Metformin as a potential longevity medication: where do we stand?

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Peter Attia February 26, 2025

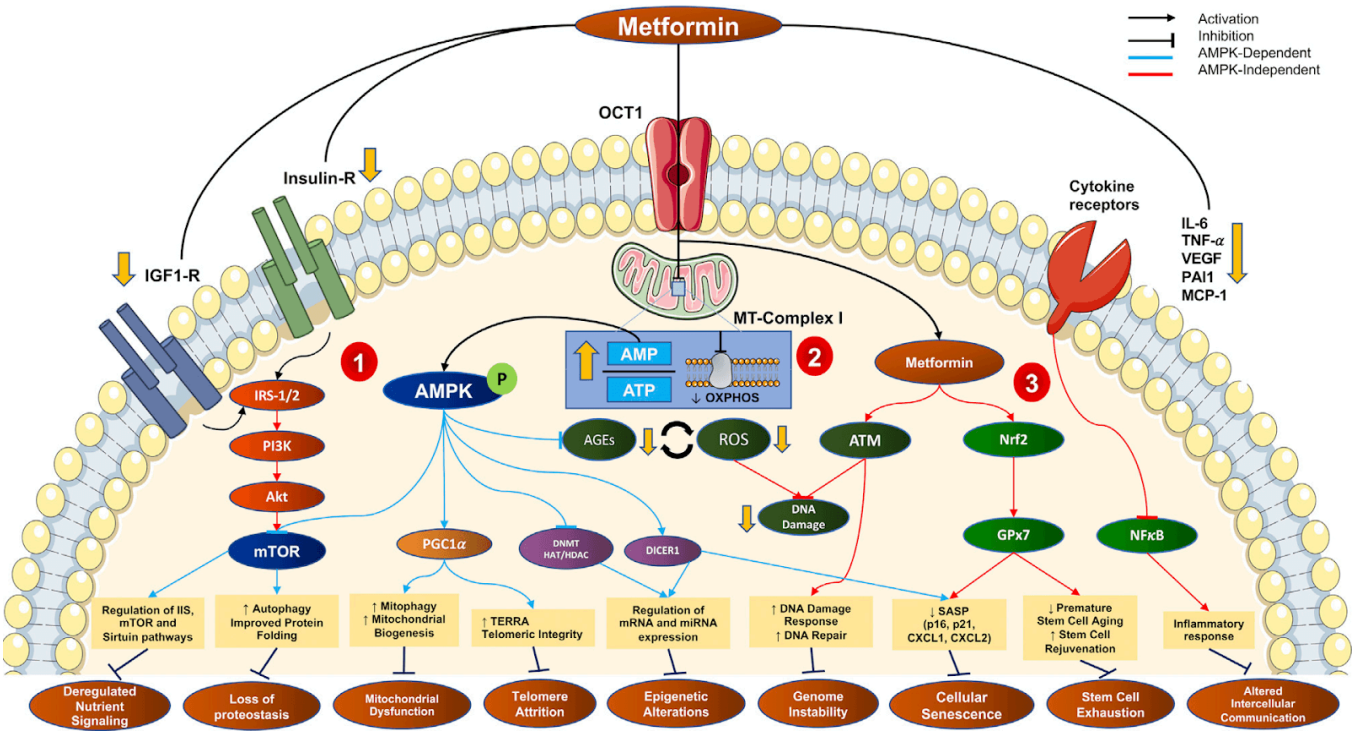

Figure 1. Metformin's mechanisms of action decrease insulin signaling, reduce inflammatory markers, and potentially attenuate each of the nine original hallmarks of aging. Metformin directly activates AMPK by inhibiting complex I in the mitochondria leading to activation of PGC-1α (improved mitochondrial biogenesis). The activation of AMPK along with reduced insulin signaling inhibits mTORC1 (improved nutrient sensing and autophagy).[11]

Humans have sought interventions for lifespan extension for millennia, though over the last century, this quest has taken on a more formal, scientific approach. Since the early 20th century, such research has led to the identification of several *potential* "longevity molecules,"[1] and in recent years, metformin has emerged as one of the most discussed candidates for this role, generating both excitement and skepticism within the scientific community.

While many are familiar with metformin as a common medication for the treatment of type 2 diabetes, the narrative around potential *anti-aging* properties of this drug began to take shape in the early 2000s with the discovery of life-extension effects in certain animal models. Subsequent observational data from humans fueled further excitement, but as conflicting evidence emerged in more recent years, interest in the possible role of metformin in human life extension began to lose steam. Yet in the late summer of 2024, a new study showing positive effects on aging markers in monkeys caught the attention of scientists and the popular press alike, and suddenly, metformin appeared to be back at the forefront of optimism over longevity drugs.

So where does this leave us? How does the strength of evidence in favor of metformin as a longevity drug compare to the strength of evidence against it? What are the implications for the use of this drug in promoting healthspan versus lifespan? And what questions remain to be answered?

Metformin as a diabetes drug

Before we dive into the complex web of research surrounding metformin's effects on longevity, we need to understand a little more about the drug itself and the mechanisms through which it operates. The story of metformin begins with a plant called *Galega officinalis*, commonly known as goat's rue or French lilac. For centuries, this herb was used in traditional medicine to treat what we now recognize as symptoms of diabetes. After identification of guanidine as the active compound responsible for these effects, researchers in the 1920s developed guanidine derivatives known as biguanides, including metformin. After showing promise with lowering glycemia in animal studies, metformin began to be used as a diabetes treatment in the UK by the late 1950s.[2] However, it took almost another forty years to bring metformin to the United States, as the FDA didn't approve metformin for treating diabetes until 1995. (The delay was partly due to serious side effects observed with *other* biguanide medications, though subsequent studies confirmed that metformin differed from its chemical cousins in this respect.)

After FDA approval, clinical trials in the US demonstrated that in patients with non-insulin-dependent diabetes mellitus (NIDDM), metformin could lower fasting glucose and hemoglobin A1c to the same extent as sulfonylurea therapy, and combination therapy was even more effective.[3] Although other anti-diabetic drugs have since been approved for use, metformin remains a first-line therapy and has even demonstrated efficacy in reducing progression to type 2 diabetes (T2D) among those with prediabetes.[4]

While further consideration of metformin's efficacy as a diabetes drug is beyond the scope of this piece, this "traditional" indication for metformin use is relevant to our evaluation of potential longevity effects for two primary reasons. First, metformin's history as a diabetes and prediabetes treatment means that we already have a great deal of data on side effects and long-term safety associated with this medication – in contrast to far more limited data that exist for many other alleged longevity molecules. For instance, the Diabetes Prevention Program (DPP) and its follow-up Outcomes Study (DPPOS) demonstrated continued safety and efficacy of metformin over a 15-year follow-up period, though temporary gastrointestinal (GI) effects were fairly common.[5] Thus, many potential barriers to metformin's use as a longevity drug have already been eliminated. The drug is low in cost, has extensive safety data, has broad availability due to its FDA approval, and has manageable side effects, so when evidence began to arise about potential effects on life extension, excitement was amplified due to its wide accessibility and low risk profile in diabetic humans.

The second reason why metformin's use in diabetes is pertinent to our present discussion is the interplay between metabolic health and lifespan. As we've explained on countless occasions, poor metabolic health (of which insulin resistance and type 2 diabetes are often characteristic components) drastically increases risk of several other deadly chronic diseases – including heart disease, neurodegenerative disease, and many types of cancer. Therefore, for

those with diabetes, proper management with metformin or other medications is expected to have substantial positive effects on lifespan – just as antibiotics are likely to extend lifespan in someone with tuberculosis. But to have true geroprotective effects, metformin must be capable of extending lifespan *beyond* what would be expected from disease management alone. When it comes to metabolic disease, the two can be especially difficult to disentangle. The cellular pathways of aging are intricately tied to those of cellular metabolism, and the mechanisms by which metformin functions as a diabetes treatment are likely to overlap and intersect with those by which this drug may protect against aging.

A complex web of cellular effects

As a diabetes drug, metformin is understood to work by reducing glucose production by the liver and perhaps by additional effects on the gastrointestinal tract. But at a more basic cellular and molecular level, the drug's mechanisms of action as both a diabetes treatment and a potential longevity drug are multitudinous and have yet to be fully elucidated. Unlike many drugs that operate through a single pathway, metformin influences several fundamental cellular processes. This complexity has earned it the designation of a "dirty" drug – not because it's unsafe, but because it has numerous molecular targets.

A key mechanism through which metformin affects cellular metabolism begins with its interaction with the electron transport chain in mitochondria, a series of enzymes responsible for producing cellular energy in the form of adenosine triphosphate (ATP). Specifically, metformin inhibits complex I of the electron transport chain, which leads to a reduction in ATP production. This drop in cellular energy activates AMP-activated protein kinase (AMPK), an enzyme that triggers a variety of downstream energy-conserving and efficiency-boosting measures throughout the cell, including inhibition of the mTORC1 pathway – a key regulator of cell growth and metabolism.

In this way, metformin's cellular actions mirror some of the cellular changes seen with caloric restriction – one of the most robust life-extending interventions known in animal models. Both metformin and caloric restriction lead to a drop in cellular energy, resulting in AMPK activation, mTORC1 inhibition, decreased insulin signaling, and reduced inflammation. Indeed, metformin-treated mice demonstrated similar genetic transcriptional changes as long-term (75% transcriptional overlap) and short-term (92% transcriptional overlap) calorie restriction.[6,7] These findings were supported by experiments in *C. elegans* (nematode worms), in which metformin created a similar state to restricted energy intake, mediated by the activation of AMPK and antioxidant defenses.[8]

As is thought to be the case with calorie restriction, the cascade of cellular effects initiated by metformin might plausibly impact the so-called "hallmarks of aging" – a set of cellular and molecular changes that contribute to functional decline and disease susceptibility with age **(Figure 1)**. Originally, researchers identified nine such hallmarks: genomic instability, epigenetic alterations, loss of proteostasis (protein homeostasis), deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered cellular communication, and the gradual shortening of telomeres,[9] though in subsequent years, more

have been added to this list, including chronic inflammation ("inflammaging"), gut dysbiosis, and disabled macroautophagy (a decline in the cellular mechanism that breaks down damaged cellular contents and protein aggregates).[10]

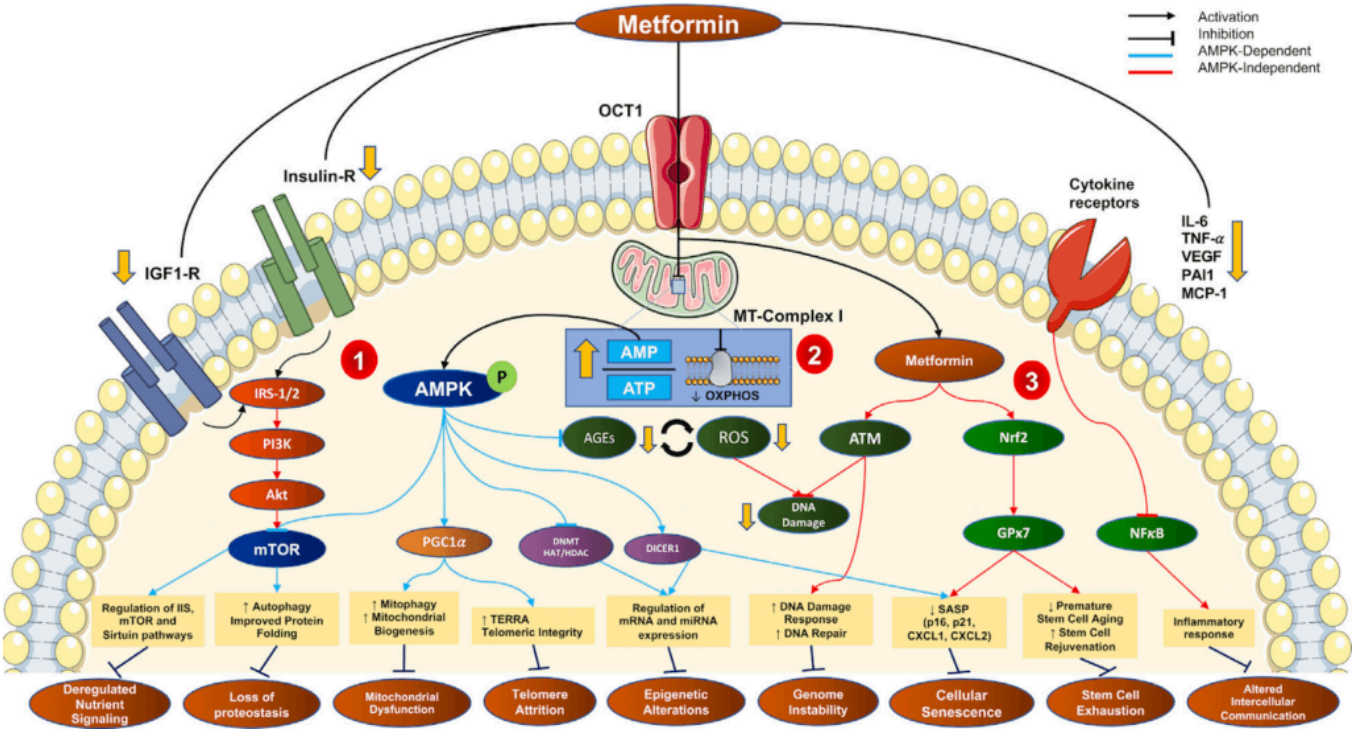

Figure 1. Metformin's mechanisms of action decrease insulin signaling, reduce inflammatory markers, and potentially attenuate each of the nine original hallmarks of aging. Metformin directly activates AMPK by inhibiting complex I in the mitochondria leading to activation of PGC-1α (improved mitochondrial biogenesis). The activation of AMPK along with reduced insulin signaling inhibits mTORC1 (improved nutrient sensing and autophagy).[11]

Early clues of longevity effects

The first hints about metformin effects on lifespan arose from experiments in various model organisms. Some of the most consistent findings come from research in *C. elegans*, in which metformin-treated animals exhibited a 27% extension in median (but not maximal) lifespan relative to controls,[8] though only at the highest doses tested. While these results seem promising, a meta-analysis demonstrated that metformin generally only has significant positive effects on lifespan in *C. elegans* when treatment is started early in adulthood *and* when the worms are fed a diet of OP50 *E. coli*, as the metformin appears to alter *E. coli* metabolism which then in turn alters the metabolism of the worm.[12] This finding highlighted an important principle in aging research: the effects of potential longevity drugs can be highly dependent on context, including diet, age, genetics, and other factors.

Subsequent studies in rodents added further complexity to the question of metformin as a longevity drug. An early study indicated that the medication extended both mean and maximum lifespan in female inbred mice, along with increasing the latency of tumor development,[13] and this result was repeated in other female mice strains.[14] However, in other mouse strains, metformin has resulted in a mild increase (4.4%) in average lifespan in females but a *shortening* of average lifespan in males (13.4%).[15] In yet two more inbred strains of male mice, 0.1% metformin in diet led to a 4-6% extension of mean lifespan when started at 27 weeks of

age, but a 1% concentration shortened average lifespan by 14.4%. Again, these data suggest that genetics, age of initiation, and metformin concentrations likely play a role in any lifespan extending effects.

Taken together with results showing no effect of metformin on lifespan in rats or fruit flies,[16] the inconsistency in mouse results and apparent strain dependence offered little reason for excitement over metformin's prospects as a longevity drug in humans, but that changed when an observational study on metformin use among diabetic patients yielded unexpected and intriguing results.

A pivotal spark: the Bannister study

In 2014, Bannister et al. published results from a retrospective case-control study showing that diabetics on metformin monotherapy – but not those on sulphonylurea monotherapy – had lower all-cause mortality (ACM) than *non-diabetic controls*, despite controls having a clear advantage in baseline health due to their lack of diabetes.[17] The UK-based study, which compared over 78,000 subjects on metformin monotherapy to over 78,000 matched controls without T2D over a mean follow-up of 2.8 years, reported that the crude unadjusted death rate was higher in matched non-diabetic controls (15.2 deaths/1000 person-years) compared to T2D patients on metformin (14.4 deaths/1000 person-years). This remarkable finding captured headlines, as it suggested that metformin can extend lifespan *beyond* its effects on controlling blood glucose and avoiding the many health complications attributable to diabetes. This would in turn mean that *anyone* – diabetic or not – might derive longevity benefits from this medication.

Still, despite the excitement engendered by these findings, they hardly constituted a definitive smoking gun. The study only included diabetic patients who *remained* on metformin monotherapy throughout the follow-up period, but diabetes usually requires increasingly aggressive treatment and the addition of other medications as the disease progresses. Thus, by limiting the subject pool to those who did not need to add other antidiabetes therapies, the study selected for the healthiest subset of diabetic patients. More importantly, it created a situation in which the final analysis was based on a metformin group that was *defined* by a variable that directly related to the outcome of interest (in this case, survival), as participants who progressed to other therapies would also have been much more likely to die from diabetes complications over the course of the study. As explained in a previous newsletter, this bias is known as informative censoring and can be illustrated with an analogy: let's say a study compared survival among smokers vs. non-smokers, but anyone in the smoking group who died of cancer or lung disease was disqualified; smoking would probably appear to confer a survival advantage simply because we've eliminated the most relevant causes of death for smokers.

Additionally, the health of the non-diabetic controls is uncertain. Controls were matched for age, gender, prior cancer status, and smoking status, and were required to have neither a T2D diagnosis nor exposure to metformin and to survive a minimum of 180 days from the starting date. But a lack of a T2D diagnosis or antidiabetes medication does not guarantee that a given individual does not have diabetes – it could instead reflect a tendency to ignore one's health

and avoid seeking medical attention that might otherwise lead to a diagnosis. Thus, it's possible that the selection criteria for "non-diabetic" controls resulted in a control group that was, on average, less health-conscious than the metformin group. The fact that controls had >9,000 fewer follow-up years compared to those on metformin monotherapy might support this idea, as the lower number of follow-up years might indicate that controls died before their matched metformin-therapy case.

Finally, when stratified by age, metformin was only associated with a lower death rate than controls among participants under 60 years of age. In participants 60 and older, matched controls had a lower death rate than those with diabetes.

Regardless of these limitations, Bannister et al.'s results sparked substantial public and research interest in metformin as a potential longevity drug. The study served as a catalyst in motivating further investigations, including rigorous tests in mice conducted by the Interventions Testing Program (ITP, a program run by the National Institute on Aging to identify compounds with beneficial effects on aging and lifespan), as well as additional observational studies.

A pessimistic turn: ITP studies and unreplicable epidemiology

Following the Bannister et al. publication, the ITP undertook assessment of metformin as a potential longevity compound, applying their routine (and thorough) approach of repeatedly testing the medication in a genetically diverse mouse population at three different testing sites. Unfortunately, the results were less promising than metformin advocates might have hoped. Metformin administered to mice through food (at 0.1% concentration) starting at 9 months of age did not lead to significant median or maximal lifespan extension, though males showed a non-significant trend toward a 7% increase in average lifespan.[18] This failure of metformin to extend lifespan lends further support to the notion that previous positive outcomes were due to a favorable genetic profile, making the results less likely to translate to humans.

The wind in metformin's proverbial sail lagged even further when, in 2022, a Denmark-based study by Keys et al. was unable to replicate the results by Bannister et al., despite applying largely the same methodology.[19] Keys et al. used singleton cohorts from a 5% random sample of the Danish population and twin cohorts from the population-based Danish Twin Registry to better control for unobservable confounders including shared early-life environment, genetic risk, and some social indicators. The sets of same-sex twins each had one metformin initiator and one twin without diabetes, and average follow-up was around four years.

The results of this newer study contradicted the earlier results by Bannister et al., showing *no survival advantage* or equalization for diabetics on metformin relative to a general, non-diabetic population. In fact, quite the opposite was true. In their primary analysis, for which participants who added or changed medications after metformin initiation remained included in the analysis, results showed that both cohorts exhibited significantly higher crude and age-standardized mortality rates than their matched cohorts without diabetes. The age-standardized death rate in the singleton metformin group was 24.93 deaths/1000 person-years compared to the non-diabetic control death rate of 16.86 deaths/1000 person-years. In the twin cohorts, the age-

standardized death rate of the metformin group was 24.73 deaths/1000 person-years compared to the non-diabetic co-twin death rate of 12.94 deaths/1000 person-years. After controlling for covariates, this translated to a 33% higher risk among metformin participants relative to controls in the singleton cohort (HR: 1.33; 95% CI: 1.16–1.54) and an 80% higher risk among metformin participants relative to controls in the twin cohort (HR: 1.80; 95% CI: 1.11–2.91). Survival across the cohorts are shown in Kaplan-Meier curves in **Figure 2** below.

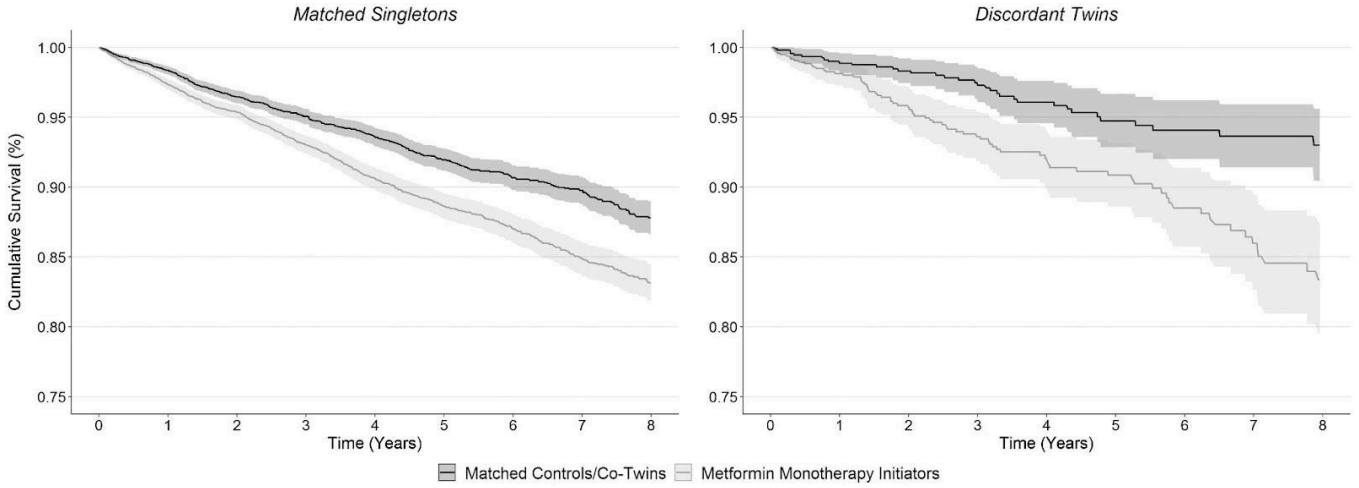

Figure 2: Kaplan–Meier cumulative survival curves in matched cohorts of metformin monotherapy initiators and those without diabetes over 8 years of follow-up. Shaded areas represent 95% confidence intervals. From Keys et al. 2022.[19]

Additionally, Keys et al. sought to determine the impact of informative censoring on their results by performing sensitivity analyses in which they, like Bannister et al., omitted participants who added or changed medications after metformin initiation. In this case, the risk of death among the metformin group was lower than in the non-censored analysis but was still significantly elevated compared to non-diabetic controls (HR: 1.48, 95% CI: 1.32–1.64). While the sum total of these results don't provide insight into whether or not metformin extends lifespan in *healthy* adults, we can more confidently say that taking metformin does not overcome (or exceed) the risk of a shortened lifespan from having T2D.

Small clinical trials further dampen excitement

In addition to negative results from the ITP and from Keys et al., several small clinical trials have sought to test metformin in healthy humans. While these studies have not been long enough to assess lifespan *per se*, the results from measurements of aging biomarkers and related metrics have generally added to the disappointments surrounding potential longevity applications.

Perhaps the most sobering recent evidence comes from the Metformin to Augment Strength Training Effective Response in Seniors (MASTERS) randomized trial, which investigated whether metformin could enhance the benefits of resistance training in older adults (age 65+).[20] This 14-week trial involved treatment with metformin or placebo along with supervised progressive resistance training, and results were not just disappointing – they were concerning. Participants taking metformin actually gained *less* muscle mass than those taking a placebo, despite following the same exercise program. Although it is generally believed that metformin is

not taken up by muscle cells, analyses of the muscle biopsies showed that the metformin group had an increase in AMPK signaling and a trend for decreases in mTORC1 signaling, which would account for the smaller gains in muscle mass (and non-significant trend toward blunted strength gains) seen in this group.

Muscle mass and strength are important indicators of health, so if metformin impedes the effects of strength training, it may actually be *harmful* to longevity. This finding thus highlights a crucial principle in longevity medicine: interventions that appear beneficial in one context might be detrimental in another. The very mechanisms that make metformin effective for diabetes treatment – particularly its activation of AMPK and inhibition of mTOR – might interfere with the body's adaptive response to exercise.

Another reality check regarding metformin's potential as a broad-spectrum anti-aging intervention came from the MET-PREVENT trial – a 4-month, randomized, placebo-controlled trial with the aim of assessing the efficacy and safety of metformin therapy for treating sarcopenia and frailty in older adults (age 65+, n=72).[21] The results were discouraging: no significant improvements in walking speed, grip strength, or other functional measures were observed.[22] (In light of the results of the MASTERS trial, these findings are perhaps unsurprising.) If anything, metformin was poorly tolerated in this older cohort, as evidenced by a higher discontinuation rate and a greater number of adverse events, including hospitalizations.

Still, not all human trials have been negative. The Metformin in Longevity Study (MILES), though small (only 14 participants), attempted to understand metformin's effects on aging-related molecular pathways in healthy older adults (age 70+). This 6-week, randomized, placebo-controlled crossover study trial showed that metformin altered the expression of multiple genes involved in aging-related pathways in muscle and adipose tissue, including those related to metabolism, inflammation, mitochondrial function, DNA repair, and extracellular matrix remodelling.[23] Although it's crucial to understand that changes in gene expression don't necessarily translate to meaningful clinical outcomes, these findings motivate additional research to determine how these changes align with functional outcomes over a longer period of time.

A recent study revives interest

Despite mounting evidence against metformin's alleged benefits for longevity, studies assessing the drug's anti-aging potential have continued. Some hope remained as a consequence of the MILES study, as well as in light of the fact that, despite seeing no effect with metformin *alone,* the ITP did observe a significant, 23% increase in mean lifespan in both sexes with a *combination* of 0.1% metformin with 14 ppm rapamycin – a greater effect than observed in previous ITP cohorts on rapamycin alone.[18] But one of the most commonly cited reasons for skepticism over the ITP's negative results with metformin alone relates to their relevance to humans in the first place. While it's true that "mice are not humans," it's worth noting that this criticism ignores the fact that many metabolic pathways are conserved across

increasingly complex organisms. Nevertheless, non-human primates certainly have much closer physiology to humans, a point which served as one of the motivations for a recent study of metformin in male cynomolgus monkeys.[24]

The study, which lasted roughly 40 months, used three groups of different ages: 3-5 years old (n=6), 10-12 years old (n=6), and 13-16 years old (n=12). The oldest group, equivalent to middle-aged humans (40-50 years of age) was divided into two groups, one that received 20 mg/kg per day metformin and one that did not. The two younger groups served as additional controls, and physical examinations were performed every three months. Though this was not a lifespan study *per se* (the monkeys were sacrificed at the study's termination), the investigators measured various aspects of aging and healthspan, including the use of a monkey "biological clock" based on DNA methylation and other data such as transcriptomics and proteomics to assess organ system aging.

In their paper, which made headlines upon its release in late summer 2024, the authors reported that the group receiving metformin had enhanced memory and improved learning abilities based on a higher accuracy in retrieving food after a delay and a better performance in an object discrimination task. The cortical thickness of the frontal and temporal lobes of the metformin group was preserved compared to the two younger cohorts, whereas in the older controls, the cortical thickness had thinned based on both magnetic resonance imaging (MRI) and histological findings. Additionally, the investigators measured biomarkers of the hallmarks of aging, finding fewer senescent cells in various tissues in metformin-treated animals relative to age-matched controls, along with a widespread reduction in inflammation, reduced epigenetic instability, less periodontal bone loss, and a slower decline in type II muscle fibers. Based on these data, it would appear that the metformin-treated monkeys had a lower "biological age" at the end of the study, as well as lower organ-specific biological ages in the brain (~6 years), along with the kidney, liver, skin, and lungs.

Substantial reasons for doubt

Once again, we must stop short before placing too much faith in these results. This study is rife with confounding factors, most of which have been buried deep within the supplemental data. The oldest group of monkeys were overweight and became obese during the study (no body weight data were reported for either of the two younger control groups). While this species is known to have a higher likelihood of obesity (especially in captivity), the steep incline from a body mass index (BMI) of a little more than 28 at three months (there is no baseline data) to BMIs of 32.6 and 30.3 at six months in the older controls and metformin group, respectively, suggests that these monkeys were not necessarily being fed for optimal health. Metformin in this case appeared to be somewhat protective against weight gain, which might easily have accounted for its apparent systemic benefits, yet this mechanism doesn't necessarily translate to humans. In humans, weight is usually only mildly affected by metformin therapy, so it is perhaps more likely that the means by which the monkeys were receiving metformin (i.e., via drinking water) may have exacerbated the consequences of a known side effect of the drug: an aversive metallic taste. When monkeys are constantly exposed to this taste through their entire supply of drinking water, it may cause them to drink less, which in turn tends to cause a reduction in food intake in animals as well.

And body weight data weren't the only eyebrow-raising omission in baseline values. There were no baseline measures of *any* non- or minimally-invasive tests to demonstrate the two groups were identical at baseline when they were randomized to the two groups – including with respect to glycemic control. Along with significant weight gain early on in the study, both the controls and metformin groups were either *prediabetic or diabetic* according to fasting glucose values for all but the first three months of the study duration. Again, because there is no baseline data, it is impossible to determine if they had impaired fasting glucose from the start, or if the experimental conditions induced this condition. Metformin slightly mitigated fasting glucose compared to controls, but if a human was on metformin monotherapy with these levels of fasting glucose, they would almost certainly be put on additional therapies.

Obesity plus diabetes would be *more* than sufficient to cause the cognitive effect, neurodegenerative effects, periodontal bone loss, and higher levels of inflammation seen in control animals. This study does not provide any additional insight into whether or not metformin has a positive impact on *healthy* aging.

Finally, while the development of "biological clocks" in animal models may aid in determining whether these tools have *any* value in predicting lifespan, the "clock" used in this particular study was essentially meaningless. The monkey "biological clock" was based on the 18 control monkeys included in the study as opposed to the *thousands* used for human aging clocks.[25–27] In any model, one set of data (e.g., blood samples from a given cohort of individuals) is generally used to develop the model, and an *independent* set is used to validate and demonstrate its accuracy and predictive value. In this study, the researchers used the same (insufficient number of) monkeys to build *and* test the model, so the only value this "clock" could report was the difference between the older controls and the metformin group at the end of the study, with no reference group against which to compare both sets of experimental data. The differences in overall and organ-specific "age" are between the controls and the intervention group – not a "before" and "after" the intervention. In that sense we have no idea how any of the monkeys "aged" over the course of the study, and given how unhealthy the metformin group was, this is essentially saying that the metformin group was slightly younger than very unhealthy controls, not that the metformin group was aging more slowly than their chronological age would predict.

The limitations of this study far outweigh any insights it might provide. If anything it simply confirms what we already know: weight gain and severe loss of glycemic control are some of the foundational drivers of chronic disease, which can in turn accelerate aging.

The TAME trial

For many alleged longevity drugs, a broad examination of data from epidemiology, animal studies, and a handful of small-scale human trials can paint a relatively detailed picture of their efficacy and potential risks, thus permitting a fairly compelling case to be made for or against their use (such is the case for NAD+ precursor supplements, for instance, which we covered in a recent premium article). Unfortunately, when it comes to metformin, existing data are less consistent. A comprehensive view would lean toward a lack of efficacy in life extension in humans, but evidence to date suffers from a number of methodological shortcomings that limit

meaningful interpretation, so room for doubt persists. Ultimately, a clear answer to the question of whether metformin might benefit human lifespan (apart from the treatment of diabetes) may require a more dedicated, large-scale clinical trial for this indication, and as it happens, such a trial is currently in the works.

The TAME (Targeting Aging with Metformin) trial is a series of nationwide, six-year clinical trials to investigate metformin's potential as a geroprotective medication in healthy adults. This trial aims to recruit 3,000 non-diabetic participants ages 65-79 years, with the primary objective of assessing metformin's role in targeting multiple age-related conditions, including the development of cardiovascular disease (e.g., myocardial infarction, stroke, congestive heart failure), cancer, cognitive impairment, and mortality.[28] Secondary and tertiary outcomes encompass a broader range of measurements of healthspan, including functional capabilities (e.g., mobility, gait speed, and overall cognitive function), and the accumulation of chronic health conditions.

While the TAME trial has received FDA approval, it has faced funding challenges, and its launch date has been subject to delays. Though proposed roughly 10 years ago, only $35-40 million in funding has been raised against the estimated cost of $50-75 million.

Although the TAME trial is important to determine whether metformin has any broad geroprotective effects in healthy adults, its value goes beyond its immediate results. Whether or not the TAME trial is successful at treating or slowing aging, it could lead to FDA recognition of aging as an indication for drug treatment, and support future clinical trials for other potential longevity therapeutics, such as the antioxidant astaxanthin, the anti-nausea drug meclizine, and rapamycin – all of which have had at least sex-specific success in ITP experiments.[29,30] This could ultimately pave the way toward viewing – and treating – aging as a medical condition rather than as an unavoidable, unalterable fact of life.

Risks with metformin

As discussed earlier, one of the advantages of metformin is that, as a diabetes medication, it is already known to have a favorable side effect profile and to be safe for long-term use. However, while the few potential risks associated with metformin use are generally outweighed by benefits related to glycemic control among those with diabetes, the downsides become more a significant consideration for those *without* diabetes who are considering metformin for *possible* longevity effects. Therefore, although we have alluded to some of these risks here and there throughout this piece, we would be remiss not to lay them out clearly and more comprehensively.

According to long-term clinical trials on the use of metformin for diabetes, about 20-25% of users experience gastrointestinal distress (e.g., nausea, diarrhea, gas) after starting this medication.[5] However, these symptoms often resolve within a few weeks of use, and in many cases, they can be avoided by a gradual escalation of dosage or by using extended-release formulations. Even so, about 4-5% of patients will experience symptoms severe enough to

discontinue metformin therapy. For those who do not have diabetes, even transient GI concerns may be enough of a nuisance to discourage continued use, as may the unappealing metallic taste that arises when metformin interacts with saliva.

Another noteworthy side effect of long-term metformin use is impaired absorption of vitamin B12 and to a lesser extent folic acid, potentially causing deficiencies in these B vitamins.[31] While B12 deficiency is estimated to affect anywhere from 6-30% of chronic metformin users, it is typically mild. However, if deficiency becomes more severe, it can lead to more serious health concerns – including neurological impairments, anemia, and osteoporosis – if left unaddressed. For this reason, periodic monitoring of B12 levels is advisable for anyone on long-term metformin therapy.[32]

As noted in our discussion of the MASTERS trial, an additional concern related to the use of metformin – particularly for otherwise healthy adults – is its potential to interfere with the body's ability to reap the full benefits of exercise. This effect appears to extend beyond the negative impacts on muscle mass gains observed in the MASTERS trial. A separate randomized trial in generally healthy adults (n=53) utilized an aerobic exercise intervention and showed that although individuals on placebo exhibited significant improvements in both VO_2 max and insulin sensitivity as a result of a 12-week exercise intervention, those randomized to metformin treatment did not.[33] These results suggest that metformin actively *blocked* the cardiorespiratory and metabolic health benefits of aerobic exercise, likely due to the drug's impact on mitochondrial function. (Importantly, this doesn't mean you can't exercise on metformin – you certainly can, and should – but you might not get all the fitness gains you otherwise would.) Since exercise is a more proven – and more potent – longevity intervention than any alleged "anti-aging drug," this downside of metformin may negate any *other* advantages the drug might have for lifespan. In other words, a healthy individual who is very physically active might actually *lose* ground by adding metformin.

What should we do with this information?

Excitement over metformin as a longevity drug has waxed and waned over time, and this cycle is likely to continue until a more definitive answer can be obtained from the TAME trial. But in the meantime, we can nevertheless form a few conclusions based on our best evaluation of evidence to date:

For Healthy Adults: Current evidence doesn't support the use of metformin as an anti-aging intervention in healthy adults. Long-term metformin use is known to have a low risk profile and few adverse side effects, so for those seeking any and every potential means of enhancing their longevity, the combination of low risk and even a small possibility of benefit might be sufficient to tip the scales in favor of use. However, the potential interference with exercise adaptation and strength building is an important concern in this respect, given the well-documented benefits of physical activity for longevity.

For Diabetic Patients: Metformin remains an excellent first-line treatment for type 2 diabetes. The benefits of glucose control in this population are clear and well-documented and have broader implications for the prevention of other chronic diseases. However, we should be

careful not to extrapolate these benefits to healthy individuals.

For the Future of Aging Research: The metformin story provides valuable lessons about the complexity of aging interventions and the importance of rigorous scientific evaluation. The hints of support for longevity indications in certain contexts merit further investigation over the genetic and lifestyle contributors to the effects of metformin on aging as well as on metabolism. While the TAME trial may yet solidify lifespan benefits that we haven't determined from animal studies and small-scale human trials, even if this turns out to be the case, our primary focus should remain on well-established interventions – proper nutrition, regular exercise, quality sleep, and stress management – and *any* alleged longevity drugs should be a very distant second.

The bottom line

Despite initial excitement about metformin's potential as a geroprotective agent, the accumulated evidence suggests its effects on longevity may be limited, particularly in healthy adults. While metformin remains a valuable first-line therapy for diabetes management, its ability to extend lifespan appears to be highly dependent on genetic factors and metabolic status, with results varying significantly across different experimental models.

As we continue to search for pharmaceutical interventions that might slow aging, the metformin experience teaches us several valuable lessons. First, we must be cautious about extrapolating results from simple organisms to humans. Second, we need to pay careful attention to study design and potential confounders when evaluating observational data. Finally, we must remember that aging is a complex process unlikely to be significantly altered by any single intervention.

The future of aging research likely lies in understanding how multiple interventions might work together to promote health and longevity. The fact that metformin showed more promise when combined with rapamycin in animal studies hints at this possibility. However, until we have more definitive evidence, the most reliable path to healthy aging remains the consistent application of fundamental lifestyle practices that we know work.

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