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Chapter

Metformin Indications, Dosage, Adverse Reactions, and Contraindications

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Abstract

Metformin or dimethyl biguanide is the oral antidiabetic drug with the most extensive experience of prescribing in the clinical practice of type 2 diabetes mellitus. In this chapter, we reviewed the indications, contraindications, and adverse drug reactions (ADR) of metformin. The most significant adverse drug reactions of metformin are lactic acidosis, allergies, hypoglycemia, vitamin B12 deficiency, altered taste, and gastrointestinal intolerance. Metformin is contraindicated in severe chronic diseases (hepatic, renal, and cardiac failure) or acute complications of diabetes (ketoacidosis and hyperosmolar state). Metformin is considered by all international guidelines the first-line treatment in type 2 diabetes mellitus (T2DM) together with medical, nutritional therapy. It is one of the most prescribed molecules worldwide. Furthermore, metformin can also be prescribed for other diseases like polycystic ovary syndrome or prediabetes (impaired glucose tolerance/fasting hyperglycemia). Recent studies have shown positive results concerning the use of metformin for cardiovascular or neuroprotective effects; also, several scientific papers are suggesting an antitumor or antiaging effect of metformin. Having such an excellent efficiency in practice, thus predicting its sustainability on the pharmaceutical market, research is directed toward characterizing metformin action on bacteria genera in the gut. Modifying the microbiota composition by pre- and probiotics could improve metformin action.

Keywords: metformin, indication, adverse reaction, gastric intolerance, lactic acidosis, diabetes

1. Introduction

Metformin or dimethyl biguanide has its origin in traditional herbal medicine (*Galega officinalis* or goat's rue) that is rich in guanidine. Guanidine was proven to have the capacity to lower blood glucose and was used as an antidiabetic treatment from the 1920s to 1930s. Its administration was interrupted prematurely due to

toxicity. The medicine was valued again between the 1940s and 1950s when Jean Sterne observed the low blood glucose values of patients that were treated with metformin for influenza. Since then, the drug class of biguanides has received much consideration, especially buformin and phenformin in the 1970s and metformin after the 1990s [1].

The 60-year history of biguanides' use is filled with victories and defeats, being the oral antidiabetic drug with the most extensive experience of prescribing in the clinical practice.

We will review in the following pages the indications, contraindications, and adverse drug reactions (ADR) of metformin and the single biguanide approved globally for use nowadays.

An ADR according to the World Health Organization is "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of a disease, or the modification of physiological function." A side effect is "an unintended effect occurring at normal dose related to the pharmacological properties" [2].

A contraindication represents "something (such as a symptom or condition) that makes a particular treatment or procedure inadvisable" [3].

2. Indications

2.1 Type 2 diabetes mellitus (T2DM)

All international guidelines consider metformin and lifestyle intervention as the first-line treatment in adults with T2DM in order to improve glycemic control [4]. It can be used either as monotherapy or combination therapy with glucagon-like peptide-1 receptor agonist (GLP-1 RA), sodium-glucose co-transporter inhibitor (SGLT2i), dipeptidyl peptidase-4 inhibitor (DPP4-I), thiazolidinedione (TZD), sulfonylurea (SU), and insulin. Metformin therapy should be continued as long as it is well tolerated and not contraindicated. All other agents, including insulin, should be added to metformin treatment [4].

2.2 Prediabetes

Metformin can be used in order to prevent or delay the onset of T2DM [5]. Although other pharmacological agents have been used in clinical trials (acarbose [6–8], orlistat [9], and rosiglitazone [10]), it appears that metformin has the most reliable evidence base [11–16]. The vast majority of international guidelines recommend metformin use in prediabetes. It can be used together with a combination of a lifestyle intervention for patients with prediabetes: impaired glucose tolerance (2-h post-load glucose 140–199 mg/dL), fasting hyperglycemia (100–125 mg/dl), or A1C 5.7–6.4% [17–23]. Metformin appears to have a more significant advantage when used in patients who are <60 years old and have a BMI >35 kg/m^2 or women with prior gestational diabetes mellitus [16].

2.3 Type 1 diabetes mellitus (T1DM)

Metformin is sometimes used in T1DM to limit insulin dose requirement [24, 25]. The American Diabetes Association states that adding metformin leads to the reduction in body weight and can improve lipid levels, but not HbA1c [4, 26]. The REMOVAL study suggests that metformin might also reduce atherosclerosis progression, thus suggesting to improve CVD risk management in type 1 diabetes [27, 28].

2.4 Gestational diabetes mellitus (GDM)

Lifestyle modification is the first-line therapy for GDM. If glycemic targets are not achieved, then insulin treatment is required for lowering blood glucose; metformin can also be considered if the patient cannot take or declines insulin [29]. Some controlled randomized trials are proving limited efficacy of metformin during pregnancy [30, 31]. Metformin therapy is associated with a lower risk of neonatal hypoglycemia and less maternal weight gain than insulin in systematic reviews [32–34]; metformin may slightly increase the risk of prematurity, and it crosses the placenta [35]. Thus, the ADA considers that metformin should not be used as first-line agents [36].

2.5 Polycystic ovary syndrome (PCOS)

PCOS patients suffer from insulin resistance and hyperinsulinemia [37]. Metformin has been used for PCOS treatment [38] for treating the metabolic abnormalities of PCOS. A recent meta-analysis [39] demonstrated that metformin could decrease testosterone and insulin level in women with PCOS.

2.6 Antitumor or antiaging effect of metformin

Several studies showed an increased life-span when using metformin (4–6% in different mouse breeds or a mean life-span increased by 14% and maximum life-span increased by 1 month of treatment with metformin is started early in life) [40, 41]. In the United Kingdom Prospective Diabetes Study (UKPDS), the use of metformin decreased the risk of cardiovascular disease, cancer incidence, and overall mortality, compared with other antidiabetic drugs [42].

Epidemiological studies reported a positive result of metformin concerning ovarian [43, 44], breast, prostate, or colorectal tumors [45–48] enhancing the antitumor effect of metformin. Furthermore, studies are demonstrating a reduced incidence of several gastroenterological cancers and a reduction in cancer mortality when using metformin [49, 50].

2.7 Cardiovascular or neuroprotective effects

UKPDS was the first study that demonstrated the cardiovascular benefit of metformin; the risk of all-cause mortality and acute myocardial infarction was significantly reduced in overweight patients with T2DM [42]. The 10-year post-interventional follow-up of the UKPDS survivor cohort revealed that metformin treatment had a long-term benefit on cardiovascular risk [51].

The cardiovascular protective effects of metformin could be explained by the reduced level of LDL cholesterol [52], the limitation of weight gain, [53] and the improvement of oxidative stress, inflammatory response, and the endothelial cell function [54].

It has been reported that patients treated with metformin have lower risk of dementia than those with other diabetes medications [55]. Metformin has a better protective effect on the domain of verbal learning, working memory, and executive function than other diabetic treatments [56].

2.8 Antipsychotic-induced weight gain

Results of meta-analyses of RCTs (primarily in patients with schizophrenia and schizoaffective disorder) support the use of metformin for weight loss, preventing weight gain associated with second-generation antipsychotics in adult patients [57].

Metformin can be recommended as a second-line option after nonpharmacologic strategies for managing weight gain in patients with mood disorders and is recognized as often being used as a secondary prevention strategy for antipsychotic-related weight gain [58].

3. Dosage

The dose for glucose-lowering efficacy is usually in the range of 500–2000 mg/day. There is no standard dosage regimen for the management of hyperglycemia in patients with type 2 diabetes. On the other side, clinically significant responses are not seen at doses below 1500–2000 mg per day.

The dosage of metformin must be individualized for every patient considering effectiveness and tolerance while not exceeding the maximum recommended daily doses (2550 mg in adults and 2000 mg in pediatric patients >10 years of age) (**Table 1**).

Patients that are receiving immediate-release metformin treatment may be switched to extended form once daily with the same total daily dose (up to 2000 mg daily).

In the case of renal impairment, the dosage of metformin must be adjusted (**Table 2**).

		Initial dose	**Titration dose**	**Maximum dose**
Adults	Immediate-release metformin	500 mg/daily or 850 mg/daily	500 mg/weekly or 850 mg/2 weeks	2550 mg/daily
	Extended-release metformin	500 mg/daily or 1000 mg/daily	500 mg/weekly	2000 mg/daily
Geriatric use	With caution; to start at the low end of the dosing range, assess renal function more frequently			
Pediatric use >10 years old	Immediate release	500 mg/daily	500 mg/weekly	2000 mg/daily
	Extended release	Not yet established		

Table 1.
Dosage of metformin.

Renal impairment	**eGFR**		
	<30	**30–45**	**>45**
Initiation	Contraindicated	Not recommended	No dose adjustment needed
If eGFR falls during treatment	Stop	Assess the benefit-risk of continuing therapy	No dose adjustment needed

Table 2.
Dosage of metformin for renal impairment.

4. Adverse drug reactions of metformin

4.1 Lactic acidosis (very rare)

Phenformin and buformin were two potent biguanides that were used in the 1970s for type 2 diabetes treatment. The Swedish Adverse Drug Reaction Committee

analyzed the reports from 1965 to 1977 that involved biguanides (0.6% of the total). The fact that attracted attention was that in 6% of the cases in which the patient died (the majority with lactic acidosis), phenformin was administered [59]. After this committee report analysis, the class was used with precaution, and metformin was favored over phenformin because there was an early study that showed that type 2 diabetic patients admitted in the hospital had a higher mean lactate level when they were treated with other medicine instead of the first-mentioned earlier [59, 60].

A Cochrane meta-analysis that was published in 2006 that analyzed data from 206 trials and cohort studies did not find any case of lactic acidosis in metformin-treated patients or the control group. Also, the lactate level was not significantly raised in the metformin group, although there was a small difference between patients treated with this biguanide and phenformin [61].

A case-control study with 10.652 Danish type 2 diabetic patients showed that the lactic acidosis incidence in patients treated with metformin was 391/100.000 person-years, but the use of the drug itself did not elevate the risk; associated diseases had greater importance [62].

4.2 Allergic reactions (infrequent)

Systemic allergic reactions to metformin are infrequent [63, 64]. It can be used in patients with asthma that have hypersensitivity, without increasing the risk of related outcomes, meaning hospitalizations, asthma-related emergency room visits, or exacerbations [65].

Cutaneous allergic reactions have been described scarcely ever, but clinicians should be aware of their existence [66].

4.3 Hypoglycemia (very rare)

In monotherapy as a first-line agent, metformin was proven to be safe and beneficial in a recent meta-analysis. The hypoglycemic risk was lower than for monotherapy with sulfonylurea [67].

Rare cases in elderly patients, with comorbidities and polypharmacy (angiotensin-converting enzyme inhibitors or nonsteroidal anti-inflammatory drugs) or combined with malnutrition, have been described [68].

4.4 Vitamin B12 deficiency (rare)

The American Diabetes Association Guidelines recommend that potential vitamin B12 deficiency should be taken into consideration and screened in type 2 diabetes patients long-treated with high-dose metformin (more than 2 g/day) [59]. A meta-analysis of 29 studies showed that the metformin-treated group had a significantly lower level of this vitamin [69]. The implied mechanisms are:

- The drug acts as a competitor for vitamin B12 absorption.
- It affects the intrinsic factor action.
- It generates bacterial overgrowth because it alters bowel movement [70].

4.5 Altered taste (frequent)

Taste disturbance is an adverse effect that can be caused by the accumulation and secretion of metformin in saliva. Lee N et al. demonstrated that the salivary

glands express the organic cation transporter-3 (OCT3) in high amounts that is responsible for metformin carriage and could be involved in the mechanism of this side effect. In animal studies, the OCT3(−/−) mice, the uptake of metformin in the saliva was downregulated [71].

4.6 Gastrointestinal intolerance (widespread)

Gastrointestinal side effects include diarrhea, nausea, meteorism, and constipation and affect approximately 20% of the patients [71, 72].

The hydrochloride salt of metformin is usually administered orally and is absorbed mostly by the small intestine. The concentration inside the enterocyte can reach up to 300 times the level in the circulation and depends on drug transport by organic cation transporter 1 (OCT1) [67]. Also, metformin increases glucose use in the anaerobic cycle and lactate production inside the enterocyte. Local higher production of lactate could be associated with adverse reactions [73].

Scarpello et al. demonstrated that metformin slows the absorption of bile acids, consequently leading to osmotic diarrhea [74]. On the contrary, the serum measures of lactate, serotonin, or bile acids were similar in normal and intolerant volunteers after a 500-mg dose of metformin, making the authors conclude that the intolerance is probably related to local factors within the lumen or enterocyte [73].

Some authors suggested that a reduced function of OCT1 could have an effect on the tolerability of metformin in the digestive system. The population with a reduced-function OCT1 alleles also had a higher increase of metformin intolerance. If this population was additionally treated with an OCT1 inhibitor, the risk increased even more [75]. Thus, patients that are under treatment with other medications that interact with OCT1 could have a higher risk for gastrointestinal ADR [75].

There are several formulations like the immediate-release (IR) tablets that result in high local concentration, extended-release tablets (XR) that have a prolonged discharge of the active molecule due to a dual polymer matrix, and delayed-release tablets (DR). The XR and the DR forms help in uniformly spreading out molecules along the intestinal membrane and prevent intolerance [75].

4.7 Hypothyroidism (controversial)

Metformin acts by activating adenosine monophosphate-activated protein kinase (AMPK), an enzyme that also activates thyroid iodine in vitro models. Thus, it was assumed that metformin could alter thyroid function [76]. In healthy volunteers, only the level of T3 was decreased by metformin administration, but not the iodine uptake, TSH, or fT4 [76].

Following this idea, observational studies proved that metformin treatment could reduce thyroid-stimulating hormone (TSH) level, but randomized control trials performed afterward failed to certify this hypothesis [77].

5. Contraindications

The indications and efficiency of metformin in type 2 diabetes are clearly stated in current guidelines [4] and continue to extend to other branches of medicine. For example, the UKPDS study revealed that metformin is associated with a lower risk of mortality [37], and some researchers tried to use metformin as an antiaging drug. Besides its broad indications, metformin remains contraindicated in many conditions associated with hypoxemia because it can lead to lactic acidosis [78].

5.1 Ketoacidosis

In type 2 diabetes patients with severe hyperglycemia and ketoacidosis or type 1 diabetes, insulin treatment should be initiated [4]. When the glycemic values are balanced, and if the patient does not have other contraindications, metformin treatment can be started in type 2 diabetes [4].

In type 1 diabetes, metformin is solely administered as an adjuvant because it can reduce the insulin requirements [25]. A randomized controlled trial found that metformin increases the risk for gastrointestinal adverse events in overweight type 1 diabetes patients, with no benefit for glycemic control, so a clinician should reach a decision depending on patient particularities and response [79].

5.2 Cardiac failure

After the warning regarding lactic acidosis, cardiac failure was put on the list with contraindications. Afterward, observational studies [80] and systematic reviews [81, 82] showed that metformin could be used in stable heart failure. If patients develop congestive heart failure or concomitantly have other contraindications or acute diseases, metformin should be stopped. The studies realized and included in the meta-analysis are very heterogeneous, most of them comparing different medications, but with no specifications regarding the mean dose of metformin or other classes. Overall, the mortality rate was 22% lower in patients with heart failure and type 2 diabetes treated with metformin [82].

5.3 Chronic kidney disease (CKD)

Metformin is restricted in patients with eGFR less than 30 ml/min/1.73 m2 (stage IV CKD), and dose must be adjusted beginning with an eGFR below 45 ml/min/1.73 m2 (stage IIIb) [4]. In a cohort study of a national registry, metformin was associated with a lower rate of mortality and serious adverse events at an eGFR between 45 and 60 ml/min/1.73 m2 and had neutral effects on the same variables at eGFR between 30 and 45 ml/min/1.73 m2. Although its effect is less evident in stage IV chronic kidney disease, the benefit of biguanide treatment outweighs the ADR risk in a 4-year follow-up [82, 83].

5.4 Hepatic failure and cirrhosis

Impaired hepatic function is another warning from the FDA [64]. This term includes a broad spectrum of liver pathology, and metformin treatment should be tailored. In a retrospective study that included patients with cirrhosis, metformin had a protective effect for encephalopathy development [84]. Likewise, in another retrospective study, biguanide treatment was continued after cirrhosis diagnosis and was associated with improved survival [85]. In patients with cirrhosis secondary to hepatitis C virus infection, the risk of hepatocellular carcinoma was reduced during a 5-year follow-up [86].

5.5 Respiratory insufficiency

Because the risk of lactic acidosis is higher in patients with altered blood gas exchange like in chronic obstructive pulmonary disease (COPD), asthma, restrictive pulmonary pathologies, the FDA and EMA recommend precaution [63, 64].
A randomized clinical trial used metformin in a rapidly escalated dose after a COPD exacerbation and showed no amelioration in glycemic profile. This could be since

mean in-hospital glycemia was assessed and it usually takes 1–2 weeks for metformin to reach its maximum hypoglycemic potential; there were no cases of lactic acidosis, and mean serum lactate was similar in the intervention and placebo group [87].

6. Special populations

6.1 Children

Metformin is indicated now in children above 10 years [63, 64], although there were studies that included obese participants above 7 years without side effects [88].

6.2 Pregnancy

There are limited data that could not identify a drug-associated risk of miscarriage or congenital disabilities. Metformin use was not associated with any of these maternal or fetal outcomes in post-marketing studies with small sample size or in meta-analyses of the randomized clinical trials that included pregnant women. The risk of stillbirth, congenital disabilities, and macrosomia can be increased if the patients do not have reasonable control under this oral treatment. Thus, the risk is falsely attributed to metformin [89].

6.3 Lactation

Metformin is present in the human milk in insignificant concentration. The potential adverse effect on the child or milk production has not been described [89].

6.4 Elderly

There is a study which compared pharmacokinetics and pharmacodynamics of metformin in the older population (65–85 years) versus young controls. Results showed that the glucose-lowering effect was similar in both groups, although the maximum concentration and exposure were two times higher in the advanced age population. Usually, it is not recommended in patients above 85 years old because they have a reduced eGFR [90].

7. Overdosage

A retrospective cohort study performed in the emergency department analyzed 56 of self-reported metformin overdose from a total of 2872 cases (1.9%). The incidence of hyperlactatemia was 56.4%, and that of metformin-associated lactic acidosis (MALA) was 17.9%. When the patient is co-ingested with acetaminophen, the risk of MALA was higher. No case resulted in death [91].

Treatment in metformin overdose includes supportive care, gastrointestinal decontamination (gastric lavage), alkalinization, and even emergency hemodialysis in severe cases [92].

8. Future directions: metformin and metagenome

There were some studies on human microbiota, which suggested that metformin induces dysbiosis and promotes nutritional imbalances for specific bacterial types

in healthy volunteers [93, 94]. *Escherichia* sp. has a selective advantage over other organisms [95].

Twelve bacterial species that were present at baseline predicted the appearance of gastrointestinal adverse events (self-reported) [94]. Characterizing these bacteria genera and modifying the microbiota composition by pre- and probiotics could improve metformin action. Also, these bacteria could be set as new targets for diabetes treatment.

9. Conclusions

Besides its controversial history, metformin remains the most used medicine in type 2 diabetes treatment. Progressive dose increases should be encouraged in order to prevent gastrointestinal adverse effects. Lactic acidosis is obsolete if the patient does not have other severe comorbidities. The indications of metformin currently extend to other areas like oncology, endocrinology, and gastroenterology and should offer the scientific world more information about its adverse effects.

Conflict of interest

Anca Pantea Stoian, MD, PhD; Cristian Serafinceanu MD, PhD; and Manfredi Rizzo, MD, PhD, were advisory boards for AstraZeneca, Eli Lilly, Merck, Novo Nordisk, Sanofi. Anca Pantea Stoian, MD, PhD, is the Vicepresident of Romanian National Committee of Diabetes, Nutrition and Metabolic Diseases, and speaker for Astra Zeneca, Eli-Lilly, Coca-Cola, NovoNordisk, Sanofi. Manfredi Rizzo, MD, PhD, is the Director, Clinical Medical & Regulatory Affairs, Novo Nordisk Europe East and South. Simona Diana Stefan, MD, received speaker fees from Merck, Novo Nordisk, Sanofi. Andra Iulia Suceveanu, MD, PhD; Adrian Paul Suceveanu, MD, PhD; and Roxana Adriana Stoica, MD, declare no conflict of interest.

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