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Antidiabetic and Pleiotropic Effects of Metformin Hydrochloride: A Review

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ABSTRACT: Metformin can cross the blood–brain barrier and reach a significant concentration in the central nervous system (CNS), causing pleiotropic effects . Although the data obtained are not always consistent, several studies have suggested the use of metformin in various diseases that affect SNC

KEYWORDS: metformin hydrochloride, antidiabetic, pleiotropic, diseases, CNS

I. INTRODUCTION

Metformin is a synthetic biguanide used as an antidiabetic drug in type 2 diabetes mellitus, achieved by studying the bioactive metabolites of *Galega officinalis* L. It is also used off-label for various other diseases, such as subclinical diabetes, obesity, polycystic ovary syndrome, etc. In addition, metformin is proposed as an add-on therapy for several conditions, including autoimmune diseases, neurodegenerative diseases, and cancer. Although metformin has been used for many decades, it is still the subject of many pharmacodynamic and pharmacokinetic studies in light of its extensive use. Metformin acts at the mitochondrial level by inhibiting the respiratory chain, thus increasing the AMP/ATP ratio and, subsequently, activating the AMP-activated protein kinase. However, several other mechanisms have been proposed, including binding to presenilin enhancer 2, increasing GLP1 release, and modification of microRNA expression. Regarding its pharmacokinetics, after oral administration, metformin is absorbed, distributed, and eliminated, mainly through the renal route, using transporters for cationic solutes, since it exists as an ionic molecule at physiological pH. In this review, particular consideration has been paid to literature data from the last 10 years, deepening the study of clinical trials inherent to new uses of metformin, the differences in effectiveness and safety observed between the sexes, and the unwanted side effects. For this last objective, metformin safety was also evaluated using both VigiBase and EudraVigilance, respectively, the WHO and European databases of the reported adverse drug reactions, to assess the extent of metformin side effects in real-life use.[1,2,3]

The involvement of the knee joint is the most common localization of the pathological process in osteoarthritis (OA), which is associated with obesity in over 50% of the patients and is mediated by mechanical, inflammatory, and metabolic mechanisms. Obesity and the associated conditions (hyperglycemia, dyslipidemia, and hypertension) have been found to be risk factors for the development of knee OA, which has led to the emerging concept of the existence of a distinct phenotype, i.e., metabolic knee OA. Combined assessment of markers derived from dysfunctional adipose tissue, markers of bone and cartilage metabolism, as well as high-sensitivity inflammatory markers and imaging, might reveal prognostic signs for metabolic knee OA. Interestingly, it has been suggested that drugs used for the treatment of other components of the metabolic syndrome may also affect the clinical course and retard the progression of metabolic-associated knee OA. In this regard, significant amounts of new data are accumulating about the role of metformin—a drug, commonly used in clinical practice with suggested multiple pleiotropic effects. The aim of the current review is to analyze the current views about the potential pleiotropic effects of metformin in OA. Upon the analysis of the different effects of metformin, major mechanisms that might be involved in OA are the influence of inflammation, oxidative stress, autophagy, adipokine levels, and microbiome modulation. There is an increasing amount of evidence from in vitro studies, animal models, and clinical trials that metformin can slow OA progression by modulating inflammatory and metabolic factors that are summarized in the current up-to-date review. Considering the

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contemporary concept about the existence of metabolic type knee OA, in which the accompanying obesity and systemic low-grade inflammation are suggested to influence disease course, metformin could be considered as a useful and safe component of the personalized therapeutic approach in knee OA patients with accompanying type II diabetes or obesity.

Osteoarthritis (OA) is the most common joint disease [1] that affects all joint structures with the development of progressive articular cartilage damage, synovial inflammation, and bony changes [2]. OA has complex pathogenesis that may manifest with different joint localization. However, a standardized approach is used in the different forms of OA, and established strategies according to the different pathogenetic mechanisms and phenotypes are lacking. Moreover, currently, there is no disease-modifying drug for OA, and the global results of treatment are unsatisfactory [1]. Combined therapeutic interventions that target specific underlying pathological processes of OA would likely have disease-modifying potential. Targeted and individualized treatment for a specific clinical case is the basis of the modern concept of personalized medicine. A new personalized approach to patients with different OA phenotypes may suggest the opportunity to slow down disease progression.

The pathogenesis of OA is complex with the involvement of different cell types (chondrocytes, synoviocytes, bone cells, inflammatory cells) and up-regulation of multiple mediators such as nitric oxide (NO), prostaglandin E2/PGE2, proinflammatory cytokines (interleukin/IL-1 β , TNF- α , IL-6), cartilage-degrading enzymes (matrix metalloproteinases (MMP) 1, 3, 9, and 13 that degrade collagen type II and “aggrecanases”, i.e., a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)-4 and -5 that degrade aggrecan) [3,4,5]. Increased expression of insulin-like growth factor/IGF, transforming growth factor/TGF- β in articular cartilage and in osteophytes has been also observed [6].

Pharmacological treatment for OA includes the use of non-steroidal anti-inflammatory drugs, analgesics, and symptomatic slow-acting agents (glucosamine, chondroitin, soy, avocado, and intra-articular hyaluronic acid). Although there is evidence that glucosamine and chondroitin have a chondroprotective effect and can slow the progression of OA, there is currently no drug registered as a disease-modifying agent in OA [7,8,9].

The involvement of the knee joint is the most common localization of the pathological process in OA that is associated with obesity in over 50% of the patients [4,5,6] and is mediated by mechanical, inflammatory, and metabolic mechanisms [1]. Obesity and the associated conditions (hyperglycemia, dyslipidemia, and hypertension) have been found to be risk factors for the development of knee OA, which has led to the emerging concept of the existence of a distinct phenotype, i.e., metabolic knee OA [10]. A younger age of onset and absence of OA with other localizations have been noted, as well as an increased level of adipokines in patients with radiologically confirmed knee OA and obesity [11]. In young patients with knee pain, other syndromes should be considered in the differential diagnosis, such as patellar tendinopathy, chondromalacia patellae, patellofemoral OA, pes anserine bursitis, plica syndrome, iliotibial band syndrome, etc. Plain radiography is indicated to rule out knee OA [12,13,14].

Interestingly, the increased risk of obese patients for the development of OA was suggested to be not only a consequence of the biomechanical load on weight-bearing joints but also of hand OA, which suggests an association with the action of systemic factors such as adipokines derived from the dysfunctional adipose tissue [3,15,16]. There is evidence that some adipokines, i.e., leptin and resistin, have catabolic effects on articular cartilage [17,18]. It is increasingly hypothesized that adipocytokines mediate the link between obesity and OA and have a negative effect on joint function and disease progression [10,11].

Combined assessment of markers derived from dysfunctional adipose tissue, markers of bone and cartilage metabolism, as well as high-sensitivity inflammatory markers and imaging, might reveal prognostic signs for metabolic knee OA. Interestingly, it has been suggested that drugs used for the treatment of other components of the metabolic syndrome may also affect the clinical course and retard the progression of metabolic-associated knee OA [1,19,20,21,22,23]. In

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this regard, significant amounts of new data are accumulating about the role of metformin—a drug, commonly used in clinical practice with suggested multiple pleiotropic effects [1,23].

The aim of the current review is to analyze the current views about the potential pleiotropic effects of metformin in OA. Metformin is a widely used biguanide with a good safety profile that is the first-line treatment for type II diabetes mellitus, especially in overweight and obese patients after the failure of diet [1,24]. Metformin is an extract of the plant *Galega officinalis* and has been used in clinical practice for more than 50 years [25]. Metformin has a glucose-lowering effect. In addition, it modulates inflammatory and metabolic factors and leads to weight loss and a decrease in the levels of plasma lipids [1]. The initial dose is 500–850 mg two or three times daily and could be gradually increased to the maximum daily dose of 1000 mg three times daily (3 g).

The most common adverse effects of metformin are gastrointestinal symptoms, i.e., increased bloating, flatulence, diarrhea, cramps, nausea, and vomiting [24,26], which in some cases may be avoided by a gradual increase in the dose. A serious adverse event is metformin-associated lactic acidosis, which in severe cases may require renal replacement therapy. However, this complication is rare, and its occurrence may be decreased by avoiding metformin administration in patients with a high risk of hypovolemia, sepsis, renal impairment, elderly patients with reduced renal capacity, hypoxic respiratory diseases, and heart failure. In addition, metformin use should be avoided preoperatively for 24–78 h as well as before intravenous injection of contrast media, as it may increase the risk of nephropathy. Another consideration for clinical practice is the development of vitamin B12 deficiency during metformin treatment and reduced folate levels [24,26]. The key advantage of metformin is that it does not cause hypoglycemia [27], including in normoglycemic patients [28].

Metformin is a hypoglycemic agent that inhibits liver gluconeogenesis, increases insulin sensitivity, promotes the uptake of glucose in peripheral tissues, i.e., skeletal muscles and fat tissue, and delays the intestinal absorption of glucose. It influences the incretin axis via an increase in the level of the glucagon-like peptide-1 that elevates insulin secretion and reduces the secretion of glucagon in response to glucose [25,29,30]. Metformin acts in an AMPK (adenosine monophosphate/AMP-activated protein kinase)-dependent and AMPK-independent pathway [30]. Metformin penetrates the mitochondrial inner membrane and directly inhibits the mitochondrial respiratory chain complex 1 [30,31]. It suppresses mitochondrial respiration, lysosomal-related pathways, and the expression of gluconeogenesis-related enzymes. It increases the level of AMP (AMP/adenosine triphosphate/ATP ratio) that activates AMPK [30]. AMPK modulates metabolism according to the energy demand and responds to changes in AMP [32]. It has been hypothesized that AMPK activity may support cartilage homeostasis, and decreased expression of AMPK was found in OA articular chondrocytes [33]. In this regard, AMPK could be a target for OA treatment. Mitochondrial injury is suggested to be associated with the pathological process in OA [31].

In mouse chondrocytes stimulated by IL-1 β to induce an OA model, decreased expression of sirtuin 3 was found. Sirtuin 3 protects mitochondria against oxidative stress, and its downregulation is associated with mitochondrial damage and oxidative stress due to the increased production of reactive oxygen species. In an in vitro model, Wang et al. (2016) have demonstrated that treatment with metformin increased sirtuin 3, decreased the production of reactive oxygen species in the mitochondria, and reduced the loss of cell viability [34].

In a cell culture of IL-1 β -induced ATDC5 cells, it has been demonstrated that metformin [7,8,9] blocks the NF- κ B pathway via activation of AMPK [35]. In OA, the chondrocytes shift to a degradative phenotype, in which NF- κ B triggers the secretion of MMPs (1,2,3,7,8,9,13) and aggrecanases. Osteoarthritic chondrocytes also express a variety of NF- κ B-mediated proinflammatory cytokines such as TNF- α , IL-1 β , IL-6, receptor activator of NF- κ B (RANK ligand/RANKL). NF- κ B mediates articular damage through the induction of nitric oxide, cyclooxygenase 2, and PGE2, which induce the synthesis of catabolic factors, cartilage inflammation, and chondrocyte apoptosis [36].

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Apart from its hypoglycemic effects in diabetes type 2, various pleiotropic effects of metformin have been suggested, i.e., cardiovascular protection, beneficial effects on obesity, musculoskeletal and reproductive diseases, cancer, and aging [27,30]

II. DISCUSSION

Cardiovascular disease (CVD) is a leading cause of mortality and morbidity among those with chronic diseases of aging as manifested by atherosclerosis.¹ However, age-related changes in blood vessels, such as senescence of vascular cells and the inflammatory milieu mediated by stimuli such as angiotensin II (Ang II) or a high-fat diet (HFD), can enable the development of atherosclerosis.²⁻⁷ Hence, therapeutic strategies targeting vascular senescence and, ultimately, atherosclerosis are of special interest.

Biguanides, notably metformin, have been used extensively as the first-line medication for treating type 2 diabetes mellitus (DM2) during the past 50 years.⁸⁻⁹ However, the mechanisms of action of metformin, especially those relevant to many of the observed benefits beyond its antihyperglycemic effects, are incompletely understood.⁹⁻¹⁰ The UK Prospective Diabetes Study (UKPDS) Group in 1998 reported the survival benefit and cardiovascular protection of metformin compared with other conventional treatments for DM2, including diet, sulfonylurea, and insulin.¹¹ While the cardiovascular benefits of metformin found in the UKPDS were not seen in a study with shorter follow-up periods, A Diabetes Outcome Progression Trial (ADOPT),¹² the vascular benefits of metformin have been further confirmed in a meta-analysis,¹³ as well as in a report of the Reduction of Atherothrombosis for Continued Health (REACH) Registry.¹⁴ In the REACH study, metformin was found to be advantageous even in patients with renal insufficiency or heart failure that were historically thought to be at higher risk of lactic acidosis, a side effect of biguanides.¹⁴⁻¹⁵ Moreover, several reports endorse metformin in contrast to phenformin, the first-generation biguanide, as a safe medication with no evidence of lactic acidosis in nondiabetic patients, even at an advanced age.¹⁶⁻¹⁸ Additionally, metformin has been suggested as a treatment for obesity,¹⁹⁻²⁰ a condition that is associated with increased mortality.²¹⁻²² Despite promising preclinical data as long ago as 30 years on the vasculoprotective effects of metformin even in the absence of diabetes,^{10,23-24} there is a paucity of information describing the cardiovascular benefits of metformin for nondiabetic patients who are at high risk of cardiovascular events. Thus, there is a need for further preclinical data to elaborate possible underlying mechanisms for such cardiovascular benefits of metformin. Here, we show, in an atherosclerotic-prone, nondiabetic mouse model, novel evidence of the protective role of metformin in attenuating atherosclerosis and/or vascular senescence induced by an HFD.

It is widely accepted that the antihyperglycemic effect of metformin occurs mainly through a mild and transient inhibition of the mitochondrial respiratory-chain complex-1,²⁵ which increases AMP:ATP ratios, leading to activation of AMP kinase. Activated AMP kinase switches cells from an anabolic to a catabolic state, resulting in inhibition of glucose, lipid, and protein synthesis while promoting the oxidation of fatty acids and glucose uptake associated with weight loss and lower triglyceride levels.⁹ This pathway has been confirmed in several cell types involved directly in metabolism and energy expenditure such as hepatocytes,²⁶ skeletal muscle cells,²⁷ and pancreatic cells.²⁸ However, there is little known on the effects of metformin on vascular cells that are directly involved in the processes of atherosclerosis.⁴ While there is evidence from clinical studies that metformin improves endothelial vascular reactivity²⁹⁻³⁰ and ameliorates hypertension,³¹⁻³² there is insufficient knowledge on underlying mechanisms. Also, metformin has been shown to decrease the extent of cardiac damage and improve survival in myocardial ischemia studies on nondiabetic murine models of heart failure, again with little knowledge on the underlying mechanism(s).³³⁻³⁴ Ang II signaling plays a critical role in regulating many of the stimuli and signals that govern vascular senescence and, ultimately, atherogenesis.³⁵ Ang II has been reported to accelerate senescence of vascular smooth muscle cells (VSMCs).³⁶ Indeed, several studies have shown that Ang II, through binding to Ang II type 1 receptor (AT1R), is involved in the progression of cardiovascular diseases including atherosclerosis, hypertension, cardiac hypertrophy, and heart failure.³⁷⁻³⁸ Furthermore, disruption or inhibition of the AT1R by Ang II receptor blockers promotes longevity in rodents.³⁹⁻⁴¹ Disruption of AT1R becomes even more clinically beneficial if we take into account that HFD upregulates

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AT1R.⁴² Here, we show that metformin decreases the expression of AT1R in the aortas of mice and attenuates vascular senescence and atherosclerosis induced by an HFD, suggesting that AT1R downregulation, at least in part, mediates the protective effect of metformin in the vascular system. These studies will further elucidate whether metformin can be used as a preventive therapy for patients at risk for or who have cardiovascular complications even in the absence of diabetes and suggest that metformin could have a broader effect in other age-related diseases.

To evaluate whether metformin can attenuate vascular senescence, we used Ang II, a strong stimulator of vascular aging and disease,³⁵ in an ApoE^{-/-} C57BL/6J mice model in which Ang II induces accelerated senescence of vascular cells.³⁵ Animals were treated daily with IP injections of metformin (100 mg/kg) or saline for 7 days and then infused with or without Ang II for an additional 10 days through the use of osmotic minipumps. We found that vascular senescence, measured as increased levels of senescence-associated β -galactosidase activity, and hypertension were induced by Ang II infusion. However, these effects of Ang II were not completely attenuated by metformin (Figure 1A and 1B). The effect of metformin was associated with a significant weight loss in both control and Ang II-treated groups (Figure 1C). Although metformin caused a reduction in plasma glucose levels in the control group, no significant differences in plasma glucose levels were observed in the Ang II-treated groups (Figure 1D). Further, no metformin-induced hypoglycemia was observed. Plasma lipid levels were relatively unchanged for total cholesterol and low- and high-density lipoprotein. Triglyceride levels, however, showed a non-statistically significant trend to be lower in metformin-treated groups compared with their control groups (Figure 1E through 1H).^[10,11,12]

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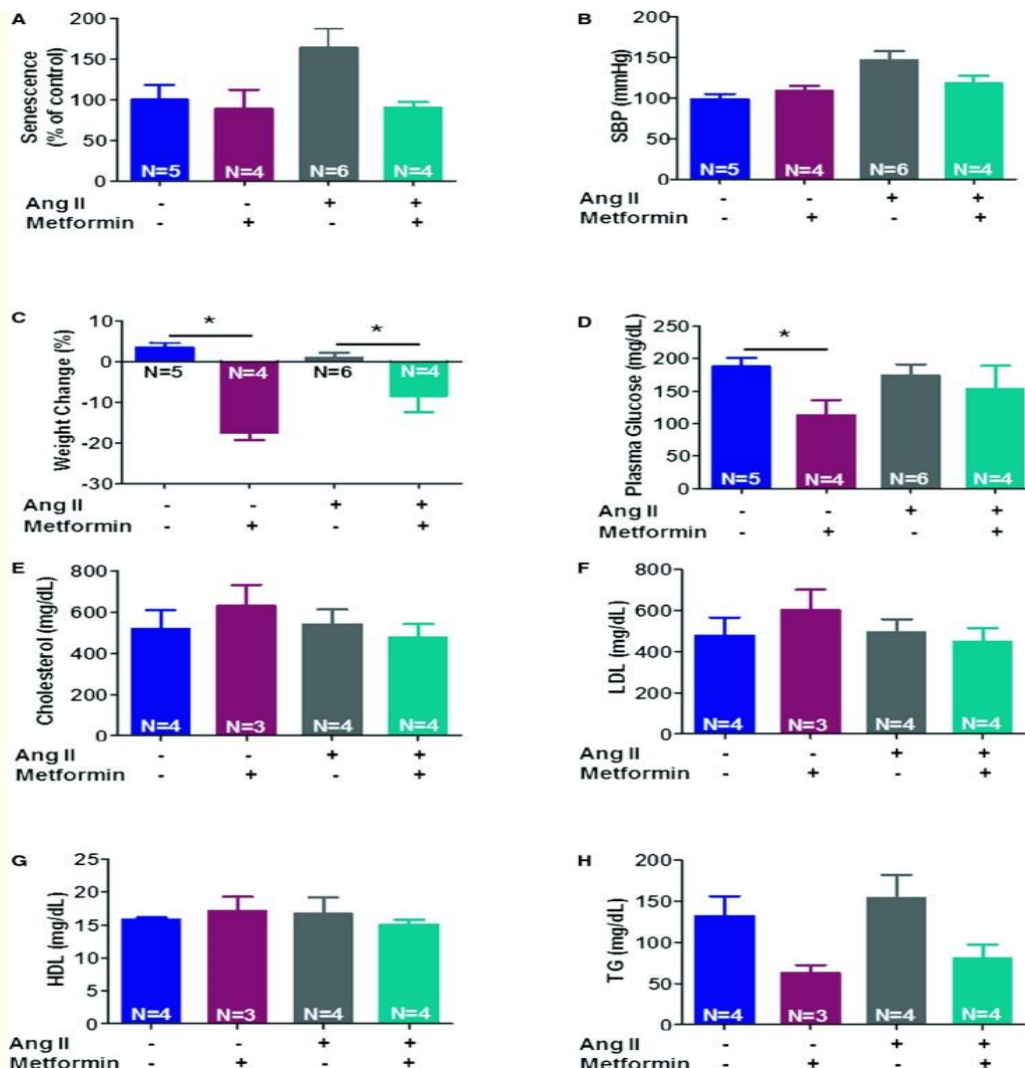


Figure 1.

Metformin causes weight loss and reduces blood glucose of ApoE^{-/-} C57BL/6J mice. Vascular senescence was evaluated using fluorescein di-β-d-galactopyranoside to perform senescence-associated β-galactosidase assay (A). Systolic blood pressure (SBP) was measured by using tail-cuff plethysmography method (B). Weight of animals was measured at the beginning and end of the study and weight changes were calculated and presented compared with the initial weights (C). Plasma glucose (D) and lipid profile (E through H) of animals were measured at the time of death (*P<0.05). HDL indicates high-density lipoprotein; Ang II, angiotensin II; LDL, low-density lipoprotein; TG, triglyceride.

III. RESULTS

Metformin, sold under the brand name Glucophage, among others, is the main first-line medication for the treatment of type 2 diabetes,^{[13][14][15][16]} particularly in people who are overweight.^[14] It is also used in the treatment of polycystic

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ovary syndrome.^[15] It is sometimes used as an off-label adjunct to lessen the risk of metabolic syndrome in people who take antipsychotics.^[17] Metformin is not associated with weight gain^[18] and is taken by mouth.^[15]

Metformin is generally well tolerated.^[19] Common adverse effects include diarrhea, nausea, and abdominal pain.^[15] It has a small risk of causing low blood sugar.^[15] High blood lactic acid level (acidosis) is a concern if the medication is used in overly large doses or prescribed in people with severe kidney problems.^{[20][21]} It also inhibits inflammation.^{[22][23]}

Metformin is a biguanide anti-hyperglycemic agent.^[15] It works by decreasing glucose production in the liver, increasing the insulin sensitivity of body tissues,^[15] and increasing GDF15 secretion, which reduces appetite and caloric intake.^{[24][25][26][27]}

Metformin was first described in scientific literature in 1922 by Emil Werner and James Bell.^[28] French physician Jean Sterne began the study in humans in the 1950s.^[28] It was introduced as a medication in France in 1957 and the United States in 1995.^{[15][29]} Metformin is on the World Health Organization's List of Essential Medicines,^[30] and is the most widely used medication for diabetes taken by mouth.^[28] It is available as a generic medication.^[15] In 2016, it was the second most commonly prescribed medication in the United States, with more than 91 million prescriptions.^{[31][32]}

Medical uses

Metformin is used to lower the blood glucose in those with type 2 diabetes.^[15] It is also used as a second-line agent for infertility in those with polycystic ovary syndrome.^{[15][33]}

Type 2 diabetes

The American Diabetes Association and the American College of Physicians both recommend metformin as a first-line agent to treat type 2 diabetes.^{[34][35][36]} It is as effective as repaglinide and more effective than all other oral drugs for type 2 diabetes.^[37]

Efficacy[13,14]

Treatment guidelines for major professional associations, including the European Association for the Study of Diabetes, the European Society for Cardiology, and the American Diabetes Association, describe evidence for the cardiovascular benefits of metformin as equivocal.^{[35][38]} A 2016 Cochrane systematic review did not find enough evidence of reduction of cardiovascular mortality, non-fatal myocardial infarction or non-fatal stroke when comparing metformin monotherapy to other glucose-lowering drugs, behavior change interventions, placebo or no intervention.^[39] The use of metformin reduces body weight in people with type 2 diabetes^{[24][40]} in contrast to sulfonylureas, which are associated with weight gain.^[40] Some evidence shows that metformin is associated with weight loss in obesity in the absence of diabetes.^{[41][42]} Metformin has a lower risk of hypoglycemia than the sulfonylureas,^{[43][44]} although hypoglycemia has uncommonly occurred during intense exercise, calorie deficit, or when used with other agents to lower blood glucose.^{[45][46]} Metformin modestly reduces low density lipoprotein and triglyceride levels.^{[43][44]}

In individuals with prediabetes, a 2016 systematic review comparing the effects of metformin with other interventions in the reduction of risk of developing type 2 diabetes^[47] found moderate-quality evidence that metformin reduced the risk of developing type 2 diabetes when compared to diet and exercise or a placebo.^[47] However, when comparing metformin to intensive diet or exercise, moderate-quality evidence was found that metformin did not reduce risk of developing type 2 diabetes and very low-quality evidence was found that adding metformin to intensive diet or exercise did not show any advantage or disadvantage in reducing risk of type 2 diabetes when compared to intensive exercise and diet alone.^[47] The same review also found one suitable trial comparing the effects of metformin and sulfonylurea in reducing risk of developing type 2 diabetes in prediabetic individuals, however this trial did not report any patient relevant outcomes.^[47]

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Polycystic ovarian syndrome

In those with polycystic ovarian syndrome (PCOS), tentative evidence shows that metformin use increases the rate of live births.^[48] This includes in those who have not been able to get pregnant with clomiphene.^[49] Metformin does not appear to change the risk of miscarriage.^[48] A number of other benefits have also been found both during pregnancy and in nonpregnant women with PCOS.^{[50][51]} In an updated Cochrane (2016) review on metformin versus placebo/no treatment before or during IVF/ICSI in women with PCOS no conclusive evidence of improved live birth rates was found.^[52] In long GnRH-agonist protocols there was uncertainty in the evidence of improved live birth rates but there could be increases in clinical pregnancy rate.^[52] In short GnRH-antagonist protocols metformin may reduce live birth rates with uncertainty on its effect on clinical pregnancy rate.^[52] Metformin may result in a reduction of OHSS but could come with a greater frequency of side effects.^[52] There was uncertainty as to metformin's impact on miscarriage.^[52] The evidence does not support general use during pregnancy for improving maternal and infant outcomes in obese women.^[53]

The United Kingdom's National Institute for Health and Clinical Excellence recommended in 2004 that women with PCOS and a body mass index above 25 be given metformin for anovulation and infertility when other therapies fail to produce results.^[54] UK and international clinical practice guidelines do not recommend metformin as a first-line treatment^[55] or do not recommend it at all, except for women with glucose intolerance.^[56] The guidelines suggest clomiphene as the first medication option and emphasize lifestyle modification independently from medical treatment. Metformin treatment decreases the risk of developing type 2 diabetes in women with PCOS who exhibited impaired glucose tolerance at baseline.^{[57][58]}

Diabetes and pregnancy

A total review of metformin use during pregnancy compared to insulin alone found good short-term safety for both the mother and baby, but unclear long-term safety.^[59] Several observational studies and randomized controlled trials found metformin to be as effective and safe as insulin for the management of gestational diabetes.^{[60][61]} Nonetheless, several concerns have been raised and evidence on the long-term safety of metformin for both mother and child is lacking.^[62] Compared with insulin, women with gestational diabetes treated with metformin gain less weight and are less likely to develop pre-eclampsia during pregnancy.^{[62][63]} Babies born to women treated with metformin have less visceral fat, and this may make them less prone to insulin resistance in later life.^[64] The use of metformin for gestational diabetes resulted in smaller babies compared to treatment with insulin. However, despite initially lower birth weight, children exposed to metformin during pregnancy had accelerated growth after birth, and were heavier [15,16,17] by mid-childhood than those exposed to insulin during pregnancy. This pattern of initial low birth weight followed by catch-up growth that surpasses comparative children has been associated with long-term cardiometabolic disease.^[65]

Weight change

Metformin use is typically associated with weight loss.^[66] It appears to be safe and effective in counteracting the weight gain caused by the antipsychotic medications olanzapine and clozapine.^{[67][68]} Although modest reversal of clozapine-associated weight gain is found with metformin, primary prevention of weight gain is more valuable.^[69]

Use with insulin

Metformin may reduce the insulin requirement in type 1 diabetes, albeit with an increased risk of hypoglycemia.^[70]

Contraindications

Metformin is contraindicated in people with:

- Severe renal impairment (estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m²)^[71]
- Known hypersensitivity to metformin^[71]
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis (from uncontrolled diabetes),^[71] with or without coma^[72]

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Adverse effects

The most common adverse effect of metformin is gastrointestinal irritation, including diarrhea, cramps, nausea, vomiting, and increased flatulence. Metformin is more commonly associated with gastrointestinal adverse effects than most other antidiabetic medications.^[44] The most serious potential adverse effect of metformin is lactic acidosis; this complication is rare, and seems to be related to impaired liver or kidney function.^[73] Metformin is not approved for use in those with severe kidney disease, but may still be used at lower doses in those with kidney problems.^[74]

Gastrointestinal

Gastrointestinal upset can cause severe discomfort; it is most common when metformin is first administered, or when the dose is increased.^[72] The discomfort can often be avoided by beginning at a low dose (1.0 to 1.7 g/day) and increasing the dose gradually, but even with low doses, 5% of people may be unable to tolerate metformin.^{[72][75]} Use of slow or extended-release preparations may improve tolerability.^[75]

Long-term use of metformin has been associated with increased homocysteine levels^[76] and malabsorption of vitamin B₁₂.^{[72][77][78]} Higher doses and prolonged use are associated with increased incidence of vitamin B₁₂ deficiency,^[79] and some researchers recommend screening or prevention strategies.^[80]

Lactic acidosis

Lactic acidosis almost never occurs with metformin exposure during routine medical care.^[81] Rates of metformin-associated lactic acidosis are about nine per 100,000 persons/year, which is similar to the background rate of lactic acidosis in the general population.^[82] A systematic review concluded no data exists to definitively link metformin to lactic acidosis.^[83]

Metformin is generally safe in people with mild to moderate chronic kidney disease, with proportional reduction of metformin dose according to severity of estimated glomerular filtration rate (eGFR) and with periodic assessment of kidney function, (e.g., periodic plasma creatinine measurement).^[84] The US Food and Drug Administration (FDA) recommends avoiding the use of metformin in more severe chronic kidney disease, below the eGFR cutoff of 30 mL/minute/1.73 m².^[85] Lactate uptake by the liver is diminished with metformin use because lactate is a substrate for hepatic gluconeogenesis, a process that metformin inhibits. In healthy individuals, this slight excess is cleared by other mechanisms (including uptake by unimpaired kidneys), and no significant elevation in blood levels of lactate occurs.^[43] Given severely impaired kidney function, clearance of metformin and lactate is reduced, increasing levels of both, and possibly causing lactic acid buildup. Because metformin decreases liver uptake of lactate, any condition that may precipitate lactic acidosis is a contraindication. Common causes include alcoholism (due to depletion of NAD⁺ stores), heart failure, and respiratory disease (due to inadequate tissue oxygenation); the most common cause is kidney disease.^[86]

Metformin-associated lactate production may also take place in the large intestine, which could potentially contribute to lactic acidosis in those with risk factors.^[87] The clinical significance of this is unknown, though, and the risk of metformin-associated lactic acidosis is most commonly attributed to decreased hepatic uptake rather than increased intestinal production.^{[43][86][88]}

Overdose[18]

The most common symptoms following an overdose include vomiting, diarrhea, abdominal pain, tachycardia, drowsiness, and rarely, hypoglycemia or hyperglycemia.^{[89][90]} Treatment of metformin overdose is generally supportive, as no specific antidote is known. Extracorporeal treatments are recommended in severe overdoses.^[91] Due to metformin's low molecular weight and lack of plasma protein binding, these techniques have the benefit of removing metformin from the blood plasma, preventing further lactate overproduction.^[91]

Metformin may be quantified in blood, plasma, or serum to monitor therapy, confirm a diagnosis of poisoning, or to assist in a forensic death investigation. Blood or plasma metformin concentrations are usually in a range of 1–4 mg/L in

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persons receiving therapeutic doses, 40–120 mg/L in victims of acute overdosage, and 80–200 mg/L in fatalities. Chromatographic techniques are commonly employed.^{[92][93]}

The risk of metformin-associated lactic acidosis is also increased by a massive overdose of metformin, although even quite large doses are often not fatal.^[94]

Interactions

The H₂-receptor antagonist cimetidine causes an increase in the plasma concentration of metformin by reducing clearance of metformin by the kidneys;^[95] both metformin and cimetidine are cleared from the body by tubular secretion, and both, particularly the cationic (positively charged) form of cimetidine, may compete for the same transport mechanism.^[8] A small double-blind, randomized study found the antibiotic cephalexin to also increase metformin concentrations by a similar mechanism;^[96] theoretically, other cationic medications may produce the same effect.^[8]

Metformin also interacts with anticholinergic medications, due to their effect on gastric motility. Anticholinergic drugs reduce gastric motility, prolonging the time drugs spend in the gastrointestinal tract. This impairment may lead to more metformin being absorbed than without the presence of an anticholinergic drug, thereby increasing the concentration of metformin in the plasma and increasing the risk for adverse effects.^[97]

Pharmacology

Mechanism of action

The molecular mechanism of metformin is not completely understood. Multiple potential mechanisms of action have been proposed: inhibition of the mitochondrial respiratory chain (complex I), activation of AMP-activated protein kinase (AMPK), inhibition of glucagon-induced elevation of cyclic adenosine monophosphate (cAMP) with reduced activation of protein kinase A (PKA), complex IV-mediated inhibition of the GPD2 variant of mitochondrial glycerol-3-phosphate dehydrogenase (thereby reducing glycerol-derived hepatic gluconeogenesis), and an effect on gut microbiota.^{[27][98][99][100]}

Metformin exerts an anorexiant effect in most people, decreasing caloric intake.^[26] Metformin decreases gluconeogenesis (glucose production) in the liver.^{[87][19]} Metformin inhibits basal secretion from the pituitary gland of growth hormone, adrenocorticotrophic hormone, follicle stimulating hormone, and expression of proopiomelanocortin,^[101] which in part accounts for its insulin-sensitizing effect with multiple actions on tissues including the liver, skeletal muscle, endothelium, adipose tissue, and the ovaries.^{[57][33]} The average patient with type 2 diabetes has three times the normal rate of gluconeogenesis; metformin treatment reduces this by over one-third.^[102] Activation of AMPK was required for metformin's inhibitory effect on liver glucose production.^[103] AMPK is an enzyme that plays an important role in insulin signaling, whole-body energy balance, and the metabolism of glucose and fats.^[104] AMPK activation is required for an increase in the expression of small heterodimer partner, which in turn inhibited the expression of the hepatic gluconeogenic genes phosphoenolpyruvate carboxykinase and glucose 6-phosphatase.^[105] Metformin is frequently used in research along with AICA ribonucleotide as an AMPK agonist. The mechanism by which biguanides increase the activity of AMPK remains uncertain: metformin increases the concentration of cytosolic adenosine monophosphate (AMP) (as opposed to a change in total AMP or total AMP/adenosine triphosphate) which could activate AMPK allosterically at high levels;^[106] a newer theory involves binding to PEN-2.^[107] Metformin inhibits cyclic AMP production, blocking the action of glucagon, and thereby reducing fasting glucose levels.^[108] Metformin also induces a profound shift in the faecal microbial community profile in diabetic mice, and this may contribute to its mode of action possibly through an effect on glucagon-like peptide-1 secretion.^[99]

In addition to suppressing hepatic glucose production, metformin increases insulin sensitivity, enhances peripheral glucose uptake (by inducing the phosphorylation of GLUT4 enhancer factor), decreases insulin-induced

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suppression of fatty acid oxidation,^[109] and decreases the absorption of glucose from the gastrointestinal tract. Increased peripheral use of glucose may be due to improved insulin binding to insulin receptors.^[110] The increase in insulin binding after metformin treatment has also been demonstrated in patients with type 2 diabetes.^[111]

AMPK probably also plays a role in increased peripheral insulin sensitivity, as metformin administration increases AMPK activity in skeletal muscle.^[112] AMPK is known to cause GLUT4 deployment to the plasma membrane, resulting in insulin-independent glucose uptake.^[113] Some metabolic actions of metformin do appear to occur by AMPK-independent mechanisms, however AMPK likely has a modest overall effect and its activity is not likely to directly decrease gluconeogenesis in the liver.^[114]

Metformin has indirect antiandrogenic effects in women with insulin resistance, such as those with PCOS, due to its beneficial effects on insulin sensitivity.^[115] It may reduce testosterone levels in such women by as much as 50%.^[115] A Cochrane review, though, found that metformin was only slightly effective for decreasing androgen levels in women with PCOS.^[116]

Metformin also has significant effects on the gut microbiome, such as its effect on increasing agmatine production by gut bacteria, but the relative importance of this mechanism compared to other mechanisms is uncertain.^{[117][118][119]} Due to its effect on GLUT4 and AMPK, metformin has been described as an exercise mimetic.^{[120][121]}

Pharmacokinetics

Metformin has an oral bioavailability of 50–60% under fasting conditions, and is absorbed slowly.^{[8][122]} Peak plasma concentrations (C_{max}) are reached within 1–3 hours of taking immediate-release metformin and 4–8 hours with extended-release formulations.^{[8][122]} The plasma protein binding of metformin is negligible, as reflected by its very high apparent volume of distribution (300–1000 L after a single dose). Steady state is usually reached in 1–2 days.^[8]

Metformin has acid dissociation constant values (pK_a) of 2.8 and 11.5, so it exists very largely as the hydrophilic cationic species at physiological pH values. The metformin pK_a values make it a stronger base than most other basic medications with less than 0.01% nonionized in blood. Furthermore, the lipid solubility of the nonionized species is slight as shown by its low logP value (log(10) of the distribution coefficient of the nonionized form between octanol and water) of -1.43 . These chemical parameters indicate low lipophilicity and, consequently, rapid passive diffusion of metformin through cell membranes is unlikely. As a result of its low lipid solubility it requires the transporter SLC22A1 in order for it to enter cells.^{[123][124]} The logP of metformin is less than that of phenformin (-0.84) because two methyl substituents on metformin impart lesser lipophilicity than the larger phenylethyl side chain in phenformin. More lipophilic derivatives of metformin are presently under investigation with the aim of producing prodrugs with superior oral absorption than metformin.^[125]

Metformin is not metabolized. It is cleared from the body by tubular secretion and excreted unchanged in the urine; it is undetectable in blood plasma within 24 hours of a single oral dose.^{[8][126]} The average elimination half-life in plasma is 6.2 hours.^[8] Metformin is distributed to (and appears to accumulate in) red blood cells, with a much longer elimination half-life: 17.6 hours^[8] (reported as ranging from 18.5 to 31.5 hours in a single-dose study of nondiabetics).^[126]

Some evidence indicates that liver concentrations of metformin in humans may be two to three times higher than plasma concentrations, due to portal vein absorption and first-pass uptake by the liver in oral administration.^[114]

Chemistry

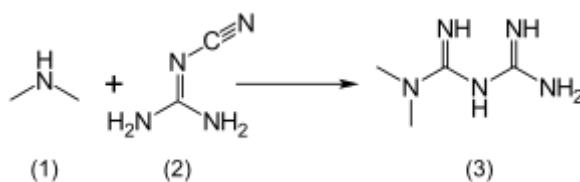
Metformin hydrochloride (1,1-dimethylbiguanide hydrochloride) is freely soluble in water, slightly soluble in ethanol, but almost insoluble in acetone, ether, or chloroform. The pK_a of metformin is 12.4.^[127] The usual synthesis of metformin, originally described in 1922, involves the one-pot reaction of dimethylamine hydrochloride and 2-cyanoguanidine over heat.^{[128][129]}

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According to the procedure described in the 1975 Aron patent,^[130] and the Pharmaceutical Manufacturing Encyclopedia,^[131] equimolar amounts of dimethylamine and 2-cyanoguanidine are dissolved in toluene with cooling to make a concentrated solution, and an equimolar amount of hydrogen chloride is slowly added. The mixture begins to boil on its own, and after cooling, metformin hydrochloride precipitates with a 96% yield.^[medical citation needed]

Impurities

In December 2016, the US FDA announced that it learned that some metformin medicines manufactured outside the United States might contain a nitrosamine impurity called N-nitrosodimethylamine (NDMA), classified as a probable human carcinogen, at low levels.^[132] Health Canada announced that it was assessing NDMA levels in metformin.^[133]

In February 2016, the FDA found NDMA levels in some tested metformin samples that did not exceed the acceptable daily intake.^{[134][135]}

In February 2016, Health Canada announced a recall of Apotex immediate-release metformin,^[136] followed in March by recalls of Ranbaxy metformin^[137] and in March by Jamp metformin.^[138]

In May 2016, the FDA asked five companies to voluntarily recall their sustained-release metformin products.^{[139][140][141][142][143][144]} The five companies were not named, but they were revealed to be Amneal Pharmaceuticals, Actavis Pharma, Apotex Corp, Lupin Pharma, and Marksans Pharma Limited in a letter sent to Valisure, the pharmacy that had first alerted the FDA to this contaminant in metformin via a Citizen Petition.^[145]

In June 2016, the FDA posted its laboratory results showing NDMA amounts in metformin products it tested.^[146] It found NDMA in certain lots of ER metformin, and is recommending companies recall lots with levels of NDMA above the acceptable intake limit of 96 nanograms per day.^[146] The FDA is also collaborating with international regulators to share testing results for metformin.^[146]

In July 2016, Lupin Pharmaceuticals pulled all lots (batches) of metformin after discovering unacceptably high levels of NDMA in tested samples.^[147]

In August 2016, Bayshore Pharmaceuticals recalled two lots of tablets.^[148]
History

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Galega officinalis is a natural source of galegine.

The biguanide class of antidiabetic medications, which also includes the withdrawn agents phenformin and buformin, originates from the plant Goat's rue (*Galega officinalis*) also known as Galega, French lilac, Italian fitch, Spanish sainfoin, Pestilenzkraut, or Professor-weed. (The plant should not be confused with plants in the genus *Tephrosia* which are highly toxic and sometimes also called Goat's rue.) *Galega officinalis* has been used in folk medicine for several centuries.^[149] *G. officinalis* itself does not contain biguanide medications which are chemically synthesized compounds composed of two guanidine molecules and designed to be less toxic than the plant-derived parent compounds guanidine and galegine (isoamylene guanidine).^[149]

Metformin was first described in the scientific literature in 1922, by Emil Werner and James Bell, as a product in the synthesis of N,N-dimethylguanidine.^[128] In 1929, Slotta and Tschesche discovered its sugar-lowering action in rabbits, finding it the most potent biguanide analog they studied.^[150] This result was ignored, as other guanidine analogs such as the synthalins, took over and were themselves soon overshadowed by insulin.^[151]

Interest in metformin resumed at the end of the 1940s. In 1950, metformin, unlike some other similar compounds, was found not to decrease blood pressure and heart rate in animals.^[152] That year, Filipino physician Eusebio Y. Garcia^[153] used metformin (he named it Fluamine) to treat influenza; he noted the medication "lowered the blood sugar to minimum physiological limit" and was not toxic. Garcia believed metformin to have bacteriostatic, antiviral, antimalarial, antipyretic, and analgesic actions.^[154] In a series of articles in 1954, Polish pharmacologist Janusz Supniewski^[155] was unable to confirm most of these effects, including lowered blood sugar. Instead he observed antiviral effects in humans.^{[156][157]}

French diabetologist Jean Sterne studied the antihyperglycemic properties of galegine, an alkaloid isolated from *G. officinalis*, which is related in structure to metformin, and had seen brief use as an antidiabetic before the synthalins were developed.^[158] Later, working at Laboratoires Aron in Paris, he was prompted by Garcia's report to reinvestigate the blood sugar-lowering activity of metformin and several biguanide analogs. Sterne was the first to try metformin on humans for the treatment of diabetes; he coined the name "Glucophage" (glucose eater) for the medication and published his results in 1957.^{[151][158]}

Metformin became available in the British National Formulary in 1958. It was sold in the UK by a small Aron subsidiary called Rona.^[159]

Broad interest in metformin was not rekindled until the withdrawal of the other biguanides in the 1970s.^[5] Metformin was approved in Canada in 1972,^[5] but did not receive approval by the U.S. Food and Drug Administration (FDA) for type 2 diabetes until 1994.^[160] Produced under license by Bristol-Myers Squibb, Glucophage was the first branded formulation of metformin to be marketed in the U.S., beginning on 3 March 1995.^[161] Generic formulations are

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available in several countries, and metformin is believed to have become the world's most widely prescribed antidiabetic medication.^[158]

Society and culture

Environmental impact

Metformin and its major transformation product guanyurea are present in wastewater treatment plant effluents and regularly detected in surface waters. Guanyurea concentrations above 200 µg/L have been measured in the German river Erpe, which are amongst the highest reported for pharmaceutical transformation products in aquatic environments.^[162]

Formulations



Generic metformin 500-mg tablets, as sold in the United Kingdom

Metformin is the British Approved Name (BAN), the United States Adopted Name (USAN), and the International Nonproprietary Name (INN). It is sold under several brand names. Common brand names include Glucophage, Riomet, Fortamet, and Glumetza in the US.^[163] In other areas of the world, there is also Obimet, Gluformin, Dianben, Diabex, Diaformin, Metsol, Siofor, Metfogamma and Glifor.^{[164][165]} There are several formulations of metformin available on the market, and all but the liquid form have generic equivalents.^[163]

Combination with other medications

When used for type 2 diabetes, metformin is often prescribed in combination with other medications. Several medications are available as fixed-dose combinations, with the potential to reduce pill burden, decrease cost, and simplify administration.^{[166][167]}

Thiazolidinediones (glitazones)

Rosiglitazone

A combination of metformin and rosiglitazone was released in 2002, and sold as Avandamet by GlaxoSmithKline,^{[168][169]} or as a generic medication.^[170] Formulations are 500/1, 500/2, 500/4, 1000/2, and 1000 mg/4 mg of metformin/rosiglitazone.

In 2009, it was the most popular metformin combination.^[171]

In 2005, the stock of Avandamet was removed from the market, after inspections showed the factory where it was produced was violating good manufacturing practices.^[172] The medication pair continued to be prescribed separately,

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and Avandamet was again available by the end of that year. A generic formulation of metformin/rosiglitazone from Teva received tentative approval from the FDA and reached the market in early 2012.^[173]

However, following a meta-analysis in 2007, that linked the medication's use to an increased risk of heart attack,^[174] concerns were raised over the safety of medicines containing rosiglitazone. In September 2010, the European Medicines Agency recommended that the medication be suspended from the European market because the benefits of rosiglitazone no longer outweighed the risks.^{[175][176]}

It was withdrawn from the market in the UK and India in 2010,^[177] and in New Zealand and South Africa in 2011.^[178] From November 2011 until November 2013 the FDA^[179] did not allow rosiglitazone or metformin/rosiglitazone to be sold without a prescription; moreover, makers were required to notify patients of the risks associated with its use, and the drug had to be purchased by mail order through specified pharmacies.^{[180][181]} In November 2013, the FDA lifted its earlier restrictions on rosiglitazone after reviewing the results of the 2009 RECORD clinical trial (a six-year, open-label randomized control trial), which failed to show elevated risk of heart attack or death associated with the medication.^{[182][183][184]}

Pioglitazone

The combination of metformin and pioglitazone (Actoplus Met, Piomet, Politor, Glubrava) is available in the US and the European Union.^{[185][186][187][188][189]}

DPP-4 inhibitors

Dipeptidyl peptidase-4 inhibitors inhibit dipeptidyl peptidase-4 and thus reduce glucagon and blood glucose levels.

DPP-4 inhibitors combined with metformin include a sitagliptin/metformin combination (Janumet),^{[190][191]} a saxagliptin/metformin combination (Kombiglyze XR, Komboglyze),^{[192][193]} and an alogliptin/metformin combination (Kazano, Vpidomet).^{[194][195]}

Linagliptin combined with metformin hydrochloride is sold under the brand name Jentaduet.^{[196][197][198]} As of August 2016, linagliptin/metformin is available as a generic medicine in the US.^[199]

SGLT-2 inhibitors

There are combinations of metformin with the SGLT-2 inhibitors dapagliflozin, empagliflozin, and canagliflozin.

Sulfonylureas

Sulfonylureas act by increasing insulin release from the beta cells in the pancreas.^[200]

A 2016 systematic review suggested that there is limited evidence if the combined use of metformin with sulfonylurea compared to the combination of metformin plus another glucose-lowering intervention, provides benefit or harm in mortality, severe adverse events, macrovascular and microvascular complications.^[201] Combined metformin and sulfonylurea therapy did appear to lead to higher risk of hypoglycaemia.^[201]

Metformin is available combined with the sulfonylureas glipizide (Metaglip) and glibenclamide (US: glyburide) (Glucovance). Generic formulations of metformin/glipizide and metformin/glibenclamide are available (the latter is more popular).^[202]

Meglitinide

Meglitinides are similar to sulfonylureas, as they bind to beta cells in the pancreas, but differ by the site of binding to the intended receptor and the drugs' affinities to the receptor.^[200] As a result, they have a shorter duration of action compared to sulfonylureas, and require higher blood glucose levels to begin to secrete insulin. Both meglitinides, known as nateglinide and repaglinide, is sold in formulations combined with metformin. A repaglinide/metformin combination is sold as Prandimet, or as its generic equivalent.^{[203][204]}

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Triple combination

The combination of metformin with dapagliflozen and saxagliptin is available in the United States as Qternmet XR.^{[205][206]}

The combination of metformin with pioglitazone and glibenclamide^[207] is available in India as Accuglim-MP, Adglim MP, and Alnamet-GP; and in the Philippines as Tri-Senza.^[165]

The combination of metformin with pioglitazone and lipoic acid is available in Turkey as Pional.^[165]

IV. CONCLUSION

Research

Metformin is a pleiotropic drug, with extensive off-target activity beyond its antidiabetic effect. Much of this has been attributed to its action on AMPK, although other mechanisms have been proposed.^{[208][209]} Metformin has been studied for its effects on multiple other conditions, including:

- Non-alcoholic fatty liver disease^{[210][211][212]}
- Premature puberty^{[213][214][215]}
- Cancer^{[164][216][217]}
- Cardiovascular disease in people with diabetes^[218]
- Aging^{[219][220]}

Aging and life extension

Metformin has received substantial interest as an agent that delays aging, possibly through similar mechanisms as its treatment of diabetes (insulin and carbohydrate regulation).^{[220][221]} It has been studied in animal models (C. elegans and crickets) for effects on aging.^{[124][222]}

A 2016 review found that people with diabetes who were taking metformin had lower all-cause mortality. They also had reduced cancer and cardiovascular disease compared with those on other therapies.^[218] In people without diabetes, metformin does not appear to reduce the risk of cancer and cardiovascular disease.^[223] Whether metformin may be helpful in extending life, even in otherwise healthy people, remains controversial; a 2016 review of the literature found it is likely to improve healthspan, i.e., the number of years spent in good health, rather than lifespan overall.^[224] Cancer^[19]

The potential anticancer effects of metformin are believed to be mediated through multiple pathways, particularly involving AMPK activation and IGF-1R modulation. Research has focused particularly on stomach cancer, with evidence of protective impact (reducing risk of cancer) and improving survival rates among patients in whom cancer has already developed.^[225] Despite promising findings, evidence is still preliminary and there is no consensus on its preventive and therapeutic role^[20]

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