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Editorial

Metformin: Not Just a Diabetes Treatment

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1. Introduction

Metformin has underpinned type 2 diabetes care for more than six decades, valued for its glucose-lowering efficacy, low cost and tolerability [1]. Metformin acts in multiple ways: reducing glucose absorption in the gut, promoting peripheral glucose uptake, decreasing fasting insulin levels, and improving insulin sensitivity [1].

Yet its clinical story is no longer confined to glycaemic control. As interest in drug repurposing accelerates, this editorial examines emerging areas of research and suggests that metformin may influence a wide range of biological pathways relevant to metabolic health, ageing, cancer, and neurodegenerative diseases.

2. Polyendocrine Metabolic Ovarian Syndrome (PMOS)

Among all its off-label uses, the evidence for metformin in PMOS, previously known as polycystic ovary syndrome (PCOS), is the most robust. Its ability to reduce insulin resistance, lower circulating insulin, and subsequently decrease ovarian androgen production is well established [2,3]. These endocrine effects help restore ovulatory cycles and improve menstrual regularity. Features of PMOS may also be metabolic, such as obesity, type 2 diabetes, and dysglycaemia, highlighting the role of metformin, which is already embedded in many clinical guidelines [2,3].

3. Ageing and Longevity

Metformin is currently being studied for its potential effects on ageing and longevity (living a long life, as well as healthspan, defined as the period of life in good health) [4,5].

Ageing is characterised by the gradual accumulation of cellular and organ-level damage that arises as endogenous prevention and repair pathways progressively decline. Chronic diseases associated with ageing, including cardiovascular disease and cancer, reflect this cumulative biological deterioration [4,5].

Evidence from multiple model organisms is mixed. Campbell et al.'s review [4] synthesised several proposed mechanisms, including modulation of insulin/insulin-like growth factor 1 (IGF-1) signalling, inhibition of mechanistic target of rapamycin (mTOR), reductions in oxidative stress and inflammation, improved genomic stability, and activation of adenosine monophosphate-activated protein kinase (AMPK). Among these, AMPK activation has attracted particular attention because it modulates pathways linked to mitochondrial function, inflammation, epigenetic regulation, cellular senescence and the gut microbiome. These processes are central to the hallmarks of ageing, with a 2024 review highlighting that metformin may reduce multimorbidity, although many results are undermined by confounding bias [5].

The landmark TAME (Targeting Aging with Metformin) trial, designed to test whether metformin delays age-related multimorbidity, remains the pivotal study. If results are positive, metformin could become the first widely used gerotherapeutic within the next decade [6]. However, regulatory frameworks for ageing-modifying drugs are still evolving, and translation will depend on whether ageing is recognised as a treatable biological process.

4. Cancer

Across oncology, metformin's potential beneficial effects have been explored for over a decade. The rationale includes reduced insulin/IGF-1 signalling, AMPK activation, altered tumour metabolism and immunomodulation [7].

The largest and most definitive trial to date, MA.32, enrolled more than 3600 non-diabetic women with high-risk breast cancer and found no improvement in invasive disease-free survival when given adjuvant metformin compared to placebo, regardless of hormone-receptor status [8]. Mixed outcomes emerge across other breast, ovarian, and prostate cancer trials. While adding metformin to standard therapy appears safe, several studies show it is largely ineffective at improving progression-free or overall survival, whereas others report reductions in cancer recurrence, enhanced immunotherapy responses and effects on tumour progression [7]. In a 100-patient randomised trial in diffuse large B-cell lymphoma, adding metformin to an R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy regimen improved remission rates and reduced relapse and mortality [9].

Given the variability in trial outcomes, metformin is unlikely to become a standard oncology therapy in the near

term. Large, adequately powered randomised controlled trials in specific tumour types, particularly where early signals exist, are needed to replicate these promising small-scale studies.

5. Neurodegeneration

Interest in metformin's neurological effects has accelerated over the past decade. Several observational studies in people with type 2 diabetes have reported lower rates of cognitive decline and dementia among long-term metformin users [10,11]. These findings, however, sit alongside contradictory data and results vulnerable to confounding, particularly around age, comorbidity, and metformin-related vitamin B_{12} deficiency, which itself can impair cognition. Some studies have associated prolonged metformin use with a higher risk of Alzheimer's disease and linked metformin to worse cognitive performance, an effect that was mitigated by vitamin B_{12} supplementation [10].

Beyond Alzheimer's disease, metformin use is being explored in other neurological conditions. Preclinical models suggest neuroprotective effects in Parkinson's disease [12]. Neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's, and multiple sclerosis, despite their different causes and presentations, share a common set of damaging biological processes. All involve chronic neuroinflammation, driven by activated microglia and astrocytes; protein misfolding and aggregation, whether amyloid-β and tau, α-synuclein, mutant huntingtin, or misfolded proteins that trigger autoimmune injury; and oxidative stress with mitochondrial dysfunction [12]. This offers several plausible biological pathways: metformin may reduce tau phosphorylation, modulate AMPK signalling, enhance neurogenesis and autophagy, and improve mitochondrial function and oxidative stress responses [12]. These findings remain preliminary but point to a broader role for metformin in disorders characterised by metabolic dysfunction and neuroinflammation.

Current clinical trial activity highlights both the promise and the limitations of metformin as a neuroprotective therapy [13]. Notably, most current trials focus on conditions such as multiple sclerosis, and completed studies have largely centred on safety and feasibility, underscoring the need for larger phase II/III randomised trials [13]. Larger phase II/III trials focusing on Alzheimer's are also ongoing. The MAP (Metformin in Alzheimer's Dementia Prevention) trial is currently testing long-acting metformin against placebo in overweight or obese adults aged 55–90 with amnestic mild cognitive impairment [14]. The MET-FINGER trial is a 24-month international study testing whether an intensive lifestyle programme combined with metformin can better preserve cognition in 600 older adults at risk of dementia [15]. If these trials replicate early findings, metformin could plausibly enter clinical guidelines for cognitive impairment within the next decade.

6. Conclusion

Metformin's evolution from a glucose-lowering agent to a potential multi-system therapy reflects a broader shift in medicine towards targeting shared biological pathways across chronic diseases. Its established role in PMOS demonstrates that metformin's benefits extend beyond diabetes, while emerging evidence in ageing, cancer, and neurodegeneration highlights its potential as a versatile therapeutic tool.

However, much of the evidence outside diabetes and PMOS demonstrates mixed outcomes. Ongoing large, randomised trials will determine whether metformin can transition from a promising repurposed candidate to a clinically endorsed therapy in new domains.

For now, metformin remains one of the most intriguing and widely studied drugs in modern medicine: inexpensive, relatively safe, and capable of reshaping how we think about ageing and chronic disease treatment and prevention.

Key Points

- Metformin's effects extend beyond glucose control, influencing endocrine, metabolic, and inflammatory pathways relevant to multiple chronic diseases.
- Evidence outside diabetes and polyendocrine metabolic ovarian syndrome (PMOS) remains mixed, with observational findings often limited by confounding biases.
- Longevity, cancer and neurodegeneration trials show promise but inconsistency, with large clinical trials currently underway to determine whether metformin can be adopted as a gerotherapeutic or neuroprotective agent or adjuvant for cancer therapy.
- Metformin remains a relatively safe, inexpensive, high-interest repurposing candidate.

Availability of Data and Materials

Not applicable.

Author Contributions

All elements of the study and subsequent write-up were carried out by the author [DK]. The author read and approved the final manuscript. The author has participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The author declares no conflicts of interest.

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