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Metformin – the old drug with new therapeutic possibilities

Abstract

Introduction. Metformin is an oral antidiabetic drug from the biguanide group, popularly referred as an aspirin of the 21st century. The therapeutic targets of metformin are expanding. It is characterized by antineoplastic, immunoregulatory, anti-aging and neuroprotective properties. We aimed to evaluate the pleiotropic effects of metformin, taking into account its different mechanisms, efficacy and safety in contemporary public health challenges.

Material and methods: We conducted the literature review from 2014 to 2024 using the PubMed and Google Scholar.

Results: Metformin, depending on the cancer and its stage, enhances the cancer treatment effects, prevents the drug resistance, lengthens overall time of survival, reduces the risk of recurrence. In the Parkinson's disease, Alzheimer's disease and depression metformin can even increase the risk of their occurrence, especially in high doses. Such doses predispose to the cobalamin deficiency, affecting the functioning of the nervous system. Metformin was effective in seizure control of epilepsy. It has positive impact on the course of some autoimmunological diseases. Among diabetics treatment, outcomes of COVID-19 and tuberculosis could be improved by metformin.

Conclusions: Metformin is pluripotential drug. Possibilities of adjuvant metformin therapy are very promising, but it cannot be recommended as standard treatment. This issue requires further investigation, preferentially randomized controlled trials on the bigger research samples.

Keywords: metformin and therapy, metformin and treatment, metformin and advances.

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INTRODUCTION

Metformin is an oral antidiabetic drug from the biguanide group. Initially it was used to treat type 2 diabetes at the end of the 1950s and presently it still remains a drug of the first choice [1-3]. Metformin is popularly referred as an aspirin of the 21st century due to its widespread use in the diabetes - civilization disease [4]. It is a safe, well-tolerated, cheap drug and effective in lowering glycemia without a significant risk of hypoglycemia [5-7]. The most common dose-dependent side effects of metformin include gastrointestinal symptoms: diarrhea, nausea, vomiting, flatulence and abdominal pain. These symptoms can occur especially when metformin is used for the first time or when the dose is high. That is the reason why metformin should be prescribed with the low dose, increased gradually. Long-term use of metformin may also cause vitamin B12 (cobalamin) deficiency resulting from malabsorption. The most serious adverse effect, but rare, is lactic acidosis [2,7-9].

The major glucose-lowering effect of metformin is the inhibition of hepatic gluconeogenesis with minimal impact on peripheral insulin-mediated glucose uptake. Metformin also sensitizes peripheral tissues (muscle tissue, adipose tissue) to the action of insulin. It alternates the intestinal microbiome and increases glucose utilisation. Metformin may also have impact on glucose metabolism by increasing glucagon-like peptide-1 (GLP-1) secretion [5,6,10].

It is worth noting that the therapeutic targets of metformin are expanding [2]. Researches indicate that metformin is characterized by antineoplastic, immunoregulatory, anti-aging and neuroprotective properties [11-14]. This biguanide may also affect the following infectious diseases: COVID-19 and tuberculosis [13]. Stopping the spread of infectious diseases constitutes one of the urgent health challenges for the World Health Organization in the next years. Global increase in the number of non-communicable diseases, including cancers and autoimmunological diseases, is also a serious problem of public health.

AIM

Thus, we aimed to evaluate the pleiotropic effects of metformin, taking into account its different mechanisms, efficacy and safety in contemporary public health challenges.

MATERIAL AND METHOD

We conducted the literature review using the PubMed and Google Scholar. We analysed reviews, systematic reviews, meta-analyses, randomized controlled trials, clinical trials, and observational studies published from 2014 to 2024.

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The following keywords were used: „metformin and therapy", „metformin and treatment" and „metformin and advances".

On the grounds of this review, we distinguished the new potential therapeutic targets of the metformin: cancers, neurological diseases, autoimmunological diseases, infectious diseases.

RESULTS

Cancers and metformin

Many studies confirm the relationship between diabetes and increased risk of developing various cancers. This risk is particularly higher in case of pancreatic, liver, endometrial, breast and colorectal cancers [12]. Therefore, there is an interest in the use of metformin for the treatment of various cancer diseases [2].

The mechanisms of metformin's anticancer properties are complex and result from both direct and indirect effects. Insulin and insulin-like growth factor 1 (IGF-1) stimulate epithelial cells proliferation and may therefore promote tumor formation. Metformin decreases insulin levels and in this way reduces the risk of carcinogenesis process. It also has anti-inflammatory effects by blocking the activity of a transcription factor (NF-κB). Thus, inflammatory processes are important in progression of cancer. On the other hand, the direct anticancer effect of the metformin results from the activation of the AMP-activated protein kinase (AMPK) pathway and thereby inhibition of the main regulator of cells' growth and proliferation, mTOR. Moreover, it inhibits cellular DNA damage, preventing the production of free oxygen radicals [11,12].

Breast cancer is the most prevalent cancer and the main cause of cancer-related death of the women. In the breast cancer, metformin can enhance the cytotoxic treatment effects and prevent the drug resistance [15,16]. A study proved that combination therapy of heme and metformin in the triple negative breast cancer (TNBC) inhibits tumor growth [17]. TNBC is characterized by the most adverse prognosis, invasiveness and ability to metastases. Moreover, it was found that metformin has an impact on decline in lymph node plasma cell proliferation and tumor angiogenesis in TNBC. In the cancers with the HER-2 overexpression, the drug reduces this expression in in vitro models [15]. Evidence for the biological effects of metformin in vivo includes up-regulation of tumor pAMPK and suppression of responses, reflecting its cytostatic properties [18].

There is a strong relationship between obesity and increased risk of endometrial cancer, what results from impaired estrogen and insulin regulation. Metformin has been shown to have anti-estrogenic effect on endometrial cells [19]. Endometrial cancer often precedes atypical endometrial hyperplasia as a precancerous lesion. Based on metanalysis, adjuvant metformin supported the regression of atypical endometrial hyperplasia to histologically correct endometrium and reduced cell proliferation biomarkers associated with tumor progression. In endometrial cancer, patients taking metformin had longer overall time of survival. Metformin also reduces the risk of endometrial cancer recurrence.

Colorectal cancer is the most prevalent among digestive system cancers and its incidence has been decreasing [20]. Metformin treatment inhibits aberrant crypt foci and polyp formation [21]. What is more, increasing data indicate a potential chemopreventive effect of metformin to colorectal cancer [22]. Scientific data suggest that metformin therapy may be associated with a decreased risk of colorectal adenomas and colorectal cancer in patients diagnosed with type 2 diabetes [23]. Potential mechanisms include: ameliorating intestinal inflammation and dysbiosis, suppressing major proliferative pathways, preventing DNA replication, accelerating tumor cells apoptosis, inhibiting intra-tumor angiogenesis [16,24].

Pancreatic ductal adenocarcinoma has the very bad prognosis [25]. In pancreatic cancer sulfonylureas that induce hyperinsulinemia increase its risk but metformin that prevent hyperinsulinemia and insulin resistance is thought to have positive impact on this cancer [26]. Metformin is associated with enhancing survival in pancreatic cancer patient with diabetes mellitus but it depends on the tumor stage [3,27,28].

Melanoma is the most aggressive form of skin cancer. Currently, ipilimumab and nivolumab are available in therapy of melanoma, but about 50% of patients do not respond to this treatment. It has been proved that metformin induces cell cycle arrest in melanoma cells in the G0-G1 phase and also causes autophagy and apoptosis in melanoma cancer cells [16,29]. There are trials that confirm efficacy of metformin in achieving better clinical outcomes in patients with melanoma [30,31].

Lung cancer divides into two types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Studies announced that both in patients with SCLC and NSCLC and diabetes mellitus type 2, treatment with metformin improved overall survival [32,33]. However, in nondiabetic patients with advanced NSCLC, metformin combined with antineoplastic drugs has been shown to improve disease control rate, but there was no improvement in long-term prognosis [34]. Metformin also may be associated with lower risk of lung cancer [35-37].

Neurological diseases

Another issue related to the extremely wide use of metformin in medicine is its impact on neurological diseases. Among them we can distinguish: multiple sclerosis (MS), Parkinson's disease, Alzheimer's disease, Huntington's disease, epilepsy, depression and others [2,38].

The anti-aging effect of metformin needs to be emphasized in the context of neurodegenerative diseases. Metformin extends lifespan in humans, mice and nematode *Caenorhabditis elegans* by changing microbial folate and methionine metabolism, but this effect is not seen in older worms, fruit fly and rats [39-41]. It is hard to explanate mechanism of this observation, however it may result from different patterns of aging in organisms [41].

The Alzheimer's disease is the most common neurodegenerative disease. Diabetes mellitus type 2 increases risk of the Alzheimer's disease [42,43]. Metformin inhibits aggregation of amyloid beta by increasing the activity of the insulin-degrading enzyme and neprilysin levels. Metanalysis showed that metformin did not decrease the risk of the Alzheimer's disease. In Asians it may even increase the risk [44]. Another metanalysis did not confirm this conclusions and indicate on neuroprotective properties of metformin [45,46].

Studies also show that type 2 diabetes mellitus increases the risk of the Parkinson's disease [42]. In the Parkinson's disease metformin decreases the expression of α-synuclein and the total of α-synuclein positive cells, diminishes the loss of dopaminergic neurons [12]. However, based on metanalysis, metformin did not change the risk of the Parkinson's disease [47]. Moreover, it may increase the risk of the Parkinson's dis-

ease development [48]. It was established that deficiency of vitamin B12, potential adverse effect of long-term metformin therapy may worsen Parkinson's disease course [49].

Multiple sclerosis (MS) is a demyelinating neurodegenerative disorder [50]. Differentiation of oligodendrocyte progenitor cells to oligodendrocytes decreases with age. Nevertheless, metformin can reverse this process and enhance oligodendrogenesis [51]. Oxidative stress accelerates the demyelination process, but adding metformin to MS therapy has an influence on oxidative stress marker and reduces inflammation [50]. Moreover, metformin treatment improves spatial memory in a rat MS model [52].

People with diabetes mellitus are at higher risk of developing epilepsy [53]. Epilepsy predisposes to the development of diabetes due to increased cortisol release [54]. In preclinical studies metformin was effective in seizure control of epilepsy [55]. AMPK activation by metformin, dysregulated in epilepsy, improved induced status epilepticus in rats. Metformin delays epilepsy onset, reduces neuronal loss in the hippocampus by improving the expression of brain-derived neurotrophic factor, prevents cognitive impairments, attenuates post-ictal depression [56]. It reduces α-synuclein and increases protein phosphatase 2A with modulation of neuroinflammation [54]. It has been even shown that metformin was effective in treating temporal lobe epilepsy which is the most common resistant form of epilepsy [54].

Huntigton's disease is neurodegenerative, hereditary disorder caused by an expansion of CAG repeats in the HTT gene. It has been found that metformin protects cells against the toxicity of the mutant Huntingtin protein and reverse symptoms associated with Huntington's disease, improves cognitive function. The metformin treatment should be introduced at a very early stage to significantly influence the disease. Then gene suppression has a more stable effect on phenotype [57,58].

Diabetes and depression often co-occur together. It was observed that metformin reduces the incidence of depression and alleviates depression, depending on the dose [59,60]. Lower doses correlated with lower risk of depression, especially in patients with glucose metabolism disorders. Contrary, higher doses of metformin increased this risk. It may be associated with side effect of metformin, more precisely cobalamin deficiency which is a risk factor of depression [61,62]. The mechanism of action of metformin is based on modifying abnormal glutamatergic transmission [63]. Inflammation and oxidative stress, processes influenced by metformin, also play important role in depression [64].

Autoimmunological diseases

Metformin has been proved to support treatment of many popular autoimmunological diseases. Studies have shown that metformin can have impact on immunopathological mechanisms associated with systemic autoimmune diseases by interference into T helper regulatory cell balance, macrophage polarization, germinal center formation, autoantibody production, cytokine secretion [65].

One of such autoimmunological diseases is Hashimoto's thyroiditis. In animal model metformin reduced thyroid globulin antibodies and lymphocyte infiltration in thyroid tissue. Intestinal flora, what is different from healthy individuals, also altered after metformin therapy [65]. What is more, impact of levothyroxine on thyroid autoimmunity and hypothalamic-pituitary-thyroid axis activity is stronger in the group of patients receiving metformin [66].

Rheumatoid arthritis is a chronic, progressive, systemic inflammatory disease that can have impact on patient's quality of life and lead to serious complications [67]. Metformin reduces cartilage degradation and inflammatory process, protects bone tissue thanks to its immunomodulatory properties [68]. In the randomized controlled trial metformin enhanced the anti-rheumatic effect of methotrexate [69]. Adding metformin to conventional synthetic disease modifying anti-rheumatic drugs decreased inflammatory parameters CRP and adiponectin levels [67]. The risk of rheumatoid arthritis is also reduced due to metformin therapy [68].

Systemic Lupus Erythematosus (SLE) is a chronic inflammatory disease, affecting potentially many organ systems. Based on randomized controlled trial metformin reduced exacerbations of the SLE in patients with low disease activity [70]. It might be an adjuvant therapy in achieving treatment targets in SLE patients [71]. This biguanide combined with abatacept decreased the development of lupus nephritis in animal model [72].

Infectious diseases

It is conceivable that metformin as an immunoregulatory drug is effective in some infectious diseases. The effectiveness of metformin has been studied in relation to COVID-19 disease. COVID-19 treatment is a serious challenge for medical staff. Hyperglycemia in the course of diabetes and obesity are associated with a more severe course of the disease [40]. Metformin did not prevent the hypoxemia, hospitalization or death associated with COVID-19 [73]. Contrary, treatment with metformin glycinate reduced the viral load in patients with COVID-19 [74]. Outpatient treatment with metformin reduced long COVID-19 incidence among patients with overweight or obesity [75].

Metformin decreases risk of active tuberculosis and mortality due to tuberculosis among patients with diabetes. Metformin enhance phagocytosis and oxidative stress in response to Mycobacterium Tuberculosis [24]. According to randomized controlled trial, the addition of metformin to standard anti-tuberculosis treatment did not accelerate sputum culture conversion. However, it reduced inflammation, what was evidenced by improvement in inflammatory markers and faster clearance on chest X-ray [76]. Thus, treatment outcomes could be improved by metformin medication among diabetics [77].

CONCLUSIONS

In conclusion, the studies confirm that metformin is pluripotential drug. Despite it is an old drug, its different mechanisms of action were discovered over time. Metformin, depending on the cancer and its stage, enhances the cancer treatment effects, prevents the drug resistance, lengthens overall time of survival, reduces the risk of recurrence. In the Parkinson's disease, Alzheimer's disease and depression metformin can even increase the risk of their occurrence, especially in high doses. Such doses predispose to the cobalamine deficiency, affecting the functioning of the nervous system. It has positive impact on the course of autoimmunological diseases, mainly Hashimoto's thyroiditis, systemic lupus erythematosus and rheumatoid arthritis. Among diabetics treatment, outcomes of COVID-19 and tuberculosis could be improved by metformin.

Reports about possibilities of adjuvant metformin therapy are very promising, but it cannot be recommended as standard

treatment. It should be highlighted that diseases, constituting therapeutic targets for metformin are associated with serious prognosis like cancers, the efficacy of their current treatment methods are still insufficient or its prevalence is increasing. In the face of public health care problems, research on other innovative methods, including metformin therapy, seems to be significant and necessary. Possibilities of using the metformin as standard treatment require further investigation, preferentially randomized controlled trials on the bigger research samples.

REFERENCES

1. Bailey CJ. Metformin: historical overview. Diabetologia. 2017;60(9):1566-76.
2. Triggle CR, Mohammed I, Bshesh K, et al. Metformin: Is it a drug for all reasons and diseases? Metabolism. 2022;133:155223.
3. Zhou PT, Li B, Liu FR, et al. Metformin is associated with survival benefit in pancreatic cancer patients with diabetes: a systematic review and meta-analysis. Oncotarget. 2017;8(15):25242-50.
4. Romero R, Erez O, Hüttemann M, et al. Metformin, the aspirin of the 21st century: its role in gestational diabetes, prevention of preeclampsia and cancer, and the promotion of longevity. Am J Obstet Gynecol. 2017;217(3):282-302.
5. LaMoia TE, Shulman GI. Cellular and molecular mechanisms of metformin action. Endocr Rev. 2021;42(1):77-96.
6. Foretz M, Guigas B, Bertrand L, et al. Metformin: from mechanisms of action to therapies. Cell Metab. 2014;20(6):953-66.
7. Sportelli C, Urso D, Jenner P, et al. Metformin as a potential neuroprotective agent in prodromal Parkinson's disease-viewpoint. Front Neurol. 2020;11:556.
8. Feng J, Wang X, Ye X, et al. Mitochondria as an important target of metformin: The mechanism of action, toxic and side effects, and new therapeutic applications. Pharmacol Res. 2022;177:106114.
9. Chen S, Gan D, Lin S, et al. Metformin in aging and aging-related diseases: clinical applications and relevant mechanisms. Theranostics. 2022;12(6):2722-40.
10. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. Diabetologia. 2017;60(9):1577-85.
11. Podhorecka M, Ibanez B, Dmoszyńska A. Metformin – its potential anti-cancer and anti-aging effects. Postepy Hig Med Dosw (Online). 2017;71(0):170-5.
12. Dutta S, Shah RB, Singhal S, et al. Metformin: A review of potential mechanism and therapeutic utility beyond diabetes. Drug Des Devel Ther. 2023;17:1907-32.
13. Naseri A, Sanaie S, Hamzehzadeh S, et al. Metformin: new applications for an old drug. J Basic Clin Physiol Pharmacol. 2023;34(2):151-60.
14. Drzewoski J, Hanefeld M. The Current and potential therapeutic use of metformin-the good old drug. Pharmaceuticals (Basel). 2021;14(2):122.
15. Cejuela M, Martin-Castillo B, Menendez JA, et al. Metformin and breast cancer: Where are we now? Int J Mol Sci. 2022;23(5):2705.
16. Lv Z, Guo Y. Metformin and its benefits for various diseases. Front Endocrinol (Lausanne). 2020;11:191.
17. Lee J, Yesilkanal AE, Wynne JP, et al. Effective breast cancer combination therapy targeting BACH1 and mitochondrial metabolism. Nature. 2019;568(7751):254-8.
18. Hadad SM, Coates P, Jordan LB, et al. Evidence for biological effects of metformin in operable breast cancer: biomarker analysis in a pre-operative window of opportunity randomized trial. Breast Cancer Res Treat. 2015;150(1):149-55.
19. Tabrizi AD, Melli MS, Foroughi M, et al. Antiproliferative effect of metformin on the endometrium – a clinical trial. Asian Pac J Cancer Prev. 2014;15(23):10067-70.
20. Anisimov VN. Metformin for prevention and treatment of colon cancer: A reappraisal of experimental and clinical data. Curr Drug Targets. 2016;17(4):439-46.
21. Higurashi T, Nakajima A. Metformin and colorectal cancer. Front Endocrinol (Lausanne). 2018;9:622.
22. Song M, Chan AT. Environmental factors, gut microbiota, and colorectal cancer prevention. Clin Gastroenterol Hepatol. 2019;17(2):275-89.
23. Liu F, Yan L, Wang Z, et al. Metformin therapy and risk of colorectal adenomas and colorectal cancer in type 2 diabetes mellitus patients: A systematic review and meta-analysis. Oncotarget. 2017;8(9):16017-26.
24. Ala M. The Emerging Role of metformin in the prevention and treatment of colorectal cancer: A game changer for the management of colorectal cancer. Curr Diabetes Rev. 2022;18(8):e051121197762.
25. Broadhurst PJ, Hart AR. Metformin as an adjunctive therapy for pancreatic cancer: A review of the literature on its potential therapeutic use. Dig Dis Sci. 2018;63(11):2840-52.
26. De Souza A, Khawaja KI, Masud F, et al. Metformin and pancreatic cancer: Is there a role? Cancer Chemother Pharmacol. 2016;77(2):235-42.
27. Li X, Li T, Liu Z, et al. The effect of metformin on survival of patients with pancreatic cancer: a meta-analysis. Sci Rep. 2017;7(1):5825.
28. Shi YQ, Zhou XC, Du P, et al. Relationships are between metformin use and survival in pancreatic cancer patients concurrent with diabetes: A systematic review and meta-analysis. Medicine (Baltimore). 2020;99(37):e21687.
29. Jaune E, Rocchi S. Metformin: Focus on melanoma. Front Endocrinol (Lausanne). 2018;9:472.
30. Augustin RC, Huang Z, Ding F, et al. Metformin is associated with improved clinical outcomes in patients with melanoma: a retrospective, multi-institutional study. Front Oncol. 2023;13:1075823.
31. Urbonas V, Rutenberge J, Patasius A, et al. The impact of metformin on survival in patients with melanoma-national cohort study. Ann Epidemiol. 2020;52:23-5.
32. Barrios-Bernal P, Zatarain-Barrón ZL, Hernández-Pedro N, et al. Will We unlock the benefit of metformin for patients with lung cancer? Lessons from current evidence and new hypotheses. Pharmaceuticals (Basel). 2022;15(7):786.
33. Cao X, Wen ZS, Wang XD, et al. The clinical effect of metformin on the survival of lung cancer patients with diabetes: A comprehensive systematic review and meta-analysis of retrospective studies. J Cancer. 2017;8(13):2532-41.
34. Duan X, Liao B, Liu X, et al. Efficacy of metformin adjunctive therapy as the treatment for non-diabetic patients with advanced non-small cell lung cancer: A Systematic review and Meta-analysis. J Res Med Sci. 2023;28:45.
35. Zhang ZJ, Bi Y, Li S, et al. Reduced risk of lung cancer with metformin therapy in diabetic patients: a systematic review and meta-analysis. Am J Epidemiol. 2014;180(1):11-4.
36. Yao L, Liu M, Huang Y, et al. Metformin use and lung cancer risk in diabetic patients: A Systematic review and meta-analysis. Dis Markers. 2019;2019:6230162.
37. Xiao K, Liu F, Liu J, et al. The effect of metformin on lung cancer risk and survival in patients with type 2 diabetes mellitus: A meta-analysis. J Clin Pharm Ther. 2020;45(4):783-92.
38. Shoshan-Barmatz V, Anand U, Nahon-Crystal E, et al. Adverse effects of metformin from diabetes to COVID-19, cancer, neurodegenerative diseases, and aging: Is VDAC1 a common target? Front Physiol. 2021;12:730048.
39. Li Z, Zhang Z, Ren Y, et al. Aging and age-related diseases: from mechanisms to therapeutic strategies. Biogerontology. 2021;22(2):165-87.
40. Triggle CR, Marei I, Ye K, et al. Repurposing metformin for vascular disease. Curr Med Chem. 2023;30(35):3955-78.
41. Soukas AA, Hao H, Wu L. Metformin as anti-aging therapy: Is it for everyone? Trends Endocrinol Metab. 2019;30(10):745-55.
42. Nowell J, Blunt E, Gupta D, et al. Antidiabetic agents as a novel treatment for Alzheimer's and Parkinson's disease. Ageing Res Rev. 2023;89:101979.
43. Al-Kuraishy HM, Al-Gareeb AI, Saad HM, Batiha GES. Long-term use of metformin and Alzheimer's disease: beneficial or detrimental effects. Inflammopharmacology. 2023;31(3):1107-15.
44. Luo A, Ning P, Lu H, et al. Association between metformin and Alzheimer's disease: A systematic review and meta-analysis of clinical observational studies. J Alzheimers Dis. 2022;88(4):1311-23.
45. Ye F, Luo YJ, Xiao J, et al. Impact of insulin sensitizers on the incidence of dementia: A meta-analysis. Dement Geriatr Cogn Disord. 2016;41(5-6):251-60.
46. Campbell JM, Stephenson MD, de Courten B, et al. Metformin use associated with reduced risk of dementia in patients with diabetes: A systematic review and meta-analysis. J Alzheimers Dis. 2018;65(4):1225-36.
47. Xie Y, Wang J, Jiang J, et al. Do oral antidiabetic medications alter the risk of Parkinson's disease? An updated systematic review and meta-analysis. Neurol Sci. 2023;44(12):4193-203.
48. Qin X, Zhang X, Li P, et al. Association between diabetes medications and the risk of Parkinson's disease: A Systematic review and meta-analysis. Front Neurol. 2021;12:678649.
49. Ping F, Jiang N, Li Y. Association between metformin and neurodegenerative diseases of observational studies: systematic review and meta-analysis. BMJ Open Diabetes Res Care. 2020;8(1):e001370.
50. Abdelgaied MY, Rashad MH, El-Tayebi HM, et al. The impact of metformin use on the outcomes of relapse-remitting multiple sclerosis patients receiving interferon beta 1a: an exploratory prospective phase II open-label randomized controlled trial. J Neurol. 2024;271(3):1124-32.

51. Neumann B, Baror R, Zhao C, et al. Metformin restores CNS remyelination capacity by rejuvenating aged stem cells. Cell Stem Cell. 2019;25(4):473-85.
52. Loan A, Syal C, Lui M, et al. Promising use of metformin in treating neurological disorders: biomarker-guided therapies. Neural Regen Res. 2024;19(5):1045-55.
53. Nandini HS, Paudel YN, Krishna KL. Envisioning the neuroprotective effect of Metformin in experimental epilepsy: A portrait of molecular cross-talk. Life Sci. 2019;233:116686.
54. Alnaaim SA, Al-Kuraishy HM, Al-Gareeb AI, et al. New insights on the potential anti-epileptic effect of metformin: Mechanistic pathway. J Cell Mol Med. 2023;27(24):3953-65.
55. Singh R, Sarangi SC, Singh S, et al. A review on role of metformin as a potential drug for epilepsy treatment and modulation of epileptogenesis. Seizure. 2022;101:253-61.
56. Sanz P, Serratosa JM, Sánchez MP. Beneficial effects of metformin on the central nervous system, with a focus on epilepsy and lafora disease. Int J Mol Sci. 2021;22(10):5351.
57. Arnoux I, Willam M, Griesche N, et al. Metformin reverses early cortical network dysfunction and behavior changes in Huntington's disease. Elife. 2018;7:e38744.
58. Hervas D, Fornes-Ferres V, Gomes Escribano AP, et al. Metformin intake associates with better cognitive function in patients with Huntington's disease. PloS One. 2017;12(6).
59. Syed SU, Cortez JI, Wilson SJ. Depression, inflammation, and the moderating role of metformin: Results from the midlife in the United States study and Sacramento area latino study on aging. Psychosom Med. 2024;86(5):473-83.
60. Kessing LV, Rytgaard HC, Ekstrøm CT, et al. Antidiabetes agents and incident depression: A nationwide population-based study. Diabetes Care. 2020;43(12):3050-60.
61. Chen F, Wei G, Wang Y, et al. Risk factors for depression in elderly diabetic patients and the effect of metformin on the condition. BMC Public Health. 2019;19(1):1063.
62. Biemans E, Hart HE, Rutten GEHM, et al. Cobalamin status and its relation with depression, cognition and neuropathy in patients with type 2 diabetes mellitus using metformin. Acta Diabetol. 2015;52(2):383-93.
63. Li S, Yang D, Zhou X, et al. Neurological and metabolic related pathophysiologies and treatment of comorbid diabetes with depression. CNS Neurosci Ther. 2024;30(4):e14497.
64. Hamal C, Velugoti LSDR, Tabowei G, et al. Metformin for the improvement of comorbid depression symptoms in diabetic patients: A systematic review. Cureus. 14(8):e28609.
65. Jia X, Zhai T, Qu C, et al. Metformin reverses Hashimoto's thyroiditis by regulating key immune events. Front Cell Dev Biol. 2021;9:685522.
66. Krysiak R, Kowalcze K, Okopień B. Differences in levothyroxine action on thyroid autoimmunity and hypothalamic-pituitary-thyroid axis activity between metformin- and myo-inositol-treated women with autoimmune subclinical hypothyroidism. J Clin Pharm Ther. 2022;47(10):1704-10.
67. Gharib M, Elbaz W, Darweesh E, et al. Efficacy and safety of metformin use in rheumatoid arthritis: A randomized controlled study. Front Pharmacol. 2021;12:726490.
68. Liang J, Cai Y, Zhang J, et al. Metformin treatment reduces the incidence of rheumatoid arthritis: A two-sample mendelian randomized study. J Clin Med. 2023;12(7):2461.
69. Abdallah MS, Alarfaj SJ, Saif DS, et al. The AMPK modulator metformin as adjunct to methotrexate in patients with rheumatoid arthritis: A proof-of-concept, randomized, double-blind, placebo-controlled trial. Int Immunopharmacol. 2021;95:107575.
70. Sun F, Geng S, Wang H, et al. Effects of metformin on disease flares in patients with systemic lupus erythematosus: post hoc analyses from two randomised trials. Lupus Sci Med. 2020;7(1):e000429.
71. Sun F, Zhang D, Wang H, et al. Attaining treat-to-target endpoints with metformin in lupus patients: a pooled analysis. Clin Exp Rheumatol. 2022;40(9):1733-7.
72. Cornaby C, Elshikha AS, Teng X, et al. Efficacy of the combination of metformin and CTLA4Ig in the (NZB × NZW)F1 mouse model of lupus nephritis. Immunohorizons. 2020;4(6):319-31.
73. Bramante CT, Huling JD, Tignanelli CJ, et al. Randomized trial of metformin, ivermectin, and fluvoxamine for COVID-19. N Engl J Med. 2022;387(7):599-610.
74. Ventura-López C, Cervantes-Luevano K, Aguirre-Sánchez JS, et al. Treatment with metformin glycinate reduces SARS-CoV-2 viral load: An in vitro model and randomized, double-blind, Phase IIb clinical trial. Biomed Pharmacother. 2022;152:113223.
75. Bramante CT, Buse JB, Liebovitz DM, et al. Outpatient treatment of COVID-19 and incidence of post-COVID-19 condition over 10 months (COVID-OUT): a multicentre, randomised, quadruple-blind, parallel-group, phase 3 trial. Lancet Infect Dis. 2023;23(10):1119-29.
76. Padmapriydarsini C, Mamulwar M, Mohan A, et al. Randomized trial of metformin with anti-tuberculosis drugs for early sputum conversion in adults with pulmonary tuberculosis. Clin Infect Dis. 2022;75(3):425-34.
77. Yu X, Li L, Xia L, et al. Impact of metformin on the risk and treatment outcomes of tuberculosis in diabetics: a systematic review. BMC Infect Dis. 2019;19(1):859.

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