D, and Chinese herbal medicine. These drugs have multifaceted effects, including blood sugar regulation, improved insulin sensitivity, and reduced insulin resistance.

Current treatments for prediabetic patients predominantly consist of lifestyle and pharmacological interventions. However, patient adherence to lifestyle interventions is often challenging to maintain in the long term, and a single lifestyle change is typically insufficient to extensively improve glycemic regulation. In contrast, a single pharmacological intervention can promptly lower blood glucose levels and enhance insulin sensitivity, yet prolonged use may lead to drug resistance over time. Combining lifestyle interventions with appropriate medication, as opposed to monotherapy, can yield a more favorable therapeutic outcome by promoting sustained weight loss,

normal blood glucose control, pancreatic islet cell repair, and improved insulin sensitivity. Integrating lifestyle and pharmacological interventions is likely to be more acceptable to prediabetic patients and aligns with current treatment trends. Furthermore, the prevention and management of prediabetes take precedence over treating diabetes. Regular monitoring of daily blood glucose, weight, and medical parameters enables timely diabetes detection and disease progression control. Safe and effective interventions for prediabetes remain a necessity. Future efforts should focus on improving standardized prediabetes diagnosis to facilitate early detection, management, and treatment of prediabetic patients. The integration of pharmacological and lifestyle interventions is poised to become a new direction in prediabetes treatment.

## **CONCLUSION**

This paper provides a comprehensive overview of the mechanisms behind prediabetes development and its associated therapeutic drugs. Prediabetes is significantly influenced by unhealthy lifestyles. To achieve complete remission, it is crucial to maintain a healthy lifestyle, including a balanced diet and regular physical activity. These practices are key in preventing or delaying the onset of diabetes and its complications. While lifestyle changes are effective short-term, their long-term efficacy is limited, making pharmacological treatments essential. Treatments such as metformin, GLP-1R agonists, SGLT2 inhibitors, vitamin D, and Chinese herbal medicine play a pivotal role in regulating glucose homeostasis, decelerating diabetes progression, and controlling glucose and lipid metabolism disorders. They also help regulate blood sugar levels, improve insulin sensitivity, and reduce insulin resistance.

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