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Metformin: New Preparations and Nonglycemic Benefits

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Abstract Metformin has been widely used for over 5 decades. New preparations have been developed for possible enhancement of efficiency, tolerability, and pleiotropic nonglycemic effects. Extended-release metformin has contributed to adherence and improved gastrointestinal tolerability. Delayed-release metformin acts in the lower gastrointestinal tract and exerts glucose-lowering effects at lower plasma metformin levels, which might suggest use of this biguanide in patients with chronic kidney disease. Metformin is also known to have numerous nonglycemic effects. Results of the UK Prospective Diabetes Study indicate improvements in cardiovascular outcome and reduced total mortality independent of glycemic control. Anticancer effects of metformin have been discussed and many clinical trials are on-going. Metformin is noted for its beneficial effects on lifespan extension and on disorders due to increased insulin resistance. Further investigations, including randomized control trials in nondiabetic individuals, are required to demonstrate the nonglycemic effects of metformin.

Keywords Metformin · Metformin XR · Metformin DR · Nonglycemic effect · Anticancer effect · Longevity

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Introduction

Metformin is a widely used oral glucose-lowering drug for type 2 diabetes (T2DM) and is recommended as a first-line drug in recent treatment guidelines of the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) [1]. The use of biguanide as a first-line drug depends on evidence showing that metformin reduces incidence of cardiovascular events as well as total mortality, in particular in mega-trials of T2DM such as the UK Prospective Diabetes Study (UKPDS) [2, 3]. Metformin is derived from the plant *Galega officinalis* (French lilac), a plant traditionally employed in Europe as a drug for diabetes (DM) treatment [4, 5]. In 1950, Stern et al discovered the clinical usefulness of metformin, and it was introduced into treatment of T2DM in 1957. Since then, the same preparation of metformin has remained in clinical use for over five decades [6].

The main target tissue of metformin is liver and its major effect is decreasing hepatic glucose output, largely due to the suppression of gluconeogenesis, which leads to lower fasting blood glucose levels without insulin stimulation and weight gain [7]. Metformin has an inhibitory effect on mitochondrial complex I, inhibition of which has been found to increase the AMP/ATP ratio [8, 9]. The altered cellular energy status induces activation of AMP-activated protein kinase (AMPK), a serine/threonine kinase, and acts as an energy sensor [10]. Zhou et al demonstrated in 2001 that the suppressing effect of metformin on hepatic gluconeogenesis is mediated by activation of AMPK [11]. Since then, various molecular mechanisms of metformin action have been proposed one after another. Shaw et al reported that liver kinase B1 (LKB1), an upstream kinase of AMPK, participates in metformin action by activation of AMPK and regulation of gluconeogenic enzymes [12]. AMPK-independent mechanisms are also proposed.

Miller et al reported a suppressing effect of hepatic glucagon signaling via inhibition of adenylyl cyclase activity that participates in metformin action [13]. Madiraju et al reported that metformin inhibits mitochondrial glycerophosphate dehydrogenase (mGPD), a glycerophosphate shuttle enzyme, to exert a suppressing effect on hepatic gluconeogenesis [14]. Besides the glucose-lowering effects, many nonglycemic effects of metformin have been reported, including endothelial function and cell proliferation [5–7, 15]. Some nonglycemic effects may be due to mechanisms in common with those of the glucose-lowering effects. Metformin inhibits mitochondrial complex I in cancer cells and reduces tumorigenesis [16]. Activation of AMPK by metformin stimulates endothelial nitric oxide synthase (eNOS) activity, which exerts a direct effect on endothelial protection in T2DM [17]. Metformin has inhibitory effects on mTOR signaling and suppresses cell proliferation via AMPK-dependent or AMPK-independent manner [18].

Recently, new preparations of metformin have been developed for possible improvements in efficiency and tolerability, expanding the clinical indications and other pleiotropic nonglycemic effects [5, 6, 19, 20••, 21, 22•] (Table 1). The extended-release formulation of metformin (metformin XR) is already in clinical use, and this formulation enables slower drug absorption in the upper gastrointestinal (GI) tract, which provides a once-daily dosing option [5, 6]. Development of delayed-release metformin (metformin DR) is in phase II clinical trials, and this formulation was developed to maximize gut-based mechanisms of metformin action by targeting the drug to the ileum [19, 20••, 21, 22•]. In this review, we discuss the new preparations of metformin and their mechanisms of action. We also discuss the nonglycemic effects of metformin such as improvement in cardiovascular outcomes, anticancer effects, and longevity, and then introduce the growing evidence on the mechanisms for these effects.

Metformin Immediate-Release

The conventional type of metformin preparation, immediate-release (IR), has been used for over 5 decades, and requires 2- or 3-times-daily dosing, which inhibits drug compliance and results in a high frequency of GI side effects that inhibits the tolerability [6, 22•] (Table 1). The main target of metformin was believed to be the liver [7]. On the other hand, reports [23, 24] that short-term intravenous metformin administration is less effective than oral administration in rats and humans suggest that the gut may be important in the glucose-lowering action of metformin. Metformin has a number of actions within the gut [22•]. Metformin increases glucose uptake, anaerobic glucose utilization, and lactate production in the intestine. In addition, metformin increases the secretion of enteroendocrine L-cell products glucagon-like peptide 1 (GLP-1) and peptide YY, and influences the gut-brain axis, bile acid metabolism, and the gut microbiome [25–29]. Each of these has been proposed as a contributing factor in the direct or indirect glucose-lowering effects of metformin. However, metformin IR is almost always absorbed in the upper GI tracts and so cannot have generally beneficial gut effects.

Metformin XR

Metformin XR (Glucophage XR/Merck Serono, Geneva, Switzerland and Bristol- Myers Squibb, New York, NY) is based on a dual hydrophilic polymer matrix system that meters metformin release over the dosing interval by means of diffusion [6, 30–32]. Metformin XR expands after uptake of fluid, which enables prolongation of gastric residence time and leads to slower drug absorption in the upper gastrointestinal tract (Table 1). Pharmacokinetic studies show that absorption of metformin XR is slower than that of metformin IR, with a maximum plasma concentration of 7 h vs 3 h [32]. In addition, the extent of absorption of metformin XR given

Table 1 Characteristics of the different preparations of metformin

Class	Administration	Costs	Pharmacokinetics	Mechanism of Action and Characteristics
Immediate release (IR)	BID or TID	Low	Acute drug absorption in the upper GI tract	Suppressing hepatic gluconeogenesis
			Maximum plasma concentration: 3 h	GI side effects
Extended release (XR)	BID or QD	Slightly high compared with IR	Slower drug absorption in the upper GI tract	Suppressing hepatic gluconeogenesis
			Maximum plasma concentration: 7 h	Lower frequency of GI side effects
Delayed release (DR)	QD	- (Phase II)	Bypassing the upper GI tract and targeting to the ileum	Gut-based mechanisms such as GLP-1 and PYY secretions
			Maximum plasma concentration: 10 h	Similar glucose-lowering efficacy with lower plasma concentrations
				Possible indication for patients with renal impairment

BID twice a day; *TID* three times a day; *QD* once daily; *GI* gastrointestinal.

once daily in healthy volunteers is similar to that when given twice daily at the same total daily dose, as measured by area under the plasma concentration-time curve [33]. A prospective, open label study assessing the effectiveness of metformin XR on blood glucose levels (hemoglobin A1c, fasting blood glucose, and postprandial blood glucose) showed no significant differences by switching to metformin XR [34]. The frequency and severity of GI side-effects, the principal tolerability issue with metformin, is lower with the metformin XR than with metformin IR [35]. Open label trials in Chinese patients showed that incidence rates, severity, and duration of GI side-effects by metformin XR show no difference between overweight/obese patients and patients of normal weight [36], which may indicate that metformin XR can be useful in East Asian as well as Western patients, who generally have greater obesity [37, 38]. Metformin XR use is associated with increased adherence compared with that of the metformin IR [5, 39]. The cost of metformin XR is slightly higher compared with metformin IR. Nevertheless, this drug is extremely low costs compared with other types of glucose-lowering agents for patients with T2DM patients. In summary, this formulation enables slower drug absorption in the upper GI tract, which provides a once-daily dosing option, and the frequency and severity of GI side-effects are lower with metformin XR than with metformin IR.

Other types of once-daily metformin such as glumetza (Depomed, Inc, Newark, CA) are approved and also provide effective and well-tolerated glycemic control [40]. Once-daily formulations of metformin facilitated development of metformin-based combination tablets. Metformin XR is available in combinations with all of the major classes of oral glucose-lowering agents such as DPP4 inhibitors [41]. These formulations also contribute to increased compliance.

Metformin DR

Metformin DR has been designed by Elcelyx Therapeutics (San Diego, CA) (NewMet), and comprises a metformin IR hydrochloride (HCl) core overlaid with a proprietary enteric coat, which includes eudragit polymers and other commonly used excipients [22•, 42••]. The enteric coat delays disintegration and dissolution of the tablet until it reaches pH of 6.5 in the distal small intestine and beyond, thus bypassing the major sites of metformin absorption. Metformin DR was developed to maximize gut-based mechanisms of metformin action by targeting the drug to the ileum, where the density of L-cells is high [20••, 22•, 42••] (Table 1). Clinical studies using metformin DR highlights the ileum as a site of uptake and as an important site of action of metformin in lowering blood glucose. Compared with metformin IR or metformin XR, the bioavailability of metformin DR is lower, yet its glucose-lowering efficacy is similar despite the lower systemic metformin exposure [42••]. With regard to the plasma metformin concentrations and bioavailability after administration of a single daily dose, patients using metformin DR 1000 mg are at about 50% compared with those using XR, but the clinical effects on lowering blood glucose levels after 4 weeks are similar [42••]. In addition, despite the extent of systemic metformin exposure reduced to 45% by twice-daily 1000 mg metformin DR compared with that by twice-daily 1000 mg metformin IR, both treatments resulted in similar increase in gut hormones such as GLP-1 and PYY [43••].

Since the US Food and Drug Administration (FDA) approved metformin in 1995, its labeling has included a contraindication against its use in some patients with renal disease or dysfunction. For this reason, metformin-containing medicines using both metformin IR and metformin XR were contraindicated in patients with moderate to severe renal impairment. However, recent publications show that metformin may be safely used in patients with mild to moderate renal impairment [44–47]. For example, in a large cohort study in Sweden, no increased risk of all-cause mortality, acidosis/serious infection, or cardiovascular disease were found in patients with glomerular filtration rate (eGFR) 30–45 mL/min/1.73 m^2 [47]. In the subgroup analysis of Reduction of Atherothrombosis for Continued Health (REACH) Registry in patients with atherothrombosis, the mortality rates were reduced by the use of metformin in patients with an estimated eGFR of 30 to 60 mL/min/1.73 m^2 (the adjusted hazard ratio; 0.64; 95% CI, 0.48–0.86; $P = 0.003$) [46]. In 2016, the FDA has revised its warnings regarding use of metformin in certain patients with chronic kidney disease (CKD), requiring manufacturers to revise the labeling of metformin-containing drugs to indicate that these products may be safely used in patients with mild to moderate renal impairment (eGFR between 30 and 60 mL/min/1.73 m^2) [48]. The FDA also recommended that the measure of kidney function used to determine whether a patient can receive metformin be changed from one based on a single laboratory parameter (blood creatinine concentration) to one that provides a better estimate of kidney function in patients with CKD (ie, eGFR).

A potential advance provided by metformin DR may be usage of biguanide for patients with CKD and those at higher risk of lactic acidosis [21]. However, the details of the efficacy and safety profile of metformin DR relative to existing IR or XR formulations remain to be confirmed [20••, 21, 49]. Efficacy and safety studies of metformin DR vs placebo or glucophage are now planned in the patient with renal impairment as a phase III trials in patients with renal impairment. In summary, the delivery of metformin to the lower bowel with metformin DR resulted in a glucose-lowering efficacy comparable to that of metformin XR, but at lower dose and significantly lower systemic exposure, which has a potential to be used in T2DM patients with CKD. Metformin DR provides strong evidence for the efficacy of lower bowel-mediated mechanism of metformin action.

Effects of Metformin on Vascular Protection beyond Glycemic Control

In UKPDS, metformin had a robust effect on cardiovascular risk [2, 3]. Metformin treatment lowered risk of myocardial infarction (MI) by 39% compared with traditional treatments over a period of 10 years [2]. Subsequent trials have supported a beneficial role of metformin in protecting against cardiovascular complications of DM, including a 10-year follow-up of the original UKPDS trial [3]. These improved cardiovascular outcomes were not observed in patients randomized to receive intensive glycemic management with a sulfonylurea or insulin, demonstrating the potential of metformin to deliver improvements in cardiovascular outcomes independent of glycemic control [6, 15]. Based largely on the findings of UKPDS, metformin has emerged as the first line therapy for the treatment of T2DM (ADA and EASD) [1]. Diabetic patients in the Prevention of Restenosis with Tranilast and its Outcomes (PRESTO) Trial suggest that metformin treatment is associated with decreased rates of death and MI in diabetic patients undergoing percutaneous coronary intervention [50]. During 9 months follow-up, significant reductions were observed with metformin for any clinical event (adjusted risk reduction 28%, $P = 0.005$), MI (adjusted risk reduction 69%, $P = 0.002$), and all-cause mortality (adjusted risk reduction 61%, $P = 0.007$). Multivariate adjustment had little effect on odds ratios for any outcome parameter, and blood glucose level differences were not significant between groups, suggesting a nonglycemic effect of metformin on these clinical outcomes.

Many different mechanisms beyond glycemic control have been implicated in vascular protection induced by metformin, such as improvements in the inflammatory pathway, coagulation, oxidative stress, endothelial dysfunction, and hemostasis [5, 51–55]. Clinical data as well as data from animal studies support a direct protective action on the vascular endothelium by metformin. Patients treated with metformin show improved endothelial function as evaluated by flow-mediated vasodilatation [56]. Significant improvement in acetylcholine-mediated vasodilation also has been documented with short-term, 12-week protocol of metformin therapy. Davis et al showed a link between dose-dependent activation of AMPK by metformin and stimulation of eNOS activity; these findings shed light on the effect of metformin's direct endothelial protection in T2DM [17]. Metformin has also been found to exhibit anti-thrombotic properties in insulin-resistant models. Specifically, metformin counteracts the stimulatory effect of hyperinsulinemia on the production of plasminogen activator inhibitor 1 (PAI-1), a negative regulator of fibrinolysis implicated in blood clot formation [57]. There is also evidence suggesting that metformin exerts a cardioprotective effect against ischemia reperfusion injury following MI. Administration of metformin during the first 15 minutes of reperfusion has been shown to reduce MI size in hearts isolated from both diabetic and nondiabetic rats [58]. Ultimately, the evidence suggests that metformin exerts varied positive effects on the cardiovascular system, particularly in diabetic models.

Metformin and Cancer

Patients with DM have higher risk of cancers such as liver, pancreas, breast, and colon [59]; incidence is estimated to be about 1.2 times higher than that in nondiabetic individuals [60]. Patients with DM also have higher rates of cancer mortality [59]. Observational epidemiologic studies suggest that some antidiabetic medications could affect cancer risk; metformin has recently received much attention in this regard. Evans et al reported that metformin use in patients with T2DM may reduce the risk of cancer [61]. They investigated databases developed in Tayside, Scotland: a diabetes clinical information system (DARTS) and a database of dispensed prescriptions (MEMO) in 1993–2001, and the unadjusted odds ratio of cancer incidence for any exposure to metformin was 0.79 (95% CI; 0.67–0.93). Since then, numerous observational studies have reported a protective role for metformin against a variety of cancer types [62]. On the other hand, recent epidemiologic studies present conflicting conclusions. A meta-analysis of currently available randomized controlled trial data, consisting of 4039 abstracts, identifying 94 publications describing 14 eligible studies, does not support the hypothesis that metformin lowers cancer risk, and eligible trials also showed no significant effect of metformin on all-cause mortality [63]. Bodmer et al found that metformin did not alter the risk of lung cancer and that metformin was not associated with a decreased risk of colorectal cancer [64, 65]. Further investigations on the association between metformin and cancer risk are required to address the methodological issues, including prevalent user bias and time-related biases [66•].

Metformin also has been tried with some success in clinical use in chemotherapy [67,]. Thus, metformin's effectiveness has been verified in cancer treatment as well as in DM treatment. Preclinical studies demonstrated metformin's broad anticancer activity across a spectrum of malignancies. Presently, there are 55 ongoing clinical trials in various stages that are evaluating metformin as a monotherapy (11 trials, 20% of all ongoing trials using metformin as an anticancer agent) or in combination with cytotoxic chemotherapy (38 trials, 69%) and/or radiotherapy (6 trials, 11%) for the treatment of various types cancer such as breast, prostate, colorectal, pancreas, and lung [69•].

The molecular mechanisms proposed to underlie the protective effect of metformin against cancer are also attracting attention (Fig. 1). Insulin and insulin-like growth factor 1 (IGF-1) are known to promote tumorigenesis, and metformin may prevent this activity by reducing hyperinsulinemia and

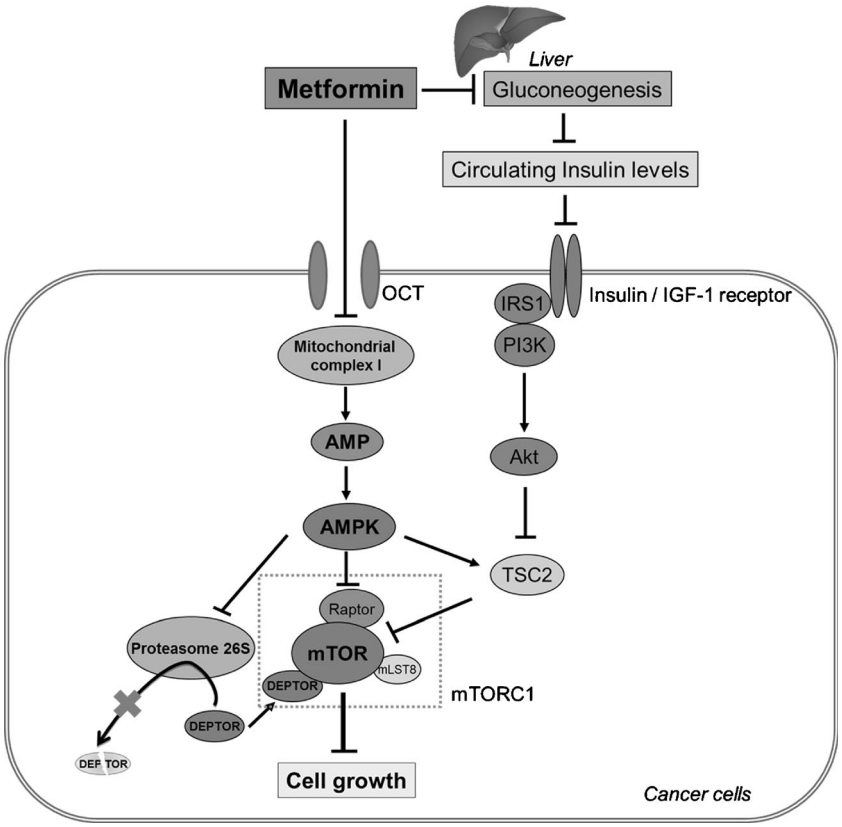

Fig. 1 Possible molecular mechanisms of the anti-cancer effect of metformin via mTORC1. The members of the OCT family play a role in intracellular uptake of metformin. Metformin inhibits oxidative phosphorylation by interacting with mitochondrial complex I, increases AMP levels, and activates AMPK, which leads to suppression of mTORC1 and cell growth. Suppression of mTORC1 is also mediated by reduction of the downstream effects of insulin and IGF-1 hormone receptor binding. *AMP* Adenosine monophosphate; *AMPK* AMP activated protein kinase; *mTORC1* Mammalian receptor of rapamycin; *TSC2* Tuberous sclerosis complex protein 2; *PI3K* Phosphoinositide 3 kinase; *Akt* Protein kinase B; *IRS-1* Insulin receptor substrate 1

lowering the levels of the signaling molecules [70]. Metformin also might modify inflammatory processes such as that of transcription factor nuclear factor-κB (NF-κB), which is known to play a role in cancer progression [71]. In addition, metformin has been found to enhance the immune response to cancer cells [72]. The molecular mechanism of metformin's anticancer effect was initially examined in breast cancer and prostate cancer cells [73–75]. In these cancer cell types, metformin was found to suppress cell proliferation by inhibiting mTOR signaling through AMPK activation [74, 75]. Phosphorylation of p70-S6 kinase (p70S6K), one of the downstream targets of mTOR, is known to be involved in cell proliferation in tumor cells [76]. The current accumulated findings suggest that both AMPK-dependent and AMPK-independent mechanisms via inhibition of the mTOR pathway could underlie anti-proliferative effects of metformin. Our group has reported a suppressing effect of metformin on mTOR signaling and cell proliferation in liver. We found that DEPTOR, an endogenous substrate of mTOR suppression [77], is involved in the suppressing effect of metformin on mTOR signaling and cell proliferation in human liver cancer cells, and that metformin increases the protein levels of DEPTOR via suppression of proteasome activity in an AMPK-dependent manner [78•]. Although the precise molecular mechanisms by which metformin affects various cancers have not been fully elucidated, suppression of mTOR signaling in AMPK-dependent and AMPK-independent pathways, along with energy metabolism aberration, cell cycle arrest, and apoptosis or autophagy induction, have emerged as crucial regulators in these processes.

Metformin and Longevity

Metformin also has drawn attention for its possible effect on extending lifespan. Studies using *C. elegans* and rodent models support this notion [7, 79, 80]. Cabreiro et al reported that metformin extends lifespan in *C. elegans* by altering microbial folate and methionine metabolism, depending on *E. coli* strain metformin sensitivity and the glucose concentration [81•]. Several studies have been performed in rodents suggesting an evolutionarily conserved pro-longevity role for biguanides. However, this effect varied depending on the strain and species of animal [82]. As a possible mechanism for the role of biguanides in aging, as a potential dietary restriction mimetic is proposed. Dietary restriction has long been known to increase health span [83–85]. Metformin mimics some of the benefits of calorie restriction, such as improved physical performance, increased insulin sensitivity, and reduced low-density lipoprotein and cholesterol levels without a decrease in caloric intake [86••]. At a molecular level, metformin increases AMPK activity and increases antioxidant protection, resulting in reductions in both oxidative damage accumulation and chronic inflammation [86••].

Results from several clinical mega-trials in patients with T2DM raise the possibility of long-term beneficial effects of metformin on human longevity. UKPDS shows long-term beneficial effects on health and survival [2, 3], including cardiac and all-cause mortality of patients on metformin compared with usual care. Reduction in all-cause mortality also was observed in patients with CKD and chronic heart failure (HF). A cohort study from the Swedish National Diabetes Registry reported that people in the registry with CKD stage-3 showed that metformin reduced all-cause mortality vs other agents by 13% [47]. The data from the observational REACH Registry in ~20,000 patients with T2DM indicate that metformin is associated with a significant, 24.0% reduction in all-cause mortality after 2-year follow-up [46]. REACH Registry showed a 31% lower HF mortality in individuals taking metformin compared with those not taking metformin. There is evidence that metformin is safe in patients with HF and associated with a reduction in newly incident HF and HF mortality. Retrospective analysis of 6185 patients with HF and DM treated in ambulatory clinics in Veterans Affairs medical centers and followed for 2 years showed a propensity score adjusted mortality in metformin-treated patients of 16.1% vs 19.8% in patients not treated with metformin (hazard ratio = 0.76; $P < 0.01$). HF hospitalization was no different between metformin treatment and no metformin treatment [87]. Shortly after metformin was approved for use in the US, HF was listed as a contraindication for its use in the package insert [88]. Nonetheless, it was noted that metformin was used frequently for the management of DM in HF patients [89]. Because of the availability of new information regarding the safety of metformin in patients with HF, the contraindication was subsequently withdrawn by the FDA [90]. A reducing effect on cancer incidence might contribute to extended longevity by metformin. On the other hand, in a more recent meta-analysis of randomized clinical trials of metformin therapy in individuals with and without DM, which includes the two UKPDS studies, Stevens et al [63] found no effects on all-cause mortality.

Other Nonglycemic Effects of Metformin

In addition to those mentioned above, many other nonglycemic effects of metformin have been reported, most of them associated with ameliorating effects on insulin resistance. Polycystic ovary syndrome (PCOS) is characterized as an endocrinological disorder due to increase in insulin resistance [91]. Metformin's role in insulin resistance in PCOS and a large number of studies support the use of metformin to improve ovulation and fertility rates and associated cardiovascular and metabolic abnormalities in women with PCOS [91, 92]. There are a large number of studies with evidence comparing metformin with control, lifestyle interventions, oral contraceptives, and clomiphene citrate, but uncertainty remains regarding the effectiveness of metformin in women with PCOS [93, 94]. Systematic review and meta-analysis of the head-to-head randomized controlled trials in PCOS patients with an ovulatory infertility and not previously treated suggest that the administration of metformin plus clomiphene citrate (CC) is not better than monotherapy (metformin alone or CC alone), whereas to date no specific recommendation can be given regarding the use of CC or metformin as first-step drug [95].

The use of metformin has shown potential as a preventive and therapeutic agent for a broad spectrum of conditions, including liver disease. Metformin has a number of biochemical effects that might suggest a benefit in treating chronic liver diseases, particularly in the context of insulin resistance and inflammation, such as that in nonalcoholic steatohepatitis (NASH)/nonalcoholic fatty liver disease (NAFLD). A meta-analysis has concluded that the addition of metformin may be an attractive option to patients who have prediabetes or DM, due to evidence of improvement in insulin resistance associated with NAFLD [96]. However, metformin has not demonstrated significant improvement in liver histology in randomized controlled studies, and therefore cannot be recommended for the treatment of NASH [97]. The use of metformin seems to be safe in patients with cirrhosis, and provides a survival benefit. Once hepatic malignancies are already established, metformin does not offer any therapeutic potential [98]. Based on our systematic review, there is insufficient evidence to recommend the use of metformin in the adjunctive treatment of NAFLD and hepatitis C. However, there is good evidence for a chemopreventive role against hepatocellular carcinoma among patients with DM and chronic liver disease, and metformin should be continued in patients even with cirrhosis to provide this benefit [98].

As insulin resistance is a major factor in the progression of DM, a possible preventive effect of metformin on the disease has been explored. Large, randomized trials have established a significant effect. The best evidence for a role of metformin in prevention of T2DM comes from the Diabetes Prevention Program (DPP) trial [99–101]. Lifestyle intervention and metformin therapy reduced DM incidence by 58% and 31%, respectively, compared with placebo. In a Chinese study, subjects with impaired glucose tolerance (IGT) randomly assigned to receive either low-dose metformin (750 mg/d) or acarbose (150 mg/d) in addition to lifestyle intervention were compared with a control group receiving only lifestyle intervention. Treatment with metformin or acarbose produced large, significant, and similar risk reductions of new onset T2DM of 77% and 88%, respectively, both of which were larger than when treated with lifestyle intervention alone [102]. Thus, efficacy in DM prevention and a good safety profile may spur future examination of metformin for DM prevention in high-risk subjects.

Adverse Events

The most life-threatening adverse event (AE) is metformin-associated lactic acidosis. However, the reported incidence of lactic acidosis in clinical practice has proved to be very low (<10 cases per 100,000 patient-years) [21]. GI intolerance occurs quite frequently and this AE induces symptoms such as abdominal pain, flatulence, and diarrhea. Most of these effects are transient; however, as many as 5% of patients do not tolerate even the lowest dose [103]. Moreover, patients on long-term metformin therapy were found to be at risk of anemia; this may be due to a metformin-related vitamin B12 reduction [104]. It is reported that 30% of patients receiving long-term metformin treatment experienced malabsorption of vitamin B12, with a decrease in serum vitamin B12 concentration of 14% to 30% [105]. Vitamin B12 deficiency has been related with dose and duration of metformin use and occurs more frequently among patients taking the drug for more than 3 years and in higher doses [105]. Thus, patients treated with metformin may benefit from vitamin B12 supplements [106].

Conclusions

Among the new preparations of metformin, metformin XR is in clinical use and has been found to be effective when administered either once-daily or twice-daily, a regimen that also contributes to adherence. Metformin XR improves GI tolerability with marked reductions in diarrhea and nausea. Metformin DR was developed to maximize gut-based mechanisms of metformin action by targeting the drug to the ileum. Similar glucose-lowering effects have been observed with the use of metformin DR, despite the lower plasma concentration compared with XR, indicating that metformin DR may be a useful biguanide in patients with CKD and at higher risk of lactic acidosis. Regarding the nonglycemic effects, the potential of metformin to deliver improvements in cardiovascular outcomes independent of glycemic control found in UKPDS suggested the presence of additional cardioprotective mechanisms with this agent. Although metformin has received much attention regarding its anticancer effect, some recent epidemiologic studies exhibit conflicting conclusions. Prospective clinical trials involving metformin in chemoprevention and treatment of cancer now number in the hundreds. Metformin also has been given much attention for its possible extension of lifespan in humans. Reductions in all-cause mortality in clinical trials were observed in patients with CKD and chronic HF, which might expand the indications for metformin in disorders presently thought to be contraindications. New preparations of metformin have intriguing potentials in nonglycemic effects as well tolerability and efficacy.

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Compliance with Ethical Standards

Conflict of Interest Nobuya Inagaki received research grants from Astellas Pharma Inc., Taisho Toyama Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Company Ltd., Daiichi Sankyo Company, Ltd., MSD, Sanofi, Dainippon Sumitomo Pharma Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Eli Lilly Japan K.K., Shiratori Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., JT, Pfizer, Nippon Boehringer Ingelheim Co., Ltd., Sanwa Kagaku Kenkyusho Co., Ltd., Kissei Pharmaceutical Co., Ltd., and Japan Diabetes Foundation. Yoshihito Fujita declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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