Metformin Fact Sheet



Metformin is a medication that affects sugar levels in your body by altering the body's response to insulin. It is the most widely prescribed drug for the treatment of Type 2 diabetes (T2D) and is considered an "essential medicine" by the World Health Organization, used daily by over 200 million patients (1, 5). It is a robust and recommended medication due to its many decades of proven sugar-lowering effects, well-established safety, and relatively low cost (2). Currently, metformin is a drug that exhibits high potential for repurposing, meaning that it may be useful in combating several other conditions (16).

How does metformin combat Type 2 Diabetes Mellitus (T2DM)?

Insulin resistance is a hallmark of T2D, causing our body to poorly control blood sugar levels by reducing glucose uptake and increasing glucose production in the liver. Metformin combats insulin resistance by inhibiting the liver's glucose production, shifting glucose uptake from liver and fat cells to muscles, and increasing the body's sensitivity to insulin (2, 3, 4).

Side Effect FAQs

What are some common side effects of metformin? Are they treatable?

Patients on metformin most commonly will experience gastrointestinal (GI) side effects, including nausea, diarrhea, bloating, and abdominal pain (8). Thankfully, an extended release formula of metformin slows the release of the drug, and is typically much better tolerated, while continuing to have the same glucose-lowering efficacy (9, 10).

Does metformin cause vitamin B12 deficiency?

Yes, there is evidence that high-dose and long-term metformin usage can lead to a vitamin B12 deficiency (11, 12, 13). In order to avoid this problem, your doctor will monitor B12 levels, and if the level declines, you may be recommended to take a B12 supplement until levels normalize.

What is lactic acidosis? Can metformin cause it?

Lactic acidosis is a clinical condition in which too much lactate is present in the blood, which can be dangerous. Metformin-associated lactic acidosis (MALA) is an extremely rare condition and will occur when a patient's body cannot rid itself of the metformin properly (15). It is mainly a concern in patients with poor kidney function. This is why your doctor will routinely monitor your kidney function and adjust your metformin dose if the kidney function declines.

Will metformin hurt my kidneys?

No, metformin will not hurt your kidneys. In fact, metformin use has been found to decrease risk for diabetic kidney disease (nephropathy) and to prevent major cardiovascular events (24). In fact, better diabetes control is one of the best ways to reduce the risk of kidney disease (25).

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New Purposes for Metformin

How can metformin affect polycystic ovarian syndrome (PCOS)?

PCOS is an endocrine and metabolic disorder that affects 6-20% of females in reproductive age (6). Hormone imbalances due to PCOS cause insulin resistance and high blood sugar, similar to the symptoms of T2D (6). As metformin lowers glucose production and increases insulin sensitivity, it is also commonly used to treat PCOS (2, 3, 4, 7).

How can metformin affect pregnancy?

There is strong evidence that suggests metformin is safe for use in early pregnancy with no risk of congenital malformations (22). Metformin use has been associated with reduced maternal weight gain, hypertensive disorders, and neonatal hypoglycemia (22, 23). Metformin use in pregnancy is a newer practice, and research is ongoing as to its risks and benefits.

How can metformin affect cancer?

Accumulating evidence suggests that metformin inhibits the growth, survival, and metastasis of several tumor cells, including those from breast, liver, bone, pancreas, endometrial, colorectal, kidney, and lung cancers (18, 19). The anticancer properties of this drug may be attributed to its direct and indirect regulation of cellular metabolism (18). Potential strategies to treat cancer using metformin is an exciting, new topic of study.

How can metformin affect inflammation?

Metformin has been found to have anti-inflammatory results in patients with T2DM (17). It is hypothesized to be useful in various infectious, autoimmune, or hyperinflammatory diseases, but its exact effect on the immune system needs further study (17). These anti-inflammatory qualities along with its robust sugar-controlling abilities make metformin a drug that provides protection for COVID-19 as well (17). Additionally, studies showed that patients with better diabetes control had better survival and recovery from COVID-19 (26).

How can metformin affect longevity and aging?

Metformin has been found to increase the lifespan in various model organisms, making it a proposed anti-aging medication (17). Negative effects of aging are often associated with inflammation (17). As metformin has been shown to have anti-inflammatory effects, it may also counter some detrimental consequences of aging (17, 20). Furthermore, aging is often accompanied by a decline in the immune system, and metformin has been found to have a hand in boosting the immune system (17). Additionally, seeing how metformin improves age-related diseases, such as diabetes, it can often lead to increased lifespan in these patients (18). However, the ability of metformin to lengthen the lifespan of patients who do not have diabetes still needs to be clearly determined (17, 21).

Metformin Resources



- 1. American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2020. Diabetes Care 2020, 43 (Suppl 1), S98–S110. <u>https://doi.org/10.2337/dc20-S009</u>.
- 2. Cellular and Molecular Mechanisms of Metformin Action PubMed. https://pubmed.ncbi.nlm.nih.gov/32897388/.
- 3. Efficacy and Metabolic Effects of Metformin and Troglitazone in Type II Diabetes Mellitus | New England Journal of Medicine. <u>https://www.nejm.org/doi/10.1056/NEJM199803263381303?url_ver=Z39.88-</u> 2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200www.ncbi.nlm.nih.gov.
- 4. Féry, F.; Plat, L.; Balasse, E. O. Effects of Metformin on the Pathways of Glucose Utilization after Oral Glucose in Non-Insulin-Dependent Diabetes Mellitus Patients. Metabolism 1997, 46 (2), 227–233. <u>https://doi.org/10.1016/s0026-0495(97)90307-3</u>.
- 5. Metformin: update on mechanisms of action and repurposing potential PubMed. https://pubmed.ncbi.nlm.nih.gov/37130947/.
- 6. Siddiqui, S.; Mateen, S.; Ahmad, R.; Moin, S. A Brief Insight into the Etiology, Genetics, and Immunology of Polycystic Ovarian Syndrome (PCOS). J Assist Reprod Genet 2022, 39 (11), 2439–2473. <u>https://doi.org/10.1007/s10815-022-02625-7</u>.
- 7. Zhao, H.; Xing, C.; Zhang, J.; He, B. Comparative Efficacy of Oral Insulin Sensitizers Metformin, Thiazolidinediones, Inositol, and Berberine in Improving Endocrine and Metabolic Profiles in Women with PCOS: A Network Meta-Analysis. Reprod Health 2021, 18, 171. <u>https://doi.org/10.1186/s12978-021-01207-7</u>.
- 8. Dujic, T.; Zhou, K.; Donnelly, L. A.; Tavendale, R.; Palmer, C. N.; Pearson, E. R. Association of Organic Cation Transporter 1 with Intolerance to Metformin in Type 2 Diabetes: A GoDARTS Study. Diabetes 2015, 64 (5), 1786–1793. https://doi.org/10.2337/db14-1388.
- 9. Metformin and the gastrointestinal tract PMC. https://pmc.ncbi.nlm.nih.gov/articles/PMC4742508/.
- 10. The Primary Glucose-Lowering Effect of Metformin Resides in the Gut, Not the Circulation: Results From Short-term Pharmacokinetic and 12-Week Dose-Ranging Studies PubMed. <u>https://pubmed.ncbi.nlm.nih.gov/26285584/</u>.
- 11.Long-term metformin therapy and vitamin B12 deficiency: An association to bear in mind PMC. <u>https://pmc.ncbi.nlm.nih.gov/articles/PMC8311483/</u>.
- 12. Metformin-Induced Vitamin B12 Deficiency in Patients With Type-2 Diabetes Mellitus PMC. <u>https://pmc.ncbi.nlm.nih.gov/articles/PMC10688235/</u>.
- 13. Association between metformin and vitamin B12 deficiency in patients with type 2 diabetes PMC. <u>https://pmc.ncbi.nlm.nih.gov/articles/PMC10236989/</u>.
- 14. Di Mauro, S.; Filippello, A.; Scamporrino, A.; Purrello, F.; Piro, S.; Malaguarnera, R. Metformin: When Should We Fear Lactic Acidosis? Int J Mol Sci 2022, 23 (15), 8320. <u>https://doi.org/10.3390/ijms23158320</u>.
- 15. DeFronzo, R.; Fleming, G. A.; Chen, K.; Bicsak, T. A. Metformin-Associated Lactic Acidosis: Current Perspectives on Causes and Risk. Metabolism Clinical and Experimental 2016, 65 (2), 20–29. <u>https://doi.org/10.1016/j.metabol.2015.10.014</u>.
- 16.Metformin: update on mechanisms of action and repurposing potential PubMed. <u>https://pubmed.ncbi.nlm.nih.gov/37130947/</u>.
- 17. Metformin and Its Benefits for Various Diseases PMC. https://pmc.ncbi.nlm.nih.gov/articles/PMC7212476/.
- 18. Podhorecka, M.; Ibanez, B.; Dmoszyńska, A. Metformin Its Potential Anti-Cancer and Anti-Aging Effects. Postepy Hig Med Dosw (Online) 2017, 71 (0), 170–175. <u>https://doi.org/10.5604/01.3001.0010.3801</u>.
- 19. Kulkarni, A. S.; Gubbi, S.; Barzilai, N. Benefits of Metformin in Attenuating the Hallmarks of Aging. Cell Metab 2020, 32 (1), 15–30. <u>https://doi.org/10.1016/j.cmet.2020.04.001</u>.
- 20. Mohammed, I.; Hollenberg, M. D.; Ding, H.; Triggle, C. R. A Critical Review of the Evidence That Metformin Is a Putative Anti-Aging Drug That Enhances Healthspan and Extends Lifespan. Front Endocrinol (Lausanne) 2021, 12, 718942. <u>https://doi.org/10.3389/fendo.2021.718942</u>.
- 21.Newman, C.; Dunne, F. P. Metformin for Pregnancy and beyond: The Pros and Cons. Diabetic Medicine 2022, 39 (3), e14700. <u>https://doi.org/10.1111/dme.14700</u>.
- 22. Efficacy and safety of metformin during pregnancy: an update PMC. https://pmc.ncbi.nlm.nih.gov/articles/PMC10850184/.
- 23. Impact of metformin on cardiovascular and kidney outcome based on kidney function status in type 2 diabetic patients: a multicentric, retrospective cohort study | Scientific Reports. <u>https://www.nature.com/articles/s41598-024-52078-4#Sec14</u>.
- 24. de Boer, I. H. Kidney Disease and Related Findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study. Diabetes Care 2014, 37 (1), 24–30. <u>https://doi.org/10.2337/dc13-2113</u>.
- 25.Insulin Treatment Is Associated with Increased Mortality in Patients with COVID-19 and Type 2 Diabetes PMC. https://pmc.ncbi.nlm.nih.gov/articles/PMC7682421/.