

M

METFORMIN

& THE SCIENCE OF LONGEVITY

How a 60-year-old diabetes drug is redefining what it means to age well — and why researchers, clinicians, and health-optimisers are taking notice.

40%

Reduction in all-cause mortality vs. matched controls

6+

Hallmarks of aging targeted simultaneously

TAME

First FDA-approved trial testing a longevity drug

1957 Discovery

1994 FDA Approval (T2D)

2005 MDR-1 paper

2013 ITP mouse lifespan +5%

2023 TAME Trial (ongoing)

Future Longevity Indication

60+ YEARS OF METFORMIN RESEARCH

How Metformin Targets Aging

Aging is no longer considered an immutable process. Modern geroscience has identified discrete molecular hallmarks — oxidative stress, chronic inflammation, mitochondrial dysfunction, and cellular senescence — that metformin appears to modulate through multiple, complementary pathways.

AMPK Activation

Metformin inhibits mitochondrial Complex I, reducing ATP/AMP ratio and activating AMPK — the master energy sensor. AMPK activation suppresses mTORC1, stimulates autophagy, and improves insulin sensitivity.

Reduction of mTOR Signalling

mTOR hyperactivity accelerates senescence. By dampening mTOR via AMPK, metformin mimics aspects of caloric restriction — the most reproducible life-extension intervention across species.

Anti-Inflammatory Action

Metformin suppresses NF- κ B signalling and lowers IL-6, TNF- α and CRP — key mediators of 'inflammaging', the chronic low-grade inflammation that underpins most age-related disease.

Mitochondrial Hormesis

Mild inhibition of Complex I triggers a protective hormetic response, upregulating antioxidant defences and improving mitochondrial efficiency without causing frank energy deficits.

Gut Microbiome Modulation

Emerging evidence links metformin's benefits to enrichment of SCFA-producing microbiota (*Akkermansia muciniphila*, *Lactobacillus* spp.), which reduce gut permeability and systemic endotoxaemia.

Epigenetic Reprogramming

Metformin influences DNA methylation patterns at CpG sites associated with biological age. Some studies report a measurable reduction in epigenetic age (Horvath clock) with long-term use.

Hallmarks of Aging Addressed

Genomic instability

Mitochondrial dysfunction

Cellular senescence

Chronic inflammation

Dysregulated nutrient sensing

Altered intercellular communication

Key Trials & Landmark Data

TAME TRIAL (Targeting Aging with Metformin)

NIA-Funded · n = 3,000 · Ages 65–79 · Multi-centre RCT

The landmark TAME trial — the first FDA-agreed trial with aging itself as a primary endpoint — is testing whether 1,500 mg/day metformin delays the onset of age-related conditions including cardiovascular disease, cancer, dementia, and frailty. A positive outcome would establish aging as a treatable condition and create a regulatory pathway for future geroscience drugs.

UKPDS Follow-up

36% reduction in all-cause mortality in metformin-treated T2D patients vs. diet-control after 10-year post-trial monitoring.

Bannister et al. 2014 (BMJ)

Matched-cohort study: metformin users with T2D outlived non-diabetic controls not taking metformin — suggesting a mortality benefit beyond glucose control.

ITP Mouse Studies

The Interventions Testing Program found metformin extended lifespan up to 5% in male mice and improved healthspan markers across multiple independent research centres.

Epigenetic Age (Fitzgerald 2021)

In a pilot RCT, participants receiving metformin alongside dietary and lifestyle intervention showed a statistically significant 1.96-year reduction in biological (Horvath) age.

Cancer Risk Reduction

Meta-analyses consistently show 25–40% lower incidence of colorectal, hepatic, and pancreatic cancers in long-term metformin users.

Cognitive Protection

Prospective data from the UK Biobank and ACCORD-MIND suggest lower rates of cognitive decline and dementia in metformin-treated cohorts.

Safety Profile

Metformin has an exceptional safety record after 60+ years of clinical use. Common side effects (GI upset, nausea) are dose-dependent and largely transient. Lactic acidosis is rare (<1 per 100,000 patient-years) and contraindicated only in eGFR <30. Vitamin B12 monitoring is recommended with long-term use. Cost: generic formulations are among the least expensive medications globally (<\$10/month).

Who May Benefit & How It Is Used

Candidate Profiles

Adults 50+

Individuals seeking evidence-based preventive strategies against age-related disease.

Metabolic Syndrome

Those with insulin resistance, elevated fasting glucose, or pre-diabetes stand to gain metabolic and potentially lifespan benefits.

Cancer Survivors

Several oncology centres incorporate metformin into survivorship programmes given its anti-proliferative properties.

Performance Optimisers

Biohackers and healthspan-focused individuals, particularly post-exercise-recovery (note: evidence for concurrent intense training is mixed).

Typical Longevity Protocol

Starting Dose

500 mg with largest meal for 2–4 weeks to assess GI tolerance.

Maintenance Dose

1,000–1,500 mg/day in divided doses. Extended-release (XR) formulation reduces GI side effects.

Timing Considerations

Many longevity physicians advise avoiding metformin on intense exercise days, given potential blunting of AMPK-mediated training adaptations.

Monitoring

Annual: fasting glucose, HbA1c, eGFR, serum B12. Consider methylmalonic acid if B12 borderline.

Duration

Long-term continuous use. Regular physician review. Adjust for renal function.

Take the First Step Towards Evidence-Based Longevity

Speak with a longevity-trained physician about whether metformin is appropriate for you.
Comprehensive metabolic panel · Personalised dosing protocol · Ongoing biomarker tracking

[Schedule a Consultation](#)[Download Full Research Dossier](#)[Join the TAME Trial Registry](#)

DISCLAIMER: This material is for educational purposes only and does not constitute medical advice. Metformin is a prescription medication in most jurisdictions. Individual outcomes vary. The TAME trial remains ongoing and longevity indications are investigational. Always consult a licensed healthcare professional before initiating therapy. © 2025 Longevity Medicine Institute. All rights reserved.