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Extending Lifespan With Metformin: A Comprehensive Review and Proposed Study

A Thesis Presented

By

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To The Keck Science Department

of

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Abstract

Aging is a non-adaptive epiphenomenon that characterizes the terminal phase of life. Aging leads to the dysregulation of metabolic processes that subsequently drive the downregulation of critical nutrient sensing pathways and autophagy, while increasing inflammation, cellular senescence, stem cell depletion, reactive oxygen species, and DNA damage; the gestalt of which is the aging phenotype. Age-induced subcellular alterations impact the whole organism, from cosmetic factors, such as grey hair and wrinkles, to the development of cardiovascular diseases, cancer, and neurodegenerative diseases. Fortunately, humans may have discovered a means of delaying aging through treatment with metformin. Metformin is an FDA-approved drug that has been a safe, inexpensive, and effective type 2 diabetes treatment for over 60 years. Research in model organisms has revealed metformin's capacity to extend both healthspan and lifespan, decrease the incidence of diseases of aging, and modulate aging-regulating metabolic pathways. In type 2 diabetics, metformin has successfully attenuated diseases of aging, decreasing the incidence of cancer and cardiovascular disease. Metformin also shows promise for the treatment and prevention of neurodegenerative diseases. Currently, two major trials (TAME and MILES) are underway to ascertain if the healthspan and lifespan-extending benefits of metformin can be generalized to the non-diabetic population. The present thesis sets forth a comprehensive review of metformin's capacity to attenuate aging and proposes a study synergistic with TAME and MILES to determine the optimal age of initiation to produce the greatest benefits from metformin treatment in the general population. Metformin demonstrates the potential to act as both a treatment and prophylactic to mitigate the progression of aging, leading to greater time spent in good health, and ultimately, a longer life.

Introduction

While death has existed as long as life, for humans, the luxury of aging is a modern invention. Rather than revel in the joy of being fortunate enough to experience aging, humans are actively searching for ways to avoid, or at the very least postpone, the process that characterizes the inevitable progression toward death. Among the scientific community, a universal theory of aging has not yet been supported, though it is widely accepted that aging is the emergent consequence of stochastic damage accumulation throughout the body over the life course of an individual (Kirkwood et al., 2005). Current research searches to identify these mechanisms of age-related deterioration and understand how and why their dysregulation gives rise to the phenotypes, known as signs of aging, with hopes of applying findings to the reversal or slowing of aging. In recent years, the scientific community has identified metformin, the most commonly prescribed medication for type 2 diabetes, as a candidate drug for life extension in humans due to its ability to impair the mechanisms of aging (Mohammed et al., 2021). The present thesis highlights the current understanding of the potential for metformin to combat the biological aging process and proposes a study to determine if metformin should be recognized as a drug capable of attenuating the diseases of aging via biological age mediation.

Is aging a disease?

It is tempting to consider a disease to simply be antagonistic to health, however, such a definition is problematic given that the concept of health is relative and heavily influenced by socio-cultural environments (Scully, 2004). The exact approach to treating the physical manifestations of aging is contingent on whether aging is viewed as a disease; a characterization that is hotly contested within the scientific community. From a medical perspective, a disease has

definite pathological signs and symptoms that negatively affect part or the whole of an organism (Calvo et al., 2003). History shows us that defining a condition as a disease is heavily influenced by society and often leads to a stretching of the definition to fit the proposed disease; as seen by the previous official classifications of masturbation and homosexuality as diseases (Reznek, 1987). Given the plethora of chronic diseases that appear with increasing chronological age, it is no wonder that in recent years the scientific community has turned its attention to understanding the mechanisms of aging and ameliorating its effects. Due to momentous improvements in healthcare in the last century, the human lifespan has been drastically extended, though the healthspan has not been proportionally elongated (Li et al., 2021). Lifespan represents the number of years an organism lives, from birth to death, which includes healthspan, the period of life spent in good health, free from the chronic diseases of aging (Kaeberlein, 2018). Efforts to match the healthspan with lifespan begin by targeting the pathogenesis of aging, though the manner in which aging is approached is heavily influenced by its classification.

Aging does not neatly fit into the requirements of a disease as outlined by the International Statistical Classification of Diseases and Related Health Problems (World Health Organization, 2021). Those against the disease label view aging as a natural process that organisms inevitably undergo and that is separate from any individual disease's pathology, though the disease and its progression might be related to aging (Hayflick, 2004). They believe that chronic diseases, such as cardiovascular diseases, diabetes, Alzheimer's, and other neurodegenerative diseases, may simply be the manifestation of age-related deregulation of metabolic processes (the progression of which may be impacted by genetics and lifestyle) and cannot simply be boiled down to phenotypes of the "aging disease" (Gladyshev and Gladyshev, 2016). Labeling aging as a disease is a drastic oversimplification as aging simultaneously causes

and is the product of the dysregulation of many metabolic processes. Additionally, though not all diseases that appear with age are a direct result of aging, any disease that progresses with chronological age is thus considered to be linked with aging (Gavrilov and Gavriola, 2006). Age should be considered an inescapable risk factor in the development of chronic diseases of aging, though it cannot be named the sole cause.

If aging were to be considered a disease, then it must also be considered to be treatable (Gladyshev and Gladyshev, 2016). Current research shows that aging is inescapable and cannot be entirely eradicated, thus it cannot be truly considered a disease, however, aging can be modified by regulating the biochemical pathways that give rise to aging phenotypes when dysregulated (Fulop et al., 2019). From a monetary point of view, the utility of naming aging a disease is clear. Supporters of aging-as-a-disease believe that proper funding for gerontological studies and drug development will only be obtained if aging is viewed as a disease, and thus a potentially treatable condition (Gavrilov and Gavriola, 2017). So, while aging does not exactly fit with the criteria to be categorized as a disease, naming aging a disease functions as a means of soliciting the necessary funding and business interest for gerontological research as if aging is labeled a disease then by definition (though the science may still disagree) it has the potential to be treated.

Aging: Genetics and Evolution

As aging is inherently deleterious to the health of the organism, from an evolutionary perspective, it is surprising that not only has it evaded the pressures of evolution but that it is a pervasive process, impacting every living animal, to a certain degree (Loison et al., 1999). Though some animals demonstrate negative or negligible senescence, where mortality risk

decreases or is stable with increasing age, meaning they do not appear to undergo aging, the process by which this occurs is not well understood and is under active research (Canwei et al., 2022). Most organisms, however, are subject to the conventional biological aging process that accompanies increasing chronological age, though the rate varies amongst species and individuals (Austad et al., 1991). If aging is found to be regulated by similar processes in most animals, disparities in aging rate show promise for a flexible aging timeline dependent on the regulation of age-related biological machinery. Before mechanisms of aging can be manipulated to extend lifespan in humans, their purpose and function must be solidly understood. While a number of biological processes have been implicated in the aging process, why these mechanisms exist in the organism, despite their life-terminating effects, is under investigation (Kenyon, 2005, Kirkwood et al., 2005, Fahy et al., 2019, Finkel et al., 2000).

Why Do We Age?

Dying is clearly detrimental to an organism's evolutionary fitness, so why does aging define the latter half of nearly all living organisms' lives? Nineteenth-century evolutionary scientists hypothesized that aging served to remove the unproductive and non-reproductive members of society to make more resources available for the younger generations and aid in their production of offspring (Partridge et al., 2002). Unfortunately, twentieth-century evolutionary biologists found this altruistic explanation for aging to be flawed. They identified that evolution typically acts in favor of the individual rather than the species if the two are in conflict (Williams et al., 1957). It can further be argued that aging acts against conventional evolutionary patterns from the focal point of cooperative care of young. Natural selection would seemingly work to extend the lives of animals that engage in such practices. If organisms

survived to aid in the rearing of their grandchildren, they would be ensuring the survival of their genetic material to subsequent generations. However, for animals that do practice cooperative care and survive to aid in the care of their grandchildren, this pattern of life extension is not visualized in the wild (Thorley, 2020).

Aging differs from other biological functions, like sexual development, in that it does not serve a purpose. Aging should be viewed as a mechanical malfunction that ultimately results in the death of the organism, rather than as a trait that living organisms simply possess. Aging is akin to an autosomal dominant mutation in that it is detrimental and manifested in the phenotype of subsequent generations. The analogy falls apart, however, given that, unlike autosomal dominant mutations which disappear from the gene pool rather quickly, aging has persisted as its symptoms materialize after the genetic material has been passed down. The evolutionary theory of aging, set forth first by JBS Haldane and supported by theoretical population genetics, formed around the concept that natural selection progressively loses its power over manipulating aspects of a lineage's biology the later in life the phenotype manifests in the organism (Partirdige et al., 2002). Aging exists as an evolutionary paradox because its onset typically occurs after an organism has reproduced and thus passed on its genetic material to the next generation. Natural selection, on the other hand, acts through reproduction. If a trait is beneficial to the organism, its fitness will increase as will reproductive rate, passing on the advantage to its progeny. By the same process, if a trait is deleterious to an organism, it will decrease its fitness and consequently, the number of progeny, preventing the harmful trait from rapidly spreading throughout the gene pool. As aging trails the reproduction process, the systematic dysregulation of cellular processes that create the aging phenotype manifest after the genetic material has already been passed down.

Without natural selection to prune away the deleterious aging process before it can be inherited by subsequent generations, aging exists out of natural selection's reach.

Processes that directly impact an organism's ability to reproduce and pass on its genetic material are subject to high evolutionary pressures and typically are explicitly programmed within the genome and serve a specific purpose. The process of aging stands in stark contrast. Currently, there are no identified genes that function solely to create damage that ultimately results in what would be defined as aging; in other words, there is no "aging gene," (Partridge et al., 2002). As aging is not coded into the genome, it exists relatively untouched by natural selection's genetic meddling, rendering aging a non-adaptive epiphenomenon resultant of late-onset genetic dysregulation (Partridge et al., 2002). To further complicate matters, aging is the outcome of an array of dysregulated processes, rather than one single link explicitly tethered to a clear-cut nucleotide sequence on a chromosome. The complex and indiscriminate nature of aging has piqued many a curious mind hungry to understand the mechanism behind the process to which all life must ultimately succumb.

Biohorology: Measuring Aging

The conventional method of measuring the lifespan by quantifying the time from birth to death, known as chronological age, is a useful tool, though it does not provide information on the rate at which an organism ages and how that rate is affected by genetic and environmental factors. Conversely, biological age can be calculated by examining factors that are altered by changes in metabolic pathways due to the organism's environment and the passage of time. Biological age is determined through analysis of telomere length, transcriptomic predictors, proteomic predictors, metabolomics predictors, composite biomarker predictors, and the

epigenetic clock. The disparity between the chronological and biological age of an organism provides insight into how its environment, both controlled and uncontrolled factors, impacts the rate at which it ages. In comparison to chronological age, biological age should give a more accurate prediction of the rate of aging, where an organism is in its aging process, and ultimately, its prospective lifespan (Johnson, 2006).

Currently, the most accurate method of calculating biological age is the epigenetic clock. In 2013, Steve Horvath and Gregory Hannum independently formulated methods of quantifying the epigenetic clock by analyzing specific sites of DNA methylation age (DNAmAge), specifically Cytosine-5 methylation within CpG dinucleotides (Horvath, 2013, Hannum et al., 2013). The Horvath clock quantifies methylation levels on 353 CpG sites, in comparison to the Hannum clock, which uses 71 CpG sites. Despite sharing only 6 CpG sites, there is a strong correlation between the Horvath and Hannum clocks' predictions where $r=0.76$ (Chen et al., 2016), though others have reported a moderate correlation of $r=0.37$ (Belskey et al., 2018). In humans, both the Horvath and Hannum clocks show statistical significance in accurately predicting chronological age, demonstrating correlations of $r=0.96$ and $r=0.91$, with average deviations of 3.6 and 4.9 years, respectively, in their validation cohorts (Horvath, 2013, Hannum et al., 2013). The Horvath and Hannum clocks have accurately predicted the ages of humans from all stages of adult lifespans and across a variety of racial and ethnic backgrounds.

The utility of the epigenetic clocks lies in their ability to accurately predict all-cause mortality independent of risk factors such as age, body mass index, education, smoking history, alcohol consumption, physical activity, and other comorbidities (Jylhävä et al., 2017). Dividing the study samples into subgroups (sex, race, smoking history, BMI, etc.), using the Hannum clock, Chen et al. 2016, found a statistically significant association between mortality and most

subgroups (Chen et al, 2016). Additionally, recent research shows that epigenetic clocks demonstrate a strong ability to predict cancer mortality, and to a lesser extent, cardiovascular disease mortality (Perna et al., 2016, Zheng et al., 2016). With regards to cancer, Zheng et al. found that each one-year increase in the difference between biological age (BA) and chronological age (CA) ($BA-CA=\Delta\text{age}$) represented a 6% increased risk of developing cancer within the next 3 years and a 17% increased risk of dying from cancer within the next five years (Zheng et al., 2016). A Δage that is negative or close to zero is a strong indicator of good health and correlates with decreased cancer incidence. Furthermore, studies on Alzheimer's disease utilizing the Horvath clock found that greater Δage was associated with the presence of the physical and cognitive manifestations of the neurodegenerative disease, whereas healthy individuals of the same age did not demonstrate the same Δage disparity (Levine et al., 2015). Hundreds of studies have demonstrated the ability of epigenetic clocks to accurately predict the biological age of individuals, as well as their mortality risks (Jylhävä et al., 2017). As such, the Hannum and Horvath clocks should be utilized to quantify the rate of aging in future studies that seek to modulate the aging process.

Methods of Manipulating Aging

Currently, studies have revealed two avenues used to delay aging and extend life in model organisms: caloric restriction and reduced reproduction (Lane et al., 2000; Lin et al., 2000). Reducing caloric intake to 60%-70% of voluntary intake levels slows biological aging markers and increases lifespan in model organisms, from yeast to mammals (Masoro et al., 1996). Caloric restriction has been shown to decrease reproduction, meaning that the lengthening effect on lifespan produced by caloric intake reduction could also be a byproduct of a decreased

lifetime and daily fecundity (Chapman et al., 1996). As aging is slowed by both caloric restriction and decreased reproduction, and reproduction is decreased by caloric restriction, it is possible that the rate of aging might be dependent on the rate of reproduction. While the exact mechanisms that link aging to calorie intake and reproduction are not fully understood, the conservation of their relationship across large evolutionary distances indicates a highly conserved mechanism that is deeply ingrained in most organisms (Fontana and Partridge, 2015).

Efforts by the scientific community to understand aging have uncovered that though aging itself is not programmed within the genetic code, it is the result of the dysregulation of highly evolutionarily conserved pathways which are essential to the survival of the organism (Guarente et al., 2000). As most studies on aging have been conducted using model organisms, notably yeast, *Drosophila*, *Caenorhabditis elegans*, and mice, when attempting to use prior studies' results to inform theories about the human aging process, it is important to differentiate between mechanisms of aging that are highly evolutionarily conserved and those that are unique to the species (Martin et al., 1996). Highly evolutionarily conserved mechanisms are potentially relevant to human aging, whereas those that are specific to the model organism pertain only to certain evolutionary lineages. Whether in humans or model organisms, the identification and subsequent analysis of genes responsible for the aging process have provided links between the dysregulation of signal transduction pathways and gene regulation to the phenotypic changes known as symptoms of aging (Guarente et al., 2000). That there exist evolutionarily conserved mechanisms that may influence aging indicates that the pace at which these processes are progressively dysregulated potentially influences the rate of damage accumulation and thus the emergence of physical indicators of aging.

While reducing calorie consumption and lifetime fecundity increases lifespan in model organisms, and could potentially increase the life span of humans, despite extensive scientific research, it is unlikely that such means of extending life will be readily accepted and practiced by society. The toll that calorie restriction and reduced reproduction would take on the psychological well-being of humans may not be viewed as an equal trade-off for longer life. Further, given that obesity levels are rising globally, calorie restriction might not be a feasible course of action for humans, as we are already struggling to limit calorie intake to neutral levels (Lifshitz et al., 2014). By 2023, nearly 50% of U.S. adults will be obese, with just under 25% qualifying as severely obese (Ward et al., 2019). If humans desire to increase their lifespan without resorting to major lifestyle changes, an alternative method to combat the aging process must be identified.

History of Metformin

In recent years, research has revealed the treatment for aging may be hidden in plain sight, under the guise of the most widely used Type 2 Diabetes Mellitus (T2DM) medications, known as metformin. Aside from metformin's potential to extend lifespan, it is made even more attractive as a potential anti-aging medication due to its long history of use by humans as a T2D treatment. Metformin's role in fighting T2D traces back to medieval-era Europe, where physicians utilized *Galega officinalis*, or goat's rue, an herb concentrated with guanidines, to treat "sweet urine" and gastrointestinal distress (Bailey, 2004). The 1920s showed a boom in the synthesis of guanidine derivatives for medicinal usage, one being metformin; however, medications containing guanidine derivatives were discontinued in the early 1930s as they were found to be toxic and overall detrimental to the users' health, despite lowering blood glucose

levels. Though metformin did not demonstrate such negative side effects, its use was similarly halted (Bailey et al., 2017). Metformin's impact on blood glucose levels caught the attention of French physician Jean Sterne, who first administered metformin to manage T2D in 1957. Today, metformin is the first line of defense against T2D and is taken by 150 million people worldwide. Despite metformin's history and widespread usage over the last 60 years in its current form, its potential to act as an anti-aging compound is only now coming into the light (Bailey et al., 2017).

Metformin

Metformin is an insulin sensitizer that displays off-target geo-protective effects which show promise for the drug to function as an anti-aging compound. In contemporary studies, metformin has been shown to significantly extend the lifespan of model organisms beyond those of untreated populations and decrease biological aging markers (Anisimov et al., 2008; Rena et al., 2017). Mechanistically, metformin targets multiple pathways known to be involved in aging when dysregulated, slowing their effects by activating AMP-protein activated kinase (AMPK) (Guo et al, 2021, Kalender et al. 2010), reducing insulin and insulin growth factor 1 (IGF-1) signaling (Xiao et al., 2020), inhibiting mammalian target of rapamycin (mTOR) (Howell et al., 2017, Wu et al., 2016), decreasing reactive oxygen species (ROS) levels (Ribiero et al., 2020), lowering DNA damage (Dogan, 2018, Wu et al, 2012), reducing inflammation (Karnewar et al. 2018), and functioning as a caloric restriction mimetic (Onken and Driscoll, 2010). Data from human research provides further support for the possibility that metformin could act to ameliorate the manifestations of aging.

Mechanisms of Metformin

Aging is the gestalt of dysregulated metabolic pathways. The aging phenotype arises as the sum of cellular and subcellular alterations, such as compromised nutrient sensing pathways, reactive oxygen species (ROS), DNA damage, cellular senescence, stem cell depletion, a decline of autophagy, and inflammation (Lopez-Otin et al., 2013). Furthermore, these pathways do not exist in isolated environments, so if aging is to be slowed, a variety of intertwined pathways must be targeted. Metformin acts on critical components of the aging process, primarily through its role as a calorie restriction mimetic. The dysregulation of nutrient sensing pathways is a crucial part in the development of the aging phenotype. Metformin acts upon these nutrient sensing pathways, restoring their capacity and thus combatting the progression of aging (Figure 1) (Lopez-Otin et al., 2013).

Metformin's proposed primary mechanism of action is the inhibition of mitochondrial complex 1 (MC1) mediated oxidative phosphorylation, the repercussions of which activate or inhibit certain pathways that are implicated in the aging process (Barzilai et al., 2018). While there has been considerable research supporting the role of MC1 in metformin's actions, more recent studies have identified substantial faults that cast doubt on the accuracy of the prior findings (Fontaine, 2018). Further research must be done to establish whether MC1 is implicated in metformin's mechanism of action.

In vivo, metformin holds a positive charge and thus, driven by differences in membrane potentials and catalyzed by organic cation transporter-1, accumulates within the mitochondria with a concentration up to 1,000 times greater than the extracellular concentration (Owen et al., 2000). MC1 inhibition suppresses ATP production, altering the AMP:ATP and ADP:ATP ratios as well as the NAD⁺/NADH ratio to those indicating a low energy state. A high AMP:ATP ratio

is a known activator of the adenosine monophosphate-activated protein kinase (AMPK) pathway. The skewed AMP:ATP ratio activates AMPK subsequently initiating a cascade of cellular-level events that mimic calorie restriction (Hawley et al., 2010). Metformin has been found to activate AMPK independent of MC1 inhibition, such as through insulin-like growth factor 1 (IGF-1) inhibition, suggesting that metformin has more widespread effects on mitochondrial function than previously thought (Glossman and Lutz, 2019).

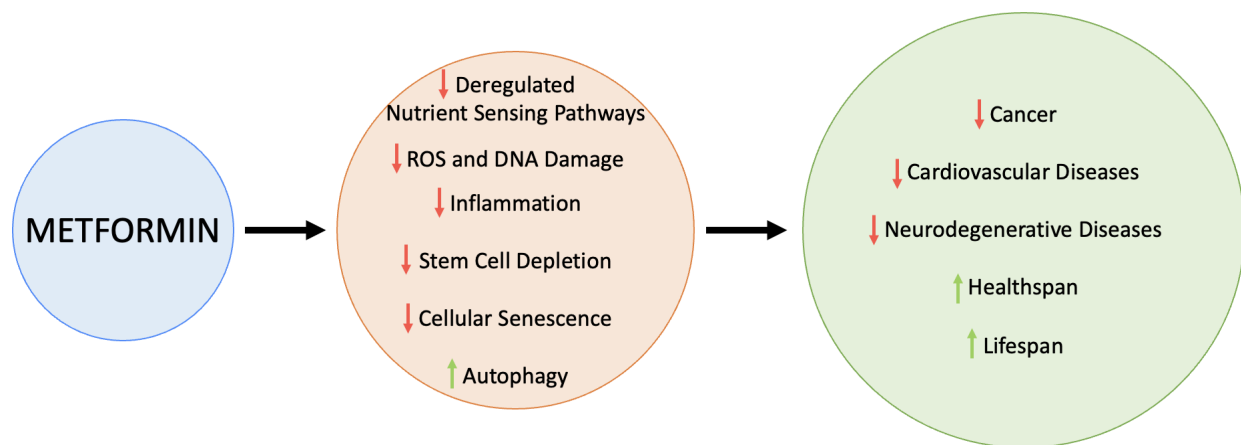


Figure 1: Summary of metformin’s mechanisms of action that attenuate aspects of aging, ultimately leading to the extension of healthspan and lifespan.

Adenosine Monophosphate-Activated Protein Kinase (AMPK)

The AMPK pathway is the energy sensor of the cell, acting in response to changes in nutrient availability or growth signals. It acts to preserve energy stores through the activation of multiple protective and conservative signaling pathways in response to calorie restriction (Mihaylova and Shaw, 2011). The metformin-induced increase in cellular AMP concentration activates AMPK in four ways: 1) allosteric AMP binding to the gamma subunit of AMPK, 2) initiation of the phosphorylation of AMPK’s threonine-172, 3) inhibition of the dephosphorylation of threonine-172, and 4) decreasing the activation of adenylate cyclase thus

limiting glucagon secretion (Hardie, 2013). Additionally, AMPK is positively regulated by NAD⁺ deacetylase, which is activated by the feigned low nutrient conditions created by metformin (Mohammed et al., 2021). AMPK regulates the metabolism of glucose and lipids and restricts gluconeogenesis in hepatic cells. The metformin-mediated inhibition of hepatic gluconeogenesis increases insulin sensitivity, beta-oxidation of fatty acids, and muscular glucose uptake (Zhou et al., 2001). Sensitivity to the AMPK pathway declines with age, accelerating the development of aging and age-related diseases (Salminen and Kaarinranta, 2011). Metformin is thought to elicit most of its anti-aging effects via AMPK-mediated pathway regulation, restoring critical nutrient sensing pathways.

Metformin and Pathways that Give Rise to the Signs of Aging

The biochemical impacts of metformin *in vivo* act to attenuate the known contributors to aging, such as decreased nutrient sensing capacity, reactive oxygen species, cellular senescence, inflammation, reduced autophagy, and stem cell depletion. The aforementioned mechanisms of metformin function in concert to attenuate these markers, essentially, slowing the formation of the aging phenotype, and most notably, diseases of aging (Cheng et al., 2022).

Deregulated Nutrient Sensing

Nutrient sensing capacity decreases with aging but can be restored with caloric restriction or by metformin, a caloric restriction mimetic. Metformin inhibits the mammalian target of rapamycin (mTOR) via the AMPK pathway and the inhibition of IGF-1, with each playing active roles in age acceleration when dysregulated (Mohammed et al., 2021). Impairment of mTOR and IGF-1 have increased both health and lifespan in model organisms (Lopez-Otin et al., 2013).

The inhibition of IGF-1 increases insulin sensitivity, and consequently, reduces circulating insulin levels (Anisimov et al., 2013). Additionally, decreased IGF-1 signaling activates AMPK which subsequently inhibits mTOR. AMPK inhibits mTOR through the phosphorylation of the regulatory associated protein of mTOR, Raptor, which prevents the mTOR protein complex from phosphorylating substrates (Zhang et al., 2006). mTOR is a highly evolutionarily conserved serine-threonine kinase that plays a vital role in the regulation of transcription, translation, autophagy, molecular transport, ribosome construction, and an organism's metabolism via nutrient signaling and cell growth mediated by IGF-1 (Saxton and Sabatini, 2011, Sorenti et al., 2022). The dysregulation of mTOR increases the risk of cancer, T2DM development, neurodegenerative, and inflammatory diseases (Dazert, 2011). With such wide varieties of functions, mTOR and AMPK are critical components in the regulation of cellular lifespan and aging modulation.

Reactive Oxygen Species and DNA Damage

As proposed by free radical theory, reactive oxygen species (ROS), produced through mitochondrial function, accelerate aging by imposing damage upon cellular organelles, DNA, and macromolecules (Gough and Cotter, 2011). ROS accumulation is especially detrimental to mitochondrial DNA and function, causing a progressive decline with aging (Bratic and Larsson, 2013). The delicate ratio of ROS production to ROS scavengers is dysregulated with aging. Not only is antioxidant enzyme manufacturing decreased, but ROS production increases with time (Obrador et al., 2019). ROS scavengers, such as mitochondrial catalase, increase lifespan when overexpressed in mice, suggesting that decreasing ROS accumulation has a beneficial impact on age retardation (Dogar et al., 2020).

Metformin activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, an antioxidant, and class 1 respiratory chain enzymes, directly, decreasing mitochondrial ROS production (Ribiero et al., 2020). Furthermore, AMPK activation turns on additional ROS-scavenging genes, such as thioredoxin, improving cellular antioxidant capacity (Hwang et al., 2019).

Not only does metformin-induced decreased ROS production help prevent oxidative nuclear and mitochondrial DNA damage, but it upregulates DNA repair mechanisms (Wu et al., 2013). In diabetics, metformin has been found to increase X-ray repair cross-complementing protein activity, a major component of the DNA base excision repair system (Dogan et al., 2018). Metformin impairs aging progression by decreasing oxidative stress and improving DNA repair mechanisms.

Cellular Senescence

Metformin has been shown to prevent cellular senescence and upregulate the removal of senescent cells effectively impairing the progressive proliferation of cellular senescence (Cheng et al., 2022). As an organism's age increases, so too does its population of senescent cells. Senescent cells accumulate in tissues as an organism ages, progressively impairing its ability to regenerate tissue (Lopez-Otin et al., 2013). Senescence is an acquired cellular state characterized by chromatin rearrangement, metabolic alterations, the excretion of pro-inflammatory factors, impairment of AMPK signaling, and most importantly, stable growth arrest (McHugh and Gil, 2018). Senescence is important for tumor suppression, however, the accumulation of senescent cells in tissues leads to the acceleration of aging (Hanahan and Weinberg, 2011). Senescent cells accelerate aging through the secretion of inflammatory factors that negatively impact

neighboring cells, inducing them to acquire the senescent phenotype (Amaya-Montoya et al., 2020). When transplanted into young mice, senescent cells significantly accelerated aging, whereas the removal of senescent cells decelerated aging (Xu et al., 2018). *In vivo* experiments with mice demonstrate metformin's ability to decrease the onset of cellular senescence and increase the clearing of senescent cells via the mTOR pathway. In humans, metformin decreased senescence induced by cigarette smoke as well as hyperglycemia (Saito et al., 2019). When administered preventatively, metformin reduced the accumulation of stress-induced senescent cells in periodontal ligament cells, myoblasts, endothelial cells, and nucleus pulposus cells (Cheng et al., 2022). Furthermore, recent findings indicate that metformin could upregulate the immune-mediated sweeping of existing senescent cells, preventing their excretion of inflammatory cytokines (Moiseeva et al., 2013). Metformin shows promise in attenuating aging progression via the prevention and removal of senescent cells.

Inflammation

Metformin significantly lowers inflammatory biomarkers that are associated with aging (Cheng et al., 2022). Chronic low-level inflammation has been implicated in the progression of age related diseases (Cesari et al., 2003). Model organisms have demonstrated the life-extending effects of decreased inflammation, and conversely, the longevity-blunting impact of chronic inflammation (Arai et al., 2015). Metformin decreases the production and secretion of a variety of proinflammatory cytokines while simultaneously increasing anti-inflammatory factors, such as interleukin-10 and adiponectin (Han et al., 2018, Sharma et al., 2013). Additionally, in an AMPK-dependent and independent manner, metformin suppresses necrosis factor- κ B, a transcription factor that leads to the production of proinflammatory cytokines and chemokines

(Hattori et al., 2006). Finally, metformin stimulates the transition of pro-inflammatory M1 macrophages to the anti-inflammatory M2 macrophage (Bharath et al., 2020). Metformin treatment impairs inflammatory pathways that are associated with the progression of aging.

Autophagy

Aging and autophagy are engaged in a detrimental positive feedback loop where aging declines autophagy which subsequently accelerates aging (Rubinzstein et al., 2011). Autophagy is important for the degradation and removal of damaged or unneeded cellular components, from proteins to whole organelles. Experiments in model organisms have demonstrated a correlation between impaired autophagy and decreased health and lifespan (Hansen et al., 2018). Via AMPK modulation, metformin upregulates pro-autophagic factors that have been shown to extend lifespan experimentally and downregulates those that prevent autophagy (Margulis et al., 2020). Additionally, metformin increased mitophagy, the catabolism of old or defective mitochondria, decreasing the production of ROS thus preventing further oxidative damage (Ma et al., 2019). Via autophagy, metformin shows potential in treating and preventing neurodegenerative disorders, in which autophagy is impaired (Wen et al., 2021). Metformin-mediated upregulation of autophagy is a therapeutic mechanism by which lifespan may be extended.

Stem Cell Depletion

Aging is associated with a decline in stem cell count, ultimately leading to reduced tissue regeneration, increased tissue degeneration, and homeostatic drift which promote the progression of age-related diseases (Zhao et al., 2020). Bone and nervous stem cells are particularly vulnerable to age-related depletion, contributing to age-associated conditions in their respective

fields (Cheng et al., 2022). Progressive stem cell decline is responsible for muscle weakness, lowered immunity, slowed recovery from illness or injury, and hair greying or loss (Schultz and Sinclair, 2016). Metformin shows promise in attenuating stem cell decline. Treatment with metformin decreased stem cell loss in the bone marrow and increased stem cell division following injury (Jiang et al., 2020). Further, metformin restored functionality in senescent stem cells and improved mitochondrial function in oligodendrocyte precursor cells, potentially boosting an organism's neural myelination capacity, which declines with age (Neumann et al., 2019). Prevention and reversal of stem cell depletion via metformin shows potential in attenuating the progression of age related diseases as well as improving one's ability to combat them, leading to an extended healthspan and lifespan.

Metformin and Longevity in Model Organisms

Metformin delays aging and increases both health and lifespan in model organisms (Asinimov et al., 2008, Cabriero et al., 2013, Mohammed et al., 2021). When fed a diet supplemented with metformin, the average mouse lifespan was extended by 8% with the final 10% of survivors living 13.1% longer than control mice (Asinimov et al., 2005). The same study found that metformin significantly decreased the size and incidence of mammary adenocarcinomas in female mice as well as delaying the mean age of cancer onset (Asinimov et al., 2005). Metformin increased the lifespan of male short-lived African fish, *Nothobranchius*, by 15.6% when fed 2 mg metformin/gram of food, though females did not demonstrate a significant extension of lifespan (Genade et al., 2005). *C. elegans*, high doses of metformin extend the lifespan by 40%, though low doses have no effect (Onken and Driscoll, 2010). Additionally, in *C. elegans* the life-extending properties appeared to be as a result of metformin's alteration of

microbial folate and methionine metabolism. Metformin-induced microbial make-up alterations have also been identified in mammals (Bytzer et al., 2001). Whether metformin elicited a life-extending or shortening properties depended upon *E. coli* strain sensitivity in the nematode's gut and glucose concentration; thus, the metformin-induced changes to the host's microbial metabolism is potentially responsible for the drug's therapeutic effects (Cabriero et al., 2013). In *N. guentheri*, metformin extended life and attenuated symptoms of aging through decreasing serum cholesterol and triglyceride levels, body mass and length, lipofuscin accumulation in the liver, and senescence-associated- β -galactosidase activity in the skin (a biological indicator of cellular senescence) (Wei et al., 2020). Overall, model organism experiments demonstrate the anti-aging capacity of metformin as seen by health and lifespan extension and quantified through biomarker analysis.

Metformin and Diseases of Aging in Humans

Modern medicine has found that aging is the primary risk factor for the development of typical adult-onset diseases, such as cancer, cardiovascular disease (CVD), T2DM, osteoporosis, atherosclerosis, liver and kidney failure, immunodeficiencies, and progressive neurodegenerative diseases such as Alzheimer's, Parkinson's, and dementia (Decker et al. 2021). Therefore, if aging itself can be slowed, so too can the onset of age-related diseases, thus increasing both healthspan and lifespan. Metformin's ability to intervene with aging-related biochemical pathway dysregulation allows for the attenuation of age related disease progression. Current research has demonstrated the beneficial pleiotropic effects of metformin on cancer, cardiovascular disease, and neurodegenerative diseases in model organisms and humans (Soukas et al., 2019). As metformin is prescribed as a T2DM treatment, major findings regarding the compound's impact

on diseases of aging in humans are restricted to diabetics. Amazingly, when compared to the general population and diabetics managing their T2DM via other means, diabetics taking metformin had a significantly lower all-cause mortality despite having T2DM, a condition that is detrimental to the health of the individual and normally increases mortality risk (Campbell et al., 2017). The conclusions can be extended to the general population, though with a limited degree of confidence, assuming that metformin's anti-aging effects are independent of the presence of diabetes. It is important that future studies examine metformin's effects in non-diabetic populations as confirmation. Though data regarding metformin's combative effect on diseases of aging is sourced nearly exclusively from diabetic populations, the positive outcomes give hope that the drug would have a similar, potentially more pronounced, impact on the general population.

Metformin and Cancer

When contrasted with both the general population and other diabetics, diabetics taking metformin had significantly lower rates of cancer incidence (Andersson et al., 2012, But et al., 2014). A meta-analysis by Campbell et al. found the greatest decrease in cancer incidence for colorectal (Hazard Risk (HR)=0.91, 95%CI=0.84-0.98), breast (HR=0.71, 95%CI=0.54-0.92), and lung cancers (HR=0.80, 95%CI=0.65-0.98) (Campbell et al., 2017) when comparing diabetics treated with metformin against diabetics not taking metformin. Metformin has also been shown to be effective, not just in cancer prevention, but also treatment (Wang et al., 2020). There is inconsistency, however, amongst studies examining the link between metformin and cancer, ranging from null to significant potentially due to methodological variations as well as differences in metformin dosage and length of treatment (Heckmann-Stoddard et al., 2017).

While a few studies report a null relationship, the vast majority found a significant association between metformin treatment and decreased cancer incidence rate.

Metformin is thought to exert its anti-cancer effects through multiple avenues. Metformin limits tumorigenesis by decreasing both insulin and IGF-1, two factors that upregulate epithelial cell proliferation (Pollack, 2007). The activation of the AMPK and suppression of mTOR signaling pathways introduces heightened surveillance over cell division, leading to the arrest and apoptosis of rapidly dividing cells, such as cancers (Wang et al., 2018). Additionally, metformin interferes with cancer cells' ability to hide from the immune system, decreasing the existing population and preventing the build-up of senescent and premalignant cells (Mendez et al., 2011). Metformin potentially interferes with self-renewal pathways that normally allow for the unchecked proliferation of cancer stem cells and subsequent metastatic identity (Cioce et al., 2020). Metformin has been found to limit the secretion of a variety of proinflammatory, and potentially tumorigenic cytokines by impairing the activity of their transcription factor, NF- κ B (Wu et al., 2021). With regards to ovarian, breast, colonic, and pancreatic cancer stem cells, metformin has shown an ability to inhibit proliferation and induce apoptosis thus preventing the reappearance and spread of cancers (Brown et al., 2020, Saini and Yang, 2018, Samuel et al., 2020).

Metformin and Cardiovascular Disease

Cardiovascular disease (CVD) is the leading cause of death for adults globally (Murphy et al., 2020). The primary risk factor for developing CVD is aging. Aging causes the progressive structural and functional deterioration of the heart and vasculature increasing one's likelihood of suffering from atherosclerosis, stroke, coronary artery disease, hypertension, heart failure, and

atrial fibrillation (Lettino et al., 2022). Human and animal studies have shown that metformin elicits a protective effect on CVD development and prevention of cardiovascular events in those with CVD (Han et al., 2019). Diabetics taking metformin have lower CVD rates than diabetics treating their T2DM via other means (Campbell et al., 2017).

The exact mechanisms behind metformin's impact on CVD remain under investigation, however, there are a few proposed avenues by which the drug may act. First, metformin decreases LDL cholesterol levels, atherosclerosis progression, blood pressure, and body weight (those taking metformin demonstrate a mean weight loss of 5.8 ± 7.0 kg (Seifarth et al., 2013)), all of which contribute to CVD development (Petrie et al., 2017). Metformin decreases the secretion of the inflammatory pro-atherogenic cytokines, IL-6 and IL-8, through its inhibition of the NF- κ B pathway, ultimately limiting atherosclerotic thrombi formation (Isoda et al., 2006). Furthermore, in patients with T2DM, metformin elicits a protective effect on cardiac endothelium and angiogenesis, though the same effects have not been confirmed within the general population (Dore et al., 2018). In mouse models, metformin has been shown to delay the onset of vascular aging and age-induced atherosclerosis (Karnewar et al., 2018). Metformin's antihyperglycemic effects protect blood vessels by decreasing circulating blood glucose levels, which if sustained at high levels, as seen in T2DM, can be detrimental to the endothelium (Niu et al., 2019). Using metformin to interfere with the development of CVD in the aging population shows promise as a means of extending health span.

Metformin and Neurodegenerative Diseases

Metformin shows promise in delaying the progression of neurodegenerative diseases, like Alzheimer's Disease (AD), Parkinson's Disease (PD), and dementia, through its suppression of

proinflammatory pathways that give rise to neuroinflammation (Syal et al., 2020). There is considerable evidence to suggest that neuroinflammation brought about by microglial cells leads to the pathogenesis of PD (Zhang et al., 2021). In PD animal models, metformin demonstrated a protective effect, increasing astrocyte functionality and locomotor and muscular activation in mice (Ryu et al., 2020, Patil et al., 2014), rescuing dopaminergic neurons in worms (Mor et al., 2020), and inhibiting microglial activity and proinflammatory cytokine secretion in rats (Tayara et al., 2018). While metformin elicits a beneficial impact on PD in animal models, in humans, metformin has been found to decrease PD risk in patients with T2DM when combined with sulfonylureas but not independently (Wahlqvist et al., 2012).

Metformin has been found to attenuate the development and progression of AD in humans. Proinflammatory cytokine secretion and glial cell activation contribute to neuroinflammation and ultimately neuronal damage that is manifested as AD (Heneka et al., 2015). AD is also characterized by the buildup of neurofibrillary tangles (NFT) and beta-amyloid plaques which impair neuronal communication (Seto et al., 2021). Metformin-mediated AMPK activation increases autophagy, decreasing the buildup of protein aggregates and damaged mitochondria that contribute to the pathogenesis of AD (Wen et al., 2021). Metformin induces lysosomal breakdown of beta-amyloid in the brain via AMPK inhibition of mTOR (Pei et al., 2008).

Additionally, a number of studies have found metformin elicits a positive effect on reducing dementia in adults with T2DM (general dementia and AD or PD-induced) (Cheng et al., 2014, Hsu et al., 2011, Samaras et al., 2020, Wang et al., 2017). Metformin was found to decrease cognitive impairment in adults with T2DM (Ng et al., 2014) and improve cognitive function in AD patients (Koenig et al., 2017). It is speculated that metformin's effect on

cognitive decline may be influenced by individual genetics, with certain predispositions resulting in negative interactions with metformin, specifically with regard to AD (Wu et al., 2020), however, the majority of studies, including two meta-analyses (Ye et al., 2016, Zhou et al., 2020), support metformin's ability to delay and attenuate the progression of neurodegenerative diseases.

Proposed Experimental Outline

Metformin is a highly promising candidate in the search for an anti-aging medication. The compound's capacity to extend life in model organisms, decrease all-cause mortality and disease of aging incidence in diabetics, and modulate pathways implicated in the development of the aging phenotype support its candidacy. Further, metformin is FDA-approved, has been effectively used for over 60 years, and is cheap to produce, with each pill costing approximately 5 cents (Mohammed et al., 2021). Metformin's anti-aging capacity is thought to stem from its impact on aging pathways that, when altered, impair the advancement of age-related diseases. If metformin is to be considered an anti-aging compound, it must demonstrate efficacy in preventing or significantly retarding the development of an array of age-related diseases, not just one.

Currently, there are two major trials underway that aim to determine whether metformin will demonstrate a life-extending effect on the general population. The Metformin in Longevity Study (MILES), now in stage 4, seeks to determine if metformin administration revives gene expression of adults aged 60+ with impaired glucose tolerance, to that of healthy subjects (Albert Einstein College of Medicine, 2021). Preliminary findings from MILES shows metformin beneficially interacts with age-modulating metabolic pathways and upregulates collagen

trimerization, extracellular matrix reconstruction, beta-oxidation, mitophagy, and expression of genes associated with DNA mismatch repair (Kulkarni et al., 2018). The Targeting Aging With Metformin (TAME) trial, though still in the fundraising stage, plans to examine 3,000 subjects ages 65-79 over the course of 6 years to analyze if treatment with metformin impacts the development of age-related diseases (AFAR, 2022). TAME has a concurrent study underway to validate the efficacy of the biomarkers that will be used to measure non-chronological aging.

The results of the aforementioned trials will shed light onto metformin's potential age modulation capability, however, both trials limit their volunteer pool to older adults, potentially stunting the impact that metformin could have on health and lifespan extension. Model organism studies have shown that earlier age of metformin administration positively impacts lifespan and healthspan and loses efficacy as age of treatment initiation increases (Martin-Montalvo, 2013). In older adults, as aging is already underway, metformin may predominantly act to treat current aging symptoms and have a blunted impact on the prevention of diseases of aging. Alternatively, beginning metformin at a younger age could serve to prevent the onset of aging, rather than simply treat the symptoms. Metformin has demonstrated the capacity to prevent the development of T2D in pre-diabetics, indicating that metformin can act as a prophylactic (Aroda and Ratner, 2018). Such data suggests that starting metformin treatment at earlier ages could optimize lifespan and healthspan extension for the general population.

The present thesis proposes a study that is synergistic with MILES and TAME. The proposed study, Extending Lifespan with Metformin (ELM), aims to determine whether early initiation of metformin treatment will optimize the potential anti-aging benefits of the drug in non-diabetic individuals. Assuming MILES and TAME produce results in support of metformin-induced aging modulation in the general population, ELM will serve as the next step

to establish if the efficacy of metformin treatment is dependent on age of initiation, and if so, to ascertain at what age metformin treatment produces the greatest benefits.

ELM's primary purpose is to test whether metformin changes the biology of aging in various tissues throughout the body to that of a younger profile by interacting with aging-related pathways, testing if treatment with metformin delays the development of age-related diseases, and if the effects differ with relation to the age at which treatment with metformin began. We hypothesize that earlier initiation of metformin treatment results in decreased incidence and delayed onset of age-related diseases, alters biological aging factors to match a younger profile, and extends lifespan (Figure 5).

The ELM trial will recruit 6,000 male and female participants above the age of 25 to participate in the trial, aiming for an equal division amongst age groups and sex. There will be no upper age limit to recruitment. Participants will be excluded from the trial on the following criteria: Diabetes (type 1 or type 2 diabetes) or impaired glucose tolerance (IGT). Serious chronic or acute illnesses such as cancer, clinically significant congestive heart failure, chronic obstructive pulmonary disease, inflammatory conditions, serum creatinine > 1.4 mg/dl (female) or > 1.5 mg/dl (male), active liver disease, a history of metabolic acidosis, poorly controlled hypertension, epilepsy, recent cardiovascular disease event (myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, stroke) (recent = within 3 months); a history of bariatric or other gastric surgery, cigarette smoking or vaping, binge alcohol use (>7 drinks in 24 hrs). Treatment with medicinally active compounds known to influence glucose metabolism (other diabetes medications, systemic glucocorticoids, pharmacologic doses of niacin). Hypersensitivity to metformin or any component of the

formulation. Exclusion Criteria Adapted from MILES guidelines (Albert Einstein College of Medicine, 2021).

The participants will be divided into two equal groups that are evenly divided to contain a similar make-up of age and sex. The groups will be randomly assigned to receive either treatment with metformin or a placebo. Allocation will be double-blind as to limit potential bias. The metformin group will be treated with one 1700 mg pill per day. The placebo group will receive sugar pills that are visually identical to the metformin pill.

The study will collect data on volunteers throughout 6 years of treatment. Ideally, the trial would continue for decades allowing for the collection of truly comprehensive data regarding long-term metformin treatment on age attenuation. If at the end of 6 years the study yields beneficial findings, the participants will be given the option to continue metformin treatment at no monetary cost to themselves if they consent to engage in the yearly data collection outlined in the study. At the 6 year marker, if the trial yields a harmful or a null result, the study will be terminated. If there is a statistically insignificant result but a promising trajectory, participants will have the option to continue the trial, though their status will be re-evaluated every 6 months. If the results do not show a stronger beneficial trajectory or they demonstrate no change, the study will be terminated.

The effects of metformin on aging will be evaluated using RNA-sequencing, the Horvath and Hannum Clocks, and by monitoring the development of diseases of aging. Prior to the initiation of treatment, muscle and adipose tissue biopsies will be taken from all participants. The initial biopsies will serve as the baseline from which total BA changes will be compared. Muscle and adipose tissue biopsies will be collected every 6 months for the first 3 years of the trial, and annually for the remaining 3 years (Figure 2). If preliminary results are supportive and the trial

continues beyond the proposed 6 year marker, biopsies will be taken once per year. If the results demonstrate a positive trajectory but lack statistical significance and the trial continues, biopsies will be taken every 6 months. RNA-sequencing analysis on muscle and adipose tissue samples will measure changes in the transcriptome, with special emphasis on aging modulators such as AMPK and mTOR. Additionally, the Horvath and Hannum clocks will be used to compare BA to CA. Biohorological analysis will be completed prior to treatment initiation and every 6 months throughout the trial. If the trial continues beyond the 6 year marker, BA will continue to be calculated every 6 months. Furthermore, the type and age at which volunteers develop aging-related diseases (cancer, CVD, Alzheimer's, Parkinson's, etc.) will be recorded at time of disease diagnosis by a physician, or if in the instance of sudden death, confirmation via autopsy. For both the metformin and placebo groups, age of disease incidence will be compared to the mean age of onset for their respective group (sex-based) and subgroup (race, ethnicity, etc.) both within the study and the general population.

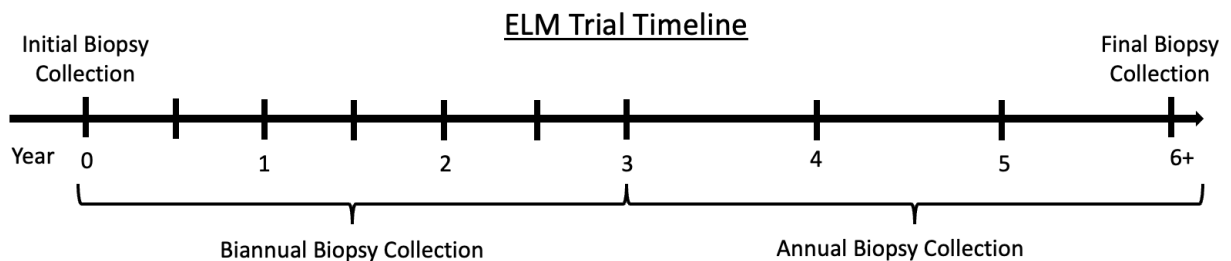


Figure 2: Timeline of the proposed ELM trial. Patient recruitment, treatment allocation, and analysis of results are not included. Data regarding the development of diseases of aging collected at time of official patient diagnosis. Biohorological analysis completed every 6 months.

Expected Results

If metformin is to be deemed an anti-aging drug, treatment with metformin must result in an decreasing difference between biological age and chronological age (Δ age) and a delayed onset of a variety of diseases of aging. As early treatment is hypothesized to optimize metformin's anti-aging capabilities, the results would need to demonstrate that a smaller Δ age at the termination of the trial is positively correlated with age of metformin treatment initiation (Figure 3). Δ age vs. initiation conclusions will be bolstered if the biopsy samples reveal statistically significant changes in the transcriptome indicating the successful modulation of aging pathways, such as the upregulation of AMPK and the inhibition of mTOR. Finally, if diseases of aging are significantly delayed in the metformin group, it can be concluded that metformin extends healthspan (Figure 4). Analyzing the effects of metformin from the subcellular level to the appearance of disease *in vivo* allows for a holistic view of the drug's impact on human health. As it is not realistic to propose a study observing the effect of metformin in humans from birth to death, analyzing data from a large population over the course of 6 years will illuminate trends that can be extrapolated to forecast how lifespan and healthspan will be altered via treatment with metformin.

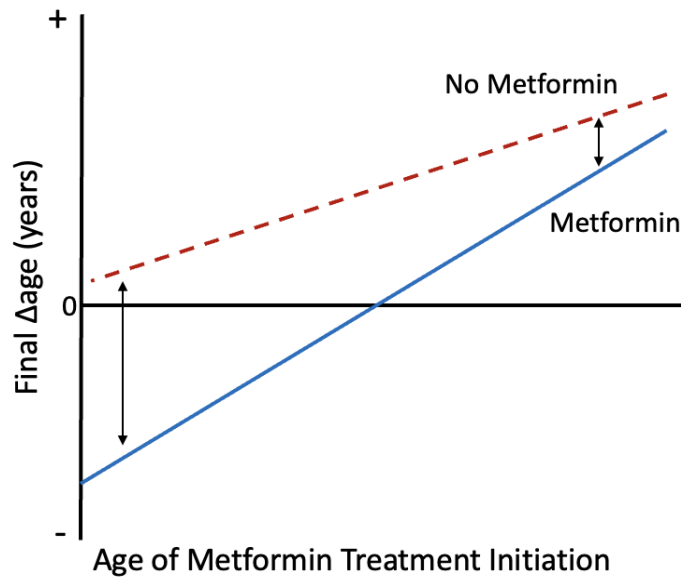


Figure 3: Early treatment with metformin leads to a decreased Δ age. Metformin loses efficacy in decreasing Δ age as the age of treatment initiation increases, as indicated by the arrows. X and y axes increase in magnitude moving away from the origin. Δ age is the difference between biological age and chronological age.

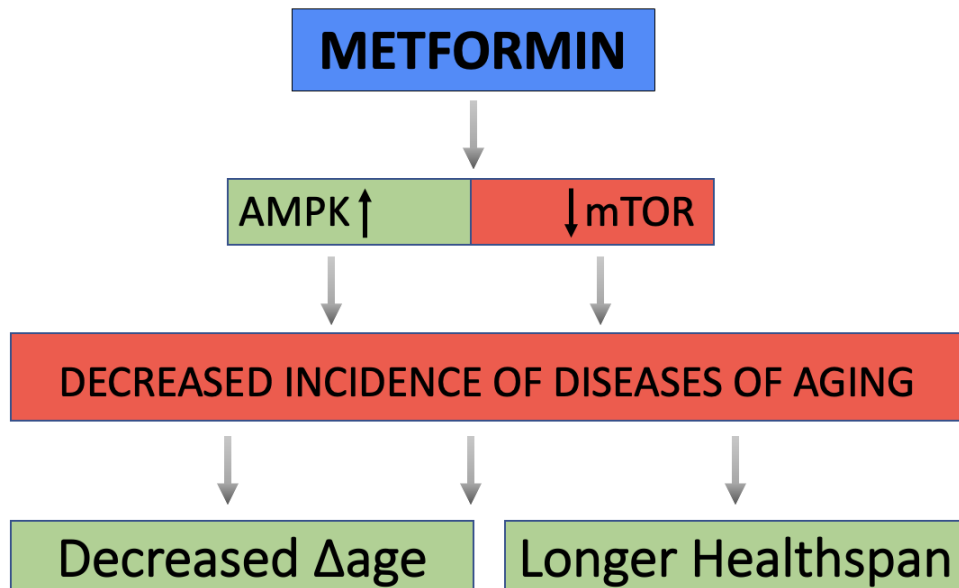


Figure 4: Results supportive of lifespan-extension will demonstrate the metformin-induced modulation of metabolic pathways elicits changes in the subcellular makeup and the disease phenotype of humans. Δ age is the difference between biological age and chronological age.

Discussion and Conclusion

Metformin shows promise as an effective tool to target aging as supported by 60 years of FDA approved use for T2D treatment, substantial research in model organisms, and conclusive findings regarding decreases in cancer, CVD, diabetes, and obesity in humans. Metformin is a comparatively safe and versatile drug, as illustrated by the comprehensive scientific literature examining the wide range of potential off-target uses for the compound. Additionally, metformin is relatively inexpensive as it is no longer protected by patents (Mohammed et al., 2021). As such, metformin-induced life extension would be accessible to the masses, rather than a luxury enjoyed by the economic elite. Though considerable research has outlined the positive impact of metformin treatment on health and lifespan, some studies in model organisms have found the positive benefits occur at doses that would be toxic if comparable quantities were used in humans (Asinimov et al., 2005). Studies in *C. elegans* have found neutral or negative effects of metformin on lifespan if administered later in life (Onken and Driscoll, 2010). Fortunately, long-term metformin use for T2D treatment has shown therapeutic doses of metformin only rarely result in negative health outcomes in humans and are typically triggered by unrelated health problems (Corcoran and Jacobs, 2022). Going forward, the optimal dosage required to produce the anti-aging effects of metformin while avoiding harmful side effects must be identified.

The benefits of living longer are not restricted to the individual but have a widespread impact on society. While the thought of extending lifespan on an increasingly overpopulated planet may seem deleterious, as the environment and natural resources are already strained, the monetary benefits of life-extension could serve to ameliorate the effects of the population increase. In model organisms and humans, longevity is associated with compressed morbidity

(Ismail et al., 2016). Though life expectancy in the U.S. is steadily increasing, healthspan is not, meaning Americans are spending a larger proportion of their life in what is known as the “disease phase,” where they are resource sinks: they are consuming more than they are generating as they are no longer productive members of society (National Research Council, 2011). Through delaying the onset of diseases of aging, metformin stands to extend healthspan as well as lifespan, effectively compressing morbidity and stunting the disease phase (Figure 5). With aging, modified or natural, a disease phase is guaranteed, however, altering its length is both economically and emotionally beneficial. Extending lifespan is only economically favorable if healthspan is increased proportionally or greater with healthspan. A retardation in aging that extends U.S. life expectancy by only one year would generate \$38 trillion, whereas ten years would produce \$367 trillion (Scott, Ellison, and Sinclair, 2021). Extending the lifespan would allow for a greater number of productive years before entering a compressed morbidity stage, effectively lowering the cost of the disease phase. Medicare spending during the final year of life decreases as the age of the patient increases (Hoover et al., 2002). If this pattern is to be extended with artificial life-extension, longer lives will result in lower end-of-life costs and greater benefits from increased productivity. The profit generated from life-extension should be funneled into programs that serve to benefit the planet and society, to help ameliorate the effects of a larger global population.

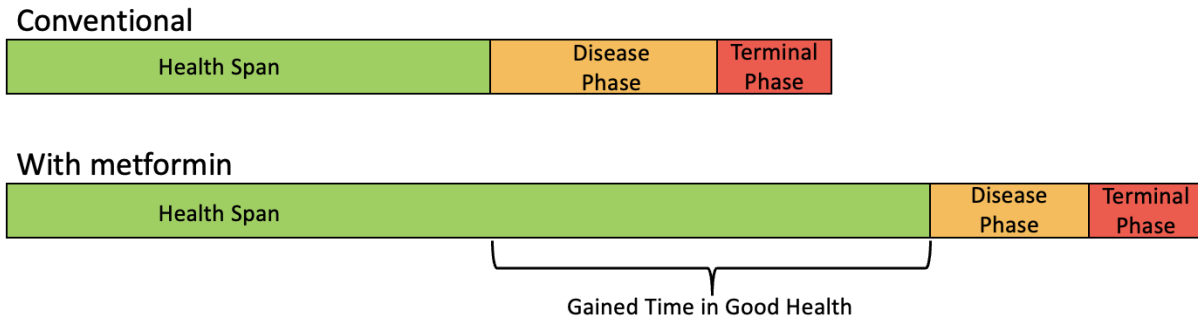


Figure 5: Treatment with metformin increases both health and lifespan while stunting the disease phase. The disease phase is characterized by the appearance of diseases of aging. The terminal phase is described as the end of life, in which organ systems fail and total loss of normal function.

Not only will life extension be monetarily profitable, but it promises physical and emotional benefits. Prominent aging-scientist at the Harvard Medical School, Dr. David Sinclair, believes that utilizing metformin combined with other anti-aging interventions, the human lifespan could surpass 120 years (Sinclair and LaPlante, 2021). Such a radical extension in life would afford humans the opportunity to accomplish much more within their lifespan. Rather than begin retirement just as one’s physical health begins to dwindle, living such a long life would allow for a “skillbattical,” as coined by Sinclair, a period in which one could take time off from conventional work to enjoy the wonders of the world, engage in other activities that make them happy, before continuing with their career or learning a new trade. An incredibly long life brings the opportunity to pursue what drives us or makes us happy, which may have previously been unattainable or even unknown with a shorter lifespan.

The extension of healthspan via the compression of morbidity promises to extend physical capacity into old age, which currently is a limiting factor for many elderly, contributing to the acceleration of aging and can impair mental health due to a loss of independence (Billot et al., 2020). Metformin could be beneficial psychologically and physically due to the compression

of the disease phase, as dying faster could lessen the emotional and corporeal pain associated with a prolonged death, both for the elder and their loved ones.

While the potential for metformin as an aging prophylactic is amazing, it should not be viewed as a “wonder drug” that is capable of preventing aging in a vacuum. The synergistic effects of metformin with other lifestyle choices on life extension are yet to be discovered. It is not yet known if or to what extent metformin can compensate for the impact that unhealthy lifestyle factors elicit on lifespan. Taking metformin to maintain one’s health should not replace other healthy habits, such as exercise, good nutrition, and other lifestyle choices. Rather, metformin should be used in conjunction with healthy habits to optimize the benefits of both on lifespan extension. Further studies are needed to determine the optimal cocktail of metformin dosage in combination with other anti-aging drugs and practices that lead to the greatest lifespan extension. With metformin, humans have the opportunity to live not only longer, but healthier lives. Currently, life is short, but with metformin, it does not have to be.

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