

Will Metformin Become the First Anti-Aging Drug?

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By Raegan Linton

A committed group of scientists is seeking to validate **metformin** as the **first-ever** anti-aging medication.^{1,2}

In this day of staggering drug prices, metformin is available as a **low-cost** generic. One mechanism by which metformin works is by activating **AMPK**, an enzyme inside cells that lowers blood sugar by promoting energy utilization.

Activating **AMPK** has broad-ranging effects that extend *far beyond* blood sugar control. Studies show that boosting **AMPK activity** can prevent—and even reverse—the life-shortening effects of aging, such as cardiovascular disease, diabetes, neurodegenerative diseases, cancer, and more.³

In this article, we'll review data that persuaded the FDA to allow **metformin** to be studied in **humans** as the first **anti-aging** drug.¹

WHAT YOU NEED TO KNOW

- Metformin has been a staunch workhorse against diabetes for more than 50 years.
- Studies show that metformin acts by boosting the activity of AMPK, a master metabolic regulator that favors fat- and sugar-burning and prevents their accumulation.
- Because AMPK is relevant in all tissues, this makes metformin extremely important in reducing metabolic imbalances in the entire body.
- Strong evidence suggests that metformin, through its protective effects and AMPK-activating properties, can help prevent cancer, cardiovascular disease, obesity and its consequences, and even neurodegenerative disorders.

Broad-Spectrum Effects



The most commonly prescribed antidiabetic drug is **metformin**. It has been in use in **England** since **1958** and in the **United States** since **1995**.

Derived from a compound found in the French Lilac, metformin has a track record of safety and effectiveness at routine doses of up to **2,000 mg** daily.⁴⁻⁷

So what evidence is there for the FDA to consider this drug as an **anti-aging medication**? The reason is simple:

Metformin can block or diminish many of the fundamental factors that accelerate aging.⁸⁻¹²

These include protecting against DNA damage glycation, poor mitochondrial function, and chronic inflammation. Metformin has been shown to facilitate **DNA repair**, which is critical for cancer prevention.

By attacking these fundamental degenerative processes, metformin can prevent the development of aging's most troubling **diseases**.

Metformin has also been shown to increase the production of known longevity-promoting signaling molecules in cells, such as **mTOR** and **AMPK**—all of which reduce fat and sugar storage and increase youthful functioning at the cellular level.^{11,13}

Studies have shown that by activating AMPK, metformin specifically impacts **lifespan**. For example, roundworms treated with metformin have higher **AMPK activity** and live about **20%** longer than untreated control animals.¹⁴ Mice treated with metformin have been found to live nearly **6%** longer than controls.¹¹ And most impressively, diabetics taking metformin were shown to live **15%** longer than healthy individuals without diabetes!¹⁵

AMPK activity declines with age,¹⁶ making us more vulnerable to many of the diseases associated with aging. Fortunately, a wealth of recent studies show that by *activating* AMPK, metformin plays a major role in preventing age-related disorders including cancer, cardiovascular disease, obesity, and neurocognitive decline.

By combatting many of the underlying **causes** of aging—and by activating AMPK—metformin can be considered a broad-spectrum anti-aging drug.

Cancer Protective Effects of Metformin

Diabetics have an increased risk of cancer. In a study of head and neck cancers, researchers were surprised to find that diabetic patients had a **46%** reduction in risk of developing these cancers compared to non-diabetic patients.¹⁷ What was the reason for this unexpected reduction? The diabetic patients were taking **metformin**. Similar effects have been seen for the risk of gastric (stomach) cancers as well, with metformin users experiencing a **55%** decrease in the risk of stomach cancer compared with nonusers.¹⁸ Important studies like these have helped to confirm a decade-long trend suggesting that metformin has anti-cancer properties.¹⁷

While these studies show that metformin has the potential to reduce the risk of *developing* cancer, others show its benefits for those who already have cancer. A study encompassing 27 clinical trials representing more than 24,000 patients found that in people with early-stage cancers of the colon and rectum, metformin use improved **recurrence-free survival** by **37%**, **overall survival** by **31%**, and **cancer-specific survival** by **42%**.¹⁹

The same study reported similar results for men with early-stage **prostate cancer**, with metformin use increasing **recurrence-free survival** by **17%**, **overall survival** by **18%**, and **cancer-free survival** by **42%** compared with non-metformin users.¹⁹

By now, metformin has been studied in the context of total tumor incidence in 17 different target organs, 21 strains of mice, and four strains of rats. It has been studied in cancers that occur spontaneously, and in those induced by 16 different chemical carcinogens from multiple classes, ionizing radiation, viruses, genetic modifications, and high-fat diets, using five different routes of administration.²⁰

A whopping **86%** of such studies showed that metformin clearly inhibited cancer development and showed zero evidence of cancer stimulation by the drug.²⁰ Indeed, as one expert recently put it, maybe it's time "to make this long story short" about metformin: It works to prevent cancer.²⁰

Metformin Prevents Cardiovascular Disease

Despite billions of dollars spent on drugs such as Crestor and Lipitor, cardiovascular disease remains the single biggest killer in America. While there are multiple causes of cardiovascular disease, most boil down to the development of **atherosclerosis**, or "hardening of the arteries."

Atherosclerosis is promoted by factors such as oxidation of LDL cholesterol, accumulation of that oxidized fat in arterial walls, and damage to the endothelium, which is the thin layer of cells lining those arterial walls.²¹

Metformin is now known to prevent these early steps in atherosclerosis development.

One of the key ways it does this is by activating the metabolic regulator **AMPK**. By activating AMPK, metformin:

- Mitigates LDL oxidation and the resulting endothelial dysfunction, which slows the development of atherosclerosis.²¹
- Reduces the conversion of harmless immune system cells (**monocytes**) into fat-laden **macrophages**, an action that reduces their accumulation in vessel walls.²² It also increases cholesterol export **out of those cells**, while also suppressing the inflammatory stimulus they normally produce.^{23,24}
- Offers critical protection to endothelial cells that line coronary arteries, which supply blood to the heart muscle itself. Specifically, metformin enhances the resistance of endothelial cells to "fat poisoning," the death of endothelial cells in the presence of high fat concentrations.²⁵ This is highly protective against heart attacks, which occur when coronary arteries, blocked by atherosclerotic plaques laden with fat and inflammatory cells, fail to provide enough blood to the hard-working heart muscle.

Metformin has also been shown to prevent the fragmentation of mitochondria in endothelial cells.²⁶ Such fragmentation is closely associated with the dysfunction of endothelial cells and is now considered an important precursor of atherosclerosis.²⁶

The results of these protective effects have been seen in numerous human studies. In one study, heart attack patients taking metformin had a significant **75%** reduction in the risk of dying after 30 days, and a **68%** reduction in their risk of dying 12 months after the attack.²⁷

Several studies have also demonstrated that metformin reduces the risk of heart attack, and is associated with reduction in stroke, atrial fibrillation (an arrhythmia), and death from all causes.²⁸

Finally, a 2016 study showed significant reductions in systolic (top number) blood pressure in nondiabetic people taking metformin. The largest reductions were seen in those having impaired glucose tolerance or obesity.²⁹

Obesity itself appears ready to yield to metformin treatment, as we'll now see.

FDA APPROVES FIRST ANTI-AGING STUDY

The FDA has approved a study that will determine if metformin can do more than lower blood sugar—it will evaluate metformin's ability to **slow aging**. This is the first ever anti-aging study approved by the FDA.

Studies have shown that metformin can block or diminish many of the underlying factors that accelerate aging, and it has also been shown to extend lifespan in animals. Dr. Nir Barzilai from the Albert Einstein College of Medicine, along with researchers from the American Federation for Aging Research (AFAR), want to find out if metformin can extend lifespan in humans as well.



The study, called **Targeting Aging with Metformin (TAME)**, will evaluate 3,000 people over a course of six years. Half of the participants will receive metformin, and the other half will receive a placebo. Since aging is largely characterized by the development of disease, the success of the study will be determined by whether or not the drug delays the onset of typical age-related diseases, such as cardiovascular disease, cancer, and cognitive decline.

This groundbreaking study has the potential to change the future of how we treat disease. Developing a single drug designed to treat multiple conditions would dramatically reduce the number of drugs a typical person would need, which would reduce overall drug side effects, eliminate contraindications, and of course, save money.

None of this is good for Big Pharma's bottom line—which is likely why no company has agreed to fund the study. Until that happens, this important study is on hold.

But you can help. AFAR is seeking individual contributions to get the TAME study started. To learn more, and make a donation if you like, visit www.afar.org/donate/

Metformin Reduces Body Weight and Fat Mass



Metformin's ability to activate AMPK makes it especially beneficial in combatting **obesity**. This is because AMPK is a **metabolic regulator** that stimulates **youthful** cellular behaviors such as burning fat (instead of storing it), taking sugar out of the blood, and recycling cellular contents to eliminate toxic proteins.³⁰

As a result, metformin can be expected to have important effects on body weight and fat deposits. And indeed, studies show that metformin fights obesity and reduces body fat mass, *even in non-diabetic patients*.

This is true in some of the most challenging populations, such as women with **polycystic ovary** syndrome, a major cause of obesity and endocrine problems in premenopausal women.

In one study, women with polycystic ovary syndrome were treated with **850 mg** of metformin or a placebo twice daily for 6 months. During that time, those in the placebo group experienced *increases* in weight and blood sugar, as expected. Those taking metformin, on the other hand, had significant *decreases* in weight and blood sugar—with metformin-treated women losing an average of **9.24 pounds**. The metformin group also had significant increases in beneficial HDL cholesterol.³¹

Metformin has been found to significantly reduce body weight, body mass index (BMI), and insulin resistance in patients taking modern **antipsychotic medications** such as olanzapine, aripiprazole, risperidone, and quetiapine.³²⁻

³⁵ These are impressive results, since major side effects of these drugs include rapid weight gain, loss of insulin sensitivity, and other features of metabolic syndrome.³⁶ But by far, the largest group of people fighting obesity are simply aging individuals who are otherwise healthy (nondiabetic). Metformin shows promise for this population as well.

An important study in a group of such people—all women with midlife weight gain but normal blood sugars—showed that taking metformin for 12 months reduced mean body weight by **11.6 pounds**.³⁷ In addition, treated subjects had significant decreases in their **body fat percentage**, a favorable change that can reduce many of the long-term consequences of obesity.

Metformin is showing promise in obese but otherwise healthy **young** people as well. A group of 10-16- year-olds took **2,000 mg** of metformin per day or a placebo for 18 months. Those taking metformin lost nearly half a pound in fat mass. By contrast, the placebo group gained almost **4.5 pounds** in fat mass.³⁸

Metformin as Neuroprotectant

There is rapidly growing literature on metformin's potential role in preventing neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. Once again, much of this literature focuses on metformin's ability to activate **AMPK**, the youth-promoting energy regulator in all of our cells.

One major effect of AMPK activation is the cleanup of accumulated misfolded proteins in brain cells. The accumulation of proteins, such as *tau* and *beta-amyloid*, contributes to brain cell death and dysfunction in neurodegenerative diseases. Thus, it makes sense that metformin might be effective in preventing disorders associated with those proteins. Numerous animal and laboratory studies show that metformin does indeed have such effects. These studies demonstrate that metformin:

- Reduces levels of an enzyme that generates *beta-amyloid* proteins³²
- Decreases the harmful effect of *beta-amyloid* on brain cell function³⁹⁻⁴¹
- Reduces levels of *alpha synuclein*, another protein that accumulates and causes damage in Parkinson's disease⁴²
- Prevents the loss of dopamine-producing brain cells in a model of Parkinson's disease^{43,44}
- Improves motor coordination in a mouse model of Parkinson's⁴⁵

In 2016, a human study showed that taking **1,000 mg** of metformin twice daily for 12 months improved memory recall in a group of older adults with a condition called amnesic mild cognitive impairment (a memory-stealing predecessor of Alzheimer's).³⁹

Given the close connections between Alzheimer's and diabetes (it's been called "Type III diabetes"), there is every reason to believe that metformin, through its AMPK-activating properties, will help in the long fight to retain our minds and personalities as we age.

PRECAUTIONS AND USEFUL SUGGESTIONS WITH METFORMIN USE

Although metformin has an outstanding track record in the fight against diabetes, cancer, obesity, neurodegenerative and cardiovascular diseases, there are some precautions to be aware of with its use.

Metformin is known to interfere with the absorption of B12, increasing the risk of **vitamin B12 deficiency**.^{46,47} Low B12 levels contribute to higher concentrations of artery-clogging **homocysteine**—an independent risk factor for cardiovascular disease.^{48,49} The

tiny amounts of vitamin B12 and other B-vitamins found in commercial supplements is usually not enough to offset this problem. Individuals using metformin should ensure that they are taking higher doses of B-vitamins (at least **300 mcg of methylcobalamin**, the active form of **vitamin B12**) and checking their homocysteine levels to ensure proper protection.

Some studies have shown that metformin reduces **free and total testosterone** levels in men.⁵⁰ Testosterone is especially important in male diabetics as it enhances insulin sensitivity.⁵¹ Life Extension has previously published clinical data on the importance of maintaining youthful testosterone levels in diabetic men to improve glucose utilization.⁵²

If a **blood test** shows low testosterone, applying a topical testosterone cream can restore levels of this vital hormone to youthful ranges.

Side effects associated with metformin use include gastrointestinal distress or a slight taste disturbance, usually a metallic taste. Rarely, metformin may cause a potentially serious lactic acidosis, a buildup of lactic acid in the blood.⁵³



If you use or are considering metformin, consult your physician, take your B-vitamins, and periodically check your kidney function, homocysteine levels, and in men, free and total testosterone.

Summary



The world's first clinical trial of a true “anti-aging” drug may be about to begin. But while the study is new, the drug is more than half a century old.

Metformin has been used for more than 50 years to treat type II diabetes. A wealth of recent studies now supports a major role for metformin in preventing age-related disorders including cancer, cardiovascular disease, obesity, and neurocognitive decline.

The American Federation for Aging Research (AFAR) has a long uphill road to get this study (called TAME, or the Targeting Aging with Metformin trial) started. They face almost-certain opposition from Big Pharma companies for whom treating—not preventing—aging is a lucrative business.

The good news is that we don't have to wait for this new metformin study to get off the ground. Metformin is already available as a prescription medication. And many thoughtful physicians who are presented with the evidence will prescribe it based on its recognized benefits against specific age-related disorders.

There are also **nutrients** that have been shown to boost **AMPK activity** and function to lower blood glucose similar to metformin.⁵⁴⁻⁵⁷

If you have any questions on the scientific content of this article, please call a Life Extension® Wellness Specialist at 1-866-864-3027.

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