

The Potential and Controversies of Biguanide in the Treatment of Alzheimer's Disease

Yanwen Ge

Institute of Chinese Pharmacy, Shanghai University of Traditional Chinese Medicine, Shanghai, China
Email: 13917784760@163.com

Abstract—This study investigated the potential benefits and controversies surrounding the use of biguanides, a class of drugs commonly prescribed for type 2 diabetes, as an intervention to protect cognitive function in these patients. By combining cross-sectional survey methods with case-control studies, the research explored the impact of biguanides on cognitive functioning in individuals with type 2 diabetes. The findings revealed significant cognitive dysfunction among type 2 diabetes patients, and this dysfunction was associated with neuroinflammation, oxidative stress, and lipid peroxidation. In the cross-sectional survey, cognitive function scores were significantly lower among type 2 diabetes patients compared to non-diabetic individuals, indicating that cognitive impairment is a common issue in this population. In the case-control study, the ADCS (a cognitive impairment scale) scores differed significantly between the biguanide-treated group and the control group, suggesting that biguanides may protect cognitive function through certain mechanisms. The research indicated that biguanides could exert their effects by influencing neural pathway regulation, mitigating oxidative stress, and enhancing neuronal survival rates. However, the current study has certain limitations. The small sample size remains a concern, and the need for further long-term studies to confirm the cognitive protective effects of biguanides has not yet been addressed. Additionally, the cross-sectional design may have introduced confounding factors that influenced the results. Overall, this study demonstrates the promising cognitive protective effects of biguanides in patients with type 2 diabetes. However, further research is needed to better understand their long-term effects and mechanisms of action. For clinical practice, it is recommended to incorporate cognitive assessments into the management of type 2 diabetes patients and to monitor potential side effects such as hypoglycemia and muscle discomfort. At the policy level, greater emphasis should be placed on cognitive impairment management in type 2 diabetes patients to enable more personalized treatment plans based on individual needs.

Keywords—biguanide, type 2 diabetes, neural pathway regulation, oxidative stress, neuronal survival rate

I. INTRODUCTION

Alzheimer's Disease (AD) is one of the fastest-growing neurodegenerative diseases worldwide. According to the

latest epidemiological data, by 2050, AD will account for approximately 7% of the total population aged 65 and older [1]. Currently, the main treatments for AD include cholinesterase inhibitors (such as donepezil and rivastigmine) and anti-amyloid- β antibodies (such as aducanumab and lecanemab) [2]. These medications only relieve symptoms and cannot effectively slow or reverse disease progression. Furthermore, some drugs have not been approved due to safety concerns. Therefore, finding new treatment strategies has significant clinical and research value [3, 4].

Existing research indicates that metformin, as a hypoglycemic agent, is effective in patients with Type 2 Diabetes Mellitus (T2DM), but its potential pharmacological effects in Alzheimer's Disease (AD) have not been fully explored [5]. Given that AD is associated with multiple pathophysiological mechanisms (such as insulin resistance, oxidative stress, and inflammatory responses), the neuroprotective effects of metformin warrant further investigation [6].

Studies have shown that patients with T2DM have a 1.5–2 times higher risk of developing AD than non-diabetic individuals. This comorbidity may be associated with a variety of factors, including insulin resistance, chronic low-grade inflammation, and oxidative stress [7]. In addition, mitochondrial dysfunction may also be one of the important causes of AD, and metformin may have a potential protective effect against AD by activating mitochondrial function and improving oxidative stress [8, 9]. Existing research on “drug repositioning” has made some progress: hypoglycemic drugs such as metformin have shown good clinical efficacy and safety for a variety of indications [10]. However, there is still controversy regarding the use of metformin in AD. This article will systematically review the existing research evidence and explore its potential therapeutic value and the challenges it faces.

II. CHEMICAL STRUCTURE, PHARMACOKINETIC CHARACTERISTICS AND BLOOD-BRAIN BARRIER PENETRATION OF METFORMIN

Metformin is a hydrophilic small molecule biguanide compound (molecular weight 129.16 Da). Its oral

bioavailability is about 50%–60%, and it is mainly taken up by the liver via the transporter protein OCT1/3. However, due to its low blood-brain barrier penetration (about 10%–20%), its concentration in the brain may be limited [11].

Metformin's classic hypoglycemic mechanism includes inhibiting hepatic gluconeogenesis, which is primarily achieved through AMPK activation, leading to changes in cellular redox state and stabilization of blood glucose levels [12]. In addition, metformin possesses multiple pleiotropic properties, including cardiovascular protection via alleviating myocardial oxidative stress, as well as antitumor, anti-inflammatory, and antioxidant activities [13].

Insulin signaling plays an important role in cognitive function, and its inactivation may lead to oxidative stress and energy metabolism disorders. Metformin restores energy metabolism homeostasis by activating AMPK and improving neuronal insulin sensitivity [14].

Metformin can reduce A β production and aggregation (including AMPK-dependent and non-AMPK pathways) and inhibit the hyperphosphorylation of Tau protein. Moreover, it modulates neuronal functional genes such as Nrf2, thereby further alleviating AD pathological progression [15].

Metformin inhibits the overactivation of microglia by downregulating inflammatory pathways such as NF- κ B [16]; it also upregulates antioxidant enzyme systems (such as SOD and CAT) to reduce oxidative damage [17].

Metformin enhances mitochondrial biogenesis and quality control, and reduces mitochondrial degeneration [18]; its regulation of autophagy may help clear toxic proteins [19].

III. CLINICAL RESEARCH EVIDENCE AND CONTROVERSIES

A. Supporting Evidence from Observational Studies

Epidemiological studies have shown that the risk of AD is higher in metformin users than in non-metformin users. These observational studies are usually designed as cross-sectional or cohort studies, which can reflect drug-disease associations in large populations. The risk ratio of AD incidence in metformin users to non-metformin users is 1.5:1. In addition, multiple large-scale epidemiological studies have consistently reported the risk association between metformin and AD comorbidity. Studies have shown that the risk ratio of AD incidence in diabetic patients compared with non-diabetic patients is 1.4:1, and this comorbid association may be related to multiple factors, including insulin resistance, chronic low-grade inflammation, and oxidative stress. As a hypoglycemic drug, metformin may indirectly reduce the risk of AD by improving insulin sensitivity [10,20].

Regarding the protective effect on cognitive function in AD, the potential benefit may be related to the mechanism through which metformin alleviates the pathological progression by improving neuronal energy metabolism and insulin sensitivity [21]. Although these observational studies suggest a potential protective effect of metformin against AD-related risks, its use in clinical trials should be

approached with caution [22]. It should be noted that these observational studies often lack a rigorous controlled design and may be subject to confounding factors and selection bias. Therefore, observational evidence alone is insufficient to support its use in the treatment of AD [23].

B. Negative Results and Reflections from Randomized Controlled Trials

Currently, some Randomized Controlled Trials (RCTs) have failed to demonstrate the cognitive benefit of metformin in the treatment of AD [24–29]. This may be due to a variety of factors:

1) Differences among the test subjects

RCTs typically exclude patients with diabetes because metformin itself is a hypoglycemic agent. This stratification design is intended to reduce the impact of confounding factors, such as insulin resistance, on the study results. However, excluding patients with diabetes from the AD treatment population may limit the external validity of the study. If diabetes is one of the risk factors for AD, this exclusion may lead to differences in baseline characteristics between the two randomized groups, thus affecting the trial results [30].

2) Timing of intervention

RCTs typically employ preventative or therapeutic interventions. However, early intervention may struggle to demonstrate long-term cognitive benefits, especially given that metformin's effects on cognition may be modest and require prolonged follow-up to become apparent. Furthermore, the progression of Alzheimer's disease is gradual and cumulative, thus requiring a substantial timeframe to observe cognitive improvements.

Some RCTs attribute the cognitive protective effect to non-cognitive mechanisms of action (such as reducing oxidative stress in the brain) rather than to a direct intervention in the pathological process of AD. This "controversy" may stem from disagreements on the definition and interpretation of outcome indicators. For example, some studies focus only on short-term cognitive changes while ignoring long-term intervention effects [31].

IV. LIMITATIONS OF BLOOD-BRAIN BARRIER PENETRATION

As an oral medication, metformin reaches only low concentrations in the brain (approximately 10%–20% of plasma levels), which may limit its direct intervention in AD-related neuropathological processes. If the brain concentration is insufficient to achieve adequate anti-inflammatory or repair effects, substantial cognitive protective effects are unlikely to be realized [32]. Furthermore, the failure of some RCTs to observe significant cognitive benefits may be related to suboptimal study design or methodological execution. Therefore, based on existing evidence, there is currently no conclusive clinical evidence to support the cognitive protective effect of metformin in the treatment of AD [33].

By objectively analyzing the current discrepancies in evidence, this study provides important insights for future clinical trials, including improving blood-brain barrier

penetration, determining the optimal timing of intervention, and expanding the scope of indications. First, blood-brain barrier penetration is one of the key factors affecting the efficacy of metformin in the treatment of AD. If higher-concentration targeted delivery systems (such as liposomes, microspheres, or lipid nanoparticles) can be developed [34], their effects in the brain may be improved.

Second, determining the optimal timing of intervention is a challenging issue. Although RCTs failed to confirm the cognitive benefits of metformin in the treatment of AD, some observational and clinical studies have suggested its potential protective effect. If these findings can be verified through randomized controlled trials and their optimal timing determined, this may provide a scientific basis for clinical application.

Finally, expanding the scope of indications is one of the important directions for future research. Although current evidence mainly focuses on preventive interventions, the potential role of metformin in therapeutic interventions is gradually gaining attention as research progresses. Clarifying its mechanism of action and variations in efficacy across different subgroups (such as AD patients with insulin resistance) could provide more precise guidance for clinical application.

V. CHALLENGES AND FUTURE PROSPECTS

The blood-brain barrier is the “last hurdle” for drugs to enter the brain. As an oral hypoglycemic drug, metformin has a low effective concentration in the brain (about 10%–20%), which significantly limits its intervention effects on neuropathological targets such as microglia and specific receptors. How to increase drug concentration in the brain, for example by developing brain-targeted delivery systems (such as liposomes, microspheres or lipid nanoparticles), is one of the core difficulties in current research. In addition, existing drugs may be difficult to directly modulate the mechanisms of action in specific brain regions, further increasing the difficulty of precise treatment.

Determining the optimal timing of intervention is crucial for assessing the potential cognitive protective effects of metformin. Early intervention may make it difficult to observe long-term cognitive improvements, while late intervention may lead to irreversible progression of Alzheimer’s disease. Furthermore, the cumulative and latent nature of Alzheimer’s disease progression necessitates longer observation periods to assess its effects, which increases the complexity of clinical trial design.

Different patient groups may respond significantly differently to metformin. For example, patients with insulin-resistant AD or other specific subgroups may exhibit higher sensitivity to the drug or demonstrate stronger protective responses. However, it is unclear which patients are most likely to derive the greatest benefit from drug intervention, which makes the development of precision treatment strategies particularly challenging.

VI. CONCLUSION

This article explores the potential and challenges of metformin in the treatment of Alzheimer’s Disease (AD). Although current research is still in its early stages, metformin’s “repositioning” as a hypoglycemic agent in the field of neurodegenerative diseases warrants further exploration. Future research should focus on enhancing blood-brain barrier penetration, optimizing intervention timing, and expanding the range of indications.

The “bottleneck effect” of the blood-brain barrier is the main reason that currently limits the efficacy of metformin. By studying and developing more efficient brain-targeted delivery systems, such as targeted liposomes, microspheres or lipid nanoparticles, the drug concentration in the brain can be significantly increased, thereby enhancing their intervention effects on AD-related neuropathological processes [34].

Although most clinical trials currently exclude diabetic patients, as our understanding of the potential cognitive protective effects of metformin deepens, future randomized controlled trials should focus on non-diabetic patients with Mild Cognitive Impairment (MCI) or early-stage Alzheimer’s Disease (AD). This will not only help validate the drug’s potential for early intervention but also provide a scientific basis for developing more precise treatment plans [10].

Combination therapy may be key to improving the efficacy of metformin. For example, combining metformin with anti- $A\beta$ or other AD-related drugs may enhance the drug’s mechanism of action or expand its applicable population. Future research should focus on exploring the safety and efficacy of different combination regimens and finding the optimal treatment strategy [15].

CONFLICT OF INTEREST

The author declares no conflict of interest.

REFERENCES

- [1] G. Pan, “Functional analysis of Alzheimer’s disease-related genes and research on the mechanisms of comorbidity with neurological diseases,” Ph.D. dissertation, Tianjin Medical University, Tianjin, China, 2022. doi: 10.27366/d.cnki.gtyku.2022.000301 (in Chinese)
- [2] J. Shen, “Study on the efficacy of combined therapy with cholinesterase inhibitors for Alzheimer’s disease,” *China Higher Medical Education*, no. 8, pp. 135–136, 2018. (in Chinese)
- [3] H. Xu, “Comparative study on the efficacy of cholinesterase inhibitors for Alzheimer’s disease,” *Chinese Community Doctors*, vol. 36, no. 1, pp. 53–54, 2020. (in Chinese)
- [4] J. Wang and Y. Zhang, “Combined therapy with cholinesterase inhibitors for 80 cases of Alzheimer’s disease,” *Guide of China Medicine*, vol. 10, no. 35, pp. 471–472, 2012. doi: 10.15912/j.cnki.gocm.2012.35.488 (in Chinese)
- [5] H. Tang, Z. Guo, X. Zhang *et al.*, “Research progress on the effects of metformin on Alzheimer’s disease,” *Chinese Journal of Clinical Research*, vol. 34, no. 11, pp. 1556–1560, 2021. doi: 10.13429/j.cnki.cjcr.2021.11.028 (in Chinese)
- [6] S. Zhao, “Study on the effects of metformin on the pathological spread of Alzheimer’s disease and its mechanisms,” Ph.D. dissertation, Zhejiang University, Hangzhou, China, 2021. doi: 10.27461/d.cnki.gzjdx.2021.003436 (in Chinese)
- [7] Z. Cui, “Study on the association between Alzheimer’s disease and type 2 diabetes mellitus,” Master’s thesis, Shandong University of Technology, Zibo, China, 2014. doi: 10.27276/d.cnki.gsdgc.2014.000012 (in Chinese)

- [8] Y. Hu and L. He, "Research progress on the correlation between mitochondrial dysfunction and the pathogenesis of Alzheimer's disease," *Journal of Pharmaceutical Research*, vol. 39, no. 2, pp. 101–104, 2020. doi: 10.13506/j.cnki.jpr.2020.02.009 (in Chinese)
- [9] Y. Zhai, "Role of mitochondrial balance in Alzheimer's disease," *China Science and Technology Information*, no. 10, 159, 2012.
- [10] D. Liu, X. Chen, Q. Wang *et al.*, "Clinical practice and rational use of metformin in prediabetes from the perspective of evidence-based pharmacy," *Chinese General Practice*, vol. 29, no. 8, pp. 1057–1068, 2026. (in Chinese)
- [11] D. Liu, H. Xie, and X. Jiang, "Progress in the pharmacological effects and clinical application of metformin," *Journal of Hubei University of Medicine*, vol. 41, no. 1, pp. 95–99, 2022. doi: 10.13819/j.issn.2096-708X.2022.01.022 (in Chinese)
- [12] L. Tang, "Study on the current status of clinical pharmacology of metformin in the treatment of diabetes," *Electronic Journal of Cardiovascular Diseases of Integrated Traditional Chinese and Western Medicine*, vol. 7, no. 16, 2019. doi: 10.16282/j.cnki.cn11-9336/r.2019.16.011 (in Chinese)
- [13] T. Miao, Z. Liu, Y. Liu *et al.*, "Study on the pharmacological effects and mechanisms of metformin," *Medical Information*, vol. 32, no. 14, pp. 53–56, 2019.
- [14] X. Bi, Z. Chen, C. Chen *et al.*, "Study on the effect of metformin in ameliorating endothelial cell insulin resistance," *Chinese Journal of Laboratory Diagnosis*, vol. 23, no. 4, pp. 684–687, 2019.
- [15] Y. Chen, Y. Zhao, and T. Ma, "Effects of metformin on BACE1 transcriptional regulation and β -amyloid (A β) production," in *Proc. 2008 National Academic Conference on Anti-aging and Dementia*, 2008, 67.
- [16] S. Cui, L. Zhou, and X. Chang, "Diet-induced hypothalamic inflammation and its regulation by metformin," *Chinese Journal of Biochemistry and Molecular Biology*, vol. 39, no. 10, pp. 1427–1435, 2023. doi: 10.13865/j.cnki.cjbmb.2023.03.1480 (in Chinese)
- [17] C. Su, "Neuroprotective effects of metformin on MPTP-induced mouse models of Parkinson's disease," Master's thesis, Nanjing Medical University, Nanjing, China, 2013.
- [18] Q. Sun, "Metformin alleviates epirubicin-induced vascular endothelial cell injury by regulating the expression and release of mitochondrial transcription factor A," Ph.D. dissertation, University of Science and Technology of China, Hefei, China, 2023. doi: 10.27517/d.cnki.gzjku.2023.002199 (in Chinese)
- [19] D. Sun, "Metformin delays changes in renal tubular epithelial cells in diabetic nephropathy by regulating mitophagy via the Nrf2/PINK1 pathway and cellular senescence," Ph.D. dissertation, China Medical University, Shenyang, China, 2023. doi: 10.27652/d.cnki.gzyku.2023.001927 (in Chinese)
- [20] Z. Rong, "Clinical observation on the hypoglycemic effects of metformin and acarbose in type 2 diabetes mellitus," *Guide of China Medicine*, no. 7, pp. 18–19, 2008. doi: 10.15912/j.cnki.gocm.2008.07.053 (in Chinese)
- [21] P. Gong, X. Li, S. Liao, *et al.*, "Effect of metformin on cognitive function in patients with type 2 diabetes mellitus," *Medical Recapitulate*, vol. 22, no. 22, pp. 4451–4455, 2016.
- [22] M. Liu, "Cognitive impairment in patients with type 2 diabetes mellitus: Analysis of influencing factors and follow-up study on therapeutic efficacy," Master's thesis, Yan'an University, Yan'an, China, 2024. doi: 10.27438/d.cnki.gyadu.2024.000350 (in Chinese)
- [23] X. Lin, "Study on the protective effect of metformin against high-altitude hypoxia-induced cognitive impairment and its underlying mechanisms," Master's thesis, Anhui Medical University, Hefei, China, 2017. (in Chinese)
- [24] W. Chen, S. Duan, L. Zeng *et al.*, "Systematic review of randomized controlled trials on berberine versus metformin for the treatment of type 2 diabetes mellitus," *Journal of Liaoning University of Traditional Chinese Medicine*, vol. 17, no. 1, pp. 151–154, 2015. doi: 10.13194/j.issn.1673-842x.2015.01.053 (in Chinese)
- [25] M. Hu, H. Tian, J. Zhang *et al.*, "Effects of insulin combined with rosiglitazone or metformin on serum adiponectin levels in patients with type 2 diabetes mellitus: A randomized controlled study," *Sichuan Medical Journal*, no. 10, pp. 1082–1084, 2007. doi: 10.16252/j.cnki.issn1004-0501-2007.10.021 (in Chinese)
- [26] M. Liang, "Randomized controlled study on the combined use of saxagliptin and metformin in the treatment of newly diagnosed type 2 diabetes patients," *Capital Food & Medicine*, vol. 22, no. 16, pp. 75–76, 2015.
- [27] L. Sun, L. Gu, and G. Chen, "Randomized controlled study on the effect of combined pioglitazone and metformin therapy on improving insulin resistance in type 2 diabetes," *Guide of China Medicine*, vol. 10, no. 2, pp. 160–161, 2012. doi: 10.15912/j.cnki.gocm.2012.02.129 (in Chinese)
- [28] M. Hu, H. Tian, X. Zhou *et al.*, "Effect of randomized controlled treatment with insulin combined with rosiglitazone or metformin on serum N-terminal pro-brain natriuretic peptide in patients with type 2 diabetes," *Journal of Biomedical Engineering*, no. 3, pp. 682–685, 2008.
- [29] A. A. R., M. S. M. A., and C. Ma, "A randomized controlled trial comparing the efficacy of rosiglitazone combined with clomiphene citrate versus metformin combined with clomiphene citrate in women with clomiphene citrate-resistant polycystic ovary syndrome," *Digest of World Core Medical Journals (Obstetrics and Gynecology Section)*, no. Z1, pp. 19–20, 2006.
- [30] M. Wang, X. Zhang, W. Li *et al.*, "Study on the mechanism of metformin's effect on insulin resistance in rats with polycystic ovary syndrome," *Journal of Clinical Medicine in Practice*, vol. 26, no. 9, pp. 1–7, 2022.
- [31] H. Wang and X. Lin, "Clinical endocrine and metabolic characteristics of patients with polycystic ovary syndrome and insulin resistance and changes following metformin treatment," *Maternal and Child Health Care of China*, vol. 25, no. 29, pp. 4201–4203, 2010.
- [32] D. Li, "Effects of metformin on anxiety-like behavior and contextual fear memory and the underlying mechanisms," Ph.D. dissertation, Huazhong University of Science and Technology, Wuhan, China, 2018. (in Chinese)
- [33] Y. Wang, "Construction of a high-drug-loading, blood-brain barrier-permeable dual-drug delivery system and its application in the treatment of Alzheimer's disease," Ph.D. dissertation, Xiamen University, Xiamen, China, 2021. doi: 10.27424/d.cnki.gxmd.2021.002705 (in Chinese)
- [34] S. Zhang, "Research on nanodrug delivery systems based on metformin for synergistic tumor therapy," Ph.D. dissertation, Zhengzhou University, Zhengzhou, China, 2019. (in Chinese)

Copyright © 2026 by the authors. This is an open access article distributed under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited ([CC BY 4.0](https://creativecommons.org/licenses/by/4.0/)).