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COMMENTARY

Metformin: clinical topics and new mechanisms of action

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Metformin is a widely used orally administerd glucose-lowering drug for type 2 diabetes 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]. Metformin is derived from the plant *Galega officinalis* (French lilac) traditionally used in Europe for diabetes treatment [2]. The main target tissue of metformin is the liver, and its major effect is to decrease hepatic glucose output largely by suppressing gluconeogenesis, which leads to lower fasting blood glucose levels without insulin stimulation and weight gain [3]. Despite metformin being first introduced as a treatment for type 2 diabetes in 1957, it's mechanism of action is not yet fully understood.

In recent decades, new mechanisms of metformin action have been proposed, along with improvements in molecular research techniques. Metformin has an inhibitory effect on mitochondrial complex I, inhibition of which increases the adenosine monophosphate/adenosine triphosphate (AMP/ATP) ratio [4, 5]. The altered cellular energy status induces activation of AMP-activated protein kinase (AMPK), a serine/threonine kinase, and acts as an energy sensor [6]. Zhou et al. demonstrated that the suppressing effect of metformin on hepatic gluconeogenesis is mediated by AMPK activation [7]. Various mechanisms by which metformin activates AMPK are proposed, some of which are mediation due to increased AMP by inhibition of AMP deaminase, and mediation by activation of endothelial nitric oxide synthase (eNOS) [8, 9]. Shaw et al. reported that liver kinase B1 (LKB1), an upstream kinase of AMPK, participates in metformin action by activating AMPK and regulating gluconeogenic enzymes [10]. 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 [11]. Madiraju et al. reported that metformin inhibits mitochondrial glycerophosphate dehydrogenase (mGPD), a glycerophosphate shuttle enzyme, to exert a suppressing effect on hepatic gluconeogenesis [12].

Although the liver is considered the main target tissue of metformin, recent basic and clinical studies indicate the gut as an important site of its action, as short-term metformin administration IV is less effective than oral administration in rats and humans [13]. Metformin performs a number of actions within the gut [14]. It increases glucose uptake, anaerobic glucose utilization, lactate production in the intestine; secretion of the enteroendocrine L-cell products glucagon-like peptide 1 (GLP-1) and peptide YY (PYY), and influences the gut–brain axis, bile acid metabolism, and gut microbiome. Each of these mechanisms has been proposed as a contributing factor in its direct and indirect glucose-lowering action.

Recently, new preparations of metformin have been developed for possible improvements in efficiency and tolerability, expanding its clinical indications. The conventional preparation, immediate release (IR), has been used for more than 5 decades and requires dosing two or three times daily, which inhibits drug compliance and results in a high frequency of gastrointestinal (GI) side

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effects, which inhibit tolerability [15]. The extended-release formulation (Metformin XR) is in use clinically and enables slower drug absorption in the upper GI tract using a once-daily dosing option, and the frequency and severity of GI side effects is lower [16]. Delayed-release metformin (Metformin DR) also provides a once-daily dosing option and was developed to maximize gut-based mechanisms of action by targeting the drug to the ileum [17, 18]. Metformin DR comprises a metformin IR hydrochloride (HCl) core overlaid with a proprietary enteric coat, which delays disintegration and dissolution of the tablet until it reaches pH of 6.5 in the distal small intestine and beyond, thus bypassing the usual, major sites of absorption. Clinical studies using metformin DR highlights the ileum as a site of uptake and as an important site of action 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 [19]. After a single daily doseof DR 1000 mg, plasma concentrations and bioavailability were ~50% compared with those using XR; however, clinical effects after 4 weeks were similar. In addition, while the extent of systemic metformin exposure is reduced by 45% with twice-daily DR 1000mg compared with twice-daily IR 1000 mg, both regimens result in a similar increase in gut hormones, such as GLP-1 and PYY [20]. A potential advance provided by metformin DR may be the use of biguanide for patients with chronic kidney disease (CKD) and those at higher risk of lactic acidosis [18]. Phase III efficacy and safety studies of DR vs. placebo or IR are now planned in patients with renal impairment.

The U.S. Food and Drug Administration (FDA) approved metformin for clinical use in 1995. At that time labeling included a contraindication for patients with moderate to severe renal impairment. Subsequently, studies found it could be safely used in patients with mild to moderate renal impairment [21, 22], and in 2016, the FDA revised its warnings accordingly to include patients with an estimated glomerular filtration rate (eGFR) between 30 and 60 ml/min/1.73 m^2 [23].

Metformin is also known to have numerous nonglycemic effects. In the UK Prospective Diabetes Study (UKPDS), metformin had a robust effect on cardiovascular risk [24, 25]. Improved cardiovascular outcome was not observed in patients randomized to receive intensive glycemic management with sulfonylurea or insulin, however, suggesting the potential of metformin to improve cardiovascular outcome independent of glycemic control. Based largely on the findings of UKPDS, metformin has emerged as the first-line therapy for treating type 2 diabetes (ADA and EASD) [1]. Clinical data and data from animal studies support a direct protective action on the vascular endothelium from metformin, and different mechanisms beyond glycemic control have been implicated: improvements in the inflammatory pathway, coagulation, oxidative stress, endothelial dysfunction, and hemostasis [3].

Patients with diabetes have a higher risk of liver, pancreas, breast, and colon cancers [26], with an incidence estimated to be about 1.2 times higher than in nondiabetic individuals [27]. Observational epidemiologic studies suggest that some antidiabetic medications might affect cancer risk; the anticancer effect of metformin has recently received much attention [3]. On the other hand, epidemiologic studies present conflicting conclusions, and a meta-analysis of available randomized controlled trial data does not support the hypothesis that metformin lowers cancer risk. Eligible trials also showed no significant effect of metformin on all-cause mortality [28]. Nevertheless, metformin has been tried with some success in clinical chemotherapy trials for treatment of various types of cancer, and many trials are ongoing, including for breast, prostate, colorectal, pancreas, and lung cancers [29].

Other nonglycemic effects of metformin have also been reported, most being associated with ameliorating effects on insulin resistance, such as polycystic ovary syndrome (PCOS) and nonalcoholic steatohepatitis (NASH)/nonalcoholic fatty liver disease (NAFLD) [15]. Further investigations and randomized controlled trials in nondiabetic individuals are required to demonstrate the nonglycemic effects of metformin.

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Compliance with ethical standards

Conflict of interest Yoshihito Fujita declares no conflict of interest.

Ethics policy This article does not report any studies with human or animal subjects that were performed by any of the authors.

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