

The expanding role of metformin: From COVID-19 outcomes to healthy aging management?

Giovanni Cangelosi¹, Fabio Petrelli¹

¹School of Pharmacy, Experimental Medicine and Public Health Departments “Stefania Scuri”, Camerino (MC), Italy

To the Editor,

The COVID-19 pandemic has been one of the most severe global health crises of the 21st century, significantly straining healthcare systems worldwide. From its onset, the scientific community has faced the challenge of managing severe complications, particularly among high-risk populations such as individuals with type 2 diabetes (T2D). Notably, studies have shown that T2D patients treated with metformin had significantly lower mortality and complication rates compared to those receiving alternative treatments or no specific therapy (1). These findings have sparked considerable interest in the potential benefits of metformin beyond its traditional use. While primarily prescribed for T2D, metformin has demonstrated effects on metabolism, inflammation, and glucose regulation, leading researchers to explore its applications in other pathological conditions (2). The question emerging from these observations is whether metformin could be leveraged not only to mitigate complications in various clinical settings but also as a tool for promoting healthy aging. If confirmed, this could redefine metformin as a multifunctional therapy addressing multiple chronic conditions associated with aging (1,2). The potential of metformin as an anti-aging intervention is one of the most promising frontiers in biomedical research (3). Aging is a multifaceted biological process driven by cellular senescence, mitochondrial dysfunction, and chronic low-grade inflammation, key factors contributing to chronic diseases such as cardiovascular disorders, neurodegenerative conditions, and diabetes itself. Metformin has been shown to modulate several of these pathways, influencing cellular energy

metabolism, reducing inflammation, and improving insulin sensitivity. Additionally, its regulatory effects on insulin and IGF-1 (Insulin-like Growth Factor 1) signaling pathways suggest that it may have the potential to slow biological aging (2,3). A pivotal study in this field is the Targeting Aging with Metformin (TAME) trial, lasting six years and will involve over 3,000 individuals aged 65-79, which investigates metformin's potential to modulate aging processes (4). This ongoing clinical study aims to determine whether metformin can slow the signs of aging and improve health outcomes by reducing the incidence of age-related diseases, including cardiovascular and neurodegenerative disorders. Preliminary findings suggest that metformin may positively impact parameters such as physical and cognitive function, muscle mass retention, and inflammation markers, which tend to increase with age and are linked to multiple age-related conditions. While still in the early stages, these results provide an optimistic outlook on the potential of metformin as an anti-aging therapeutic (2-4). Certainly, for an increasingly personalized medicine, in addition to the potential anti-aging effects of metformin, and its possible side effects, which have already been well-documented in numerous studies, such as gastrointestinal issues and vitamin B12 deficiency, must also be thoroughly investigated. Beyond clinical trials, an integrated approach to aging management that combines pharmacological interventions with lifestyle modifications is essential (5). Lifestyle Medicine (LM) emphasizes the role of a balanced diet, regular physical activity, and stress management as key components of preventive healthcare. While metformin influences metabolism and inflammation (2,3), its benefits could be significantly

enhanced when combined with a healthy lifestyle (4). For example, regular exercise improves cardiovascular function and insulin sensitivity, complementing metformin's metabolic effects. Similarly, a nutrient-rich diet low in refined sugars reduces oxidative stress and inflammation, further amplifying the drug's benefits (6). The synergy between metformin and LM may represent an optimal strategy for addressing aging (5). By integrating pharmacological approaches with behavioral modifications that promote long-term health, this strategy could effectively slow aging and improve overall well-being. As research progresses, it is evident that combining targeted pharmacotherapy with evidence-based lifestyle interventions is key to achieving healthy aging (6). However, while preliminary findings are promising, further studies are needed to fully understand the long-term effects of metformin, both as a standalone therapy and in combination with lifestyle interventions (1-3). Special attention should be given to its safety profile in elderly populations and individuals without diabetes. Although metformin is generally well-tolerated, close monitoring of potential side effects is crucial, particularly in populations not traditionally treated with the drug. Only through comprehensive clinical data, such as those from the TAME Trial and other ongoing research, will it be possible to confirm metformin's role as an anti-aging therapy (4). In conclusion (Summary in Figure 1), Metformin has demonstrated significant benefits

beyond diabetes management, including improved outcomes in COVID-19 patients (1). Its potential as an anti-aging therapy represents an exciting new avenue for research, with the possibility of becoming one of the first pharmacological interventions targeting biological aging (1-4). When combined with an integrated approach to LM, metformin could not only improve long-term health but also revolutionize aging management (5,6). Future studies will be instrumental in determining whether metformin can truly become a cornerstone of preventive medicine and longevity strategies.

Ethic Approval: "None".

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors Contribution: GC and FP conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing—original draft preparation, writing—review and editing, visualization, supervision, project administration.

Declaration on the use of AI: "None".

Consent for Publication: the authors authorize the dissemination.

Acknowledgments: "None".

Funding: "None".

References

1. Petrelli F, Grappasonni I, Nguyen CTT, et al. Metformin and Covid-19: a systematic review of systematic reviews with meta-analysis. *Acta Biomed.* 2023 Aug 30;94(S3): e2023138. doi: 10.23750/abm.v94iS3.14405.
2. Gnesin F, Thuesen ACB, Kähler LKA, Madsbad S, Hemmingsen B. Metformin monotherapy for adults with type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2020

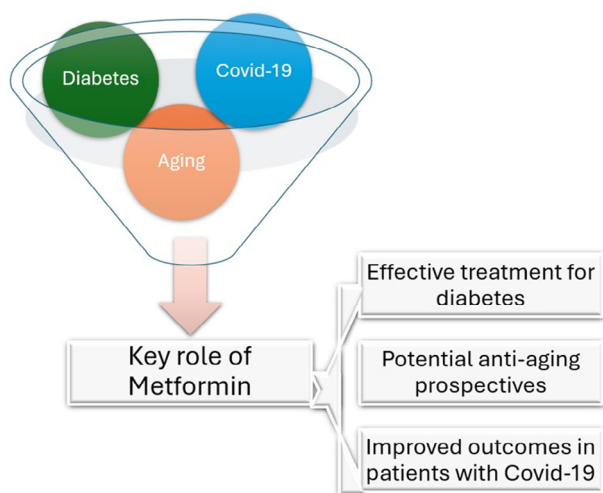


Figure 1. Conclusion

- Jun 5;6(6):CD012906. doi: 10.1002/14651858. CD012906. pub2.
3. Zhou T, Yu Y, Li L, Liu X, Xiang Q, Yu R. Bibliometric analysis of metformin as an immunomodulator (2013–2024). *Front Immunol.* 2025 Jan 8; 15:1526481. doi: 10.3389/fimmu.2024.1526481.
 4. Melberg MB, Flaa A, Andersen GØ, et al. Effects of mild hypercapnia on myocardial injury after out-of-hospital cardiac arrest. A sub-study of the TAME trial. *Resuscitation.* 2024 Aug;201:110295. doi: 10.1016/j.resuscitation.2024.110295.
 5. Alshahrani O, Almalki MS. The Efficacy of Pharmacotherapy in the Treatment of Obesity in Patients With Type 2 Diabetes: A Systematic Review. *Cureus.* 2024 Jul 24;16(7):e65242. doi: 10.7759/cureus.65242.
 6. Cangelosi G, Mancin S, Pantanetti P, et al. Lifestyle Medicine Case Manager Nurses for Type Two Diabetes

Patients: An Overview of a Job Description Framework—A Narrative Review. *Diabetology.* 2024, 5, 375–388. doi.org/10.3390/diabetology5040029.

Correspondence:

Received: 7 February 2025

Accepted: 7 March 2025

Dr. Giovanni Cangelosi

School of Pharmacy, Experimental Medicine and Public Health Departments “Stefania Scuri”

Via Madonna delle Carceri 9, 62032 Camerino (MC), Italy

ORCID ID: 0000-0002-8523-6906

E-mail: giovanni01.cangelosi@unicam.it