Accelerated Ageing in Type 2 Diabetes Mellitus: From Hyperglycaemia to Cellular Senescence

Suhas N Gowda[1], Nischitha H.S[2], Swetha Jeevan[3], Ashmitha A. S[4]
[1,3,4]*Assistant Professor, Department of Life Sciences, Acharya Bangalore B-School, Bengaluru, India*
[2]*Assistant Professor, Department of Forensic Science, Acharya Bangalore B-School, Bengaluru, India*

***Abstract*—Type 2 diabetes mellitus (T2DM) is increasingly being studied in relation to the biological changes that occur during ageing. Persistent elevation of blood glucose may accelerate several cellular disturbances, including the accumulation of advanced glycation end products, excessive oxidative stress, mitochondrial impairment, DNA damage, and prolonged inflammatory activity. These changes may interact with key features of biological ageing, such as cellular senescence, telomere shortening, epigenetic alterations, disrupted autophagy, and declining stem-cell function. This narrative review explores how chronic hyperglycaemia may influence cellular senescence and examines the potential consequences of these interconnected mechanisms across different organs. It also discusses emerging biomarkers used to investigate biological ageing and reviews current diabetes treatments alongside potential interventions targeting age-related cellular dysfunction. Although established therapies play an important role in glycaemic control and reducing diabetes-associated complications, their ability to directly reverse or slow biological ageing remains incompletely understood. Similarly, senolytic agents and other geroscience-based interventions offer promising research directions but have not yet been established as routine treatments for T2DM. A clearer understanding of these mechanisms may help identify future therapeutic opportunities. However, well-designed longitudinal studies and clinical trials are required to determine whether targeting cellular senescence can meaningfully improve long-term health outcomes in people with T2DM.**

***Index Terms*—Type 2 Diabetes Mellitus; Cellular Senescence; Biological Ageing; Hyperglycaemia; Advanced Glycation End Products; Oxidative Stress; Inflammaging; Senolytics; Epigenetic Clocks; Telomere Shortening.**

I. INTRODUCTION

Diabetes mellitus remains a major global health challenge. The International Diabetes Federation estimated that 537 million adults were living with diabetes in 2021 and projected that this number could reach 783 million by 2045 [1]. Type 2 diabetes mellitus (T2DM) accounts for the large majority of diabetes cases. Although diabetes management has traditionally focused on glycaemic control, growing research has also examined its associations with biological ageing.

Ageing is not determined by chronological time alone. Biological age reflects physiological and molecular changes that may differ from those expected for a person's chronological age. Studies have investigated whether people with T2DM show accelerated changes in ageing-related biomarkers; however, the magnitude and clinical significance of these differences vary by marker, population, and study design. Diabetes is associated with increased risks of complications such as cardiovascular disease, chronic kidney disease, cognitive impairment, muscle loss, and frailty.

Chronic hyperglycaemia is an important contributor to diabetic tissue injury. Elevated glucose can promote several interconnected processes, including advanced glycation end-product formation, oxidative stress, mitochondrial dysfunction, and inflammatory signalling [2]. These processes overlap with pathways implicated in biological ageing and cellular senescence. Understanding their relationships may help identify strategies to reduce diabetes-related complications, although the extent to which specific interventions can modify biological ageing remains an active research question.

This narrative review synthesises literature on proposed mechanisms linking hyperglycaemia with

ageing-related processes, organ-specific manifestations, candidate biomarkers, and established and emerging therapeutic approaches. It distinguishes evidence for established diabetes outcomes from evidence that an intervention directly modifies biological ageing.

1.1 Review approach and scope

This article is presented as a narrative review, organised thematically around the relationship between chronic hyperglycaemia, molecular stress pathways, cellular senescence, organ-specific manifestations, candidate biomarkers, and therapeutic approaches. The manuscript version supplied for revision did not document a reproducible database-search strategy, search dates, eligibility criteria, or a screening record. Accordingly, no database names, search counts, screening totals, or claim of exhaustive retrieval are reported here. The discussion is a qualitative synthesis of the sources cited in the manuscript rather than a systematic review; conclusions should be interpreted in light of that limitation. Before submission, the authors should document any searches actually performed and update the cited literature using a reproducible process.

1.2 Contribution and distinction from existing reviews

The intended contribution of this review is an integrated, translational overview that follows the proposed pathway from hyperglycaemic stress through glycation, oxidative and mitochondrial stress, DNA damage, inflammation, and senescence, then connects these mechanisms with organ-specific outcomes, candidate ageing biomarkers, and the evidence status of interventions. This is an integrative synthesis rather than a claim to be the first review of diabetes and ageing. A 2026 narrative review has specifically examined cellular senescence and metabolic ageing in T2DM, with emphasis on mechanisms and senolytic translation [3]. The present manuscript should therefore make its broader cross-domain organisation and explicit separation of established diabetes benefits from unproven effects on biological ageing its central contribution.

II. BIOLOGICAL AGEING: CONCEPTS AND HALLMARKS

Ageing involves a gradual loss of cellular resilience and physiological balance, which can make the body less capable of maintaining normal function and responding to stress. The number of years a person has lived represents chronological age, whereas biological age seeks to describe the condition of the body through measurable molecular and physiological characteristics. Since ageing affects multiple biological systems, its assessment requires more than a single marker. Different indicators provide information about particular ageing-related processes, and their significance depends on the methods used to measure them and the strength of the supporting evidence.

To organise the complex mechanisms underlying ageing, López-Otín and colleagues introduced a framework of nine hallmarks in 2013 [4]. The framework covers damage to genetic material, progressive telomere shortening, changes in epigenetic regulation, disruption of protein homeostasis, altered nutrient-sensing pathways, mitochondrial impairment, cellular senescence, depletion of stem-cell function, and changes in communication between cells. These interconnected processes help explain how cellular damage, impaired maintenance, and altered regulation can contribute to functional decline. A subsequent update published in 2023 broadened the framework to twelve hallmarks by including impaired macroautophagy, persistent inflammation, and changes in the composition of the microbiome, known as dysbiosis [5]. This expanded perspective recognises that ageing is influenced not only by changes within individual cells but also by the body's maintenance systems, inflammatory environment, and relationship with its resident microorganisms. Table 1 outlines the twelve hallmarks.

Hallmark	Description
Genomic instability	Gradual build-up of genetic alterations resulting from DNA damage and errors in genome maintenance.
Telomere attrition	Progressive loss of protective telomeric DNA sequences, which may limit cellular replication and promote senescence.

Epigenetic alterations	Age-associated changes in DNA methylation, histone regulation, and other mechanisms controlling gene activity.
Loss of proteostasis	Reduced ability of cells to maintain protein quality, manage misfolded proteins, and remove abnormal protein aggregates.
Deregulated nutrient sensing	Disruption of signalling networks that coordinate nutrient availability, metabolism, growth, and cellular maintenance.
Mitochondrial dysfunction	Declining mitochondrial performance that can disturb energy metabolism and alter the production of reactive oxygen species.
Cellular senescence	Entry into a persistent state of cell-cycle arrest, often accompanied by altered cellular activity and the release of inflammatory mediators.
Stem cell exhaustion	Diminished capacity of stem-cell populations to replenish damaged cells and support tissue regeneration.
Altered intercellular communication	Changes in signals exchanged between cells that may disturb tissue coordination and promote inflammatory responses.

Table 1. Biological ageing hallmarks and their associated cellular changes

Cellular senescence may contribute to the relationship between persistent cellular stress and the gradual deterioration of tissues. Under conditions such as DNA damage or prolonged stress, certain cells lose their ability to continue dividing but remain metabolically active. Rather than functioning exactly like healthy cells, they may develop altered patterns of activity and release a mixture of signalling proteins, inflammatory mediators, tissue-degrading enzymes, and growth factors. This secretory activity is known as the senescence-associated secretory phenotype (SASP). Its effects vary according to the cell type and surrounding tissue, but it can influence nearby cells and contribute to an inflammatory environment [6].

A related feature of ageing is inflammaging, which describes the persistent, low-level inflammatory activity observed in many ageing individuals. Senescence and inflammation can influence one another: inflammatory conditions may encourage cells to become senescent, while substances released by senescent cells can maintain or intensify inflammatory signalling. In type 2 diabetes mellitus (T2DM), disturbances in glucose regulation and other metabolic processes may further affect these pathways. Their interaction could contribute to tissue damage and declining physiological function, providing a potential explanation for the association between diabetes and accelerated biological ageing. Nevertheless, the magnitude and causal significance of this relationship in humans remain important questions for further research [7].

III. PATHOPHYSIOLOGY OF TYPE 2 DIABETES MELLITUS

The development of type 2 diabetes mellitus (T2DM) involves a progressive breakdown in the mechanisms that regulate blood glucose. Two major abnormalities contribute to this process: body tissues respond inadequately to insulin, and pancreatic β-cells gradually lose the capacity to produce sufficient amounts of the hormone. Although the pancreas may initially compensate by releasing additional insulin, this response becomes less effective as β-cell function declines. Glucose consequently accumulates in the bloodstream, and the underlying metabolic disturbance may remain undetected until clinical symptoms or complications appear.

The disruption of glucose homeostasis can be understood by examining the different roles of insulin-responsive tissues. Under normal conditions, skeletal muscle absorbs glucose from the circulation, the liver adjusts its glucose output according to metabolic requirements, and adipose tissue regulates the storage and release of fat. In T2DM, these processes become less effectively coordinated. Muscle glucose uptake decreases, hepatic glucose production may remain inappropriately elevated, and fat cells may release greater quantities of free fatty acids. This altered metabolic environment places additional pressure on pancreatic β-cells. Once insulin production is inadequate relative to the body's needs, persistent hyperglycaemia becomes established [8].

Excess lipid availability represents another important component of this metabolic disturbance. When tissues are exposed to high concentrations of free fatty

acids for prolonged periods, insulin signalling and cellular metabolism may be adversely affected. Pancreatic β-cells are particularly vulnerable to metabolic stress, which can impair their function and contribute to oxidative damage. These harmful effects are commonly associated with lipotoxicity and may interact with inflammatory pathways to worsen metabolic control, especially in the presence of excess body fat [9].

Inflammatory activity provides an additional link between metabolic abnormalities and progressive tissue dysfunction. Cytokines, including TNF-α and IL-6, participate in signalling processes that can reduce insulin responsiveness under certain conditions. At the same time, disturbances in glucose and fat metabolism may stimulate further inflammatory activity, allowing metabolic stress and inflammation to reinforce one another [10]. This sustained interaction may have consequences beyond glucose regulation, as prolonged cellular stress and inflammatory signalling are also investigated in the context of biological ageing. Further research is needed to establish how strongly these mechanisms contribute to age-related changes and long-term complications in people with T2DM.

IV. FROM HYPERGLYCAEMIA TO CELLULAR SENESCENCE

Prolonged exposure to elevated glucose may initiate a series of metabolic and molecular disturbances that compromise cellular integrity. These disturbances involve interconnected pathways associated with oxidative injury, protein modification, mitochondrial impairment, inflammatory activation, and changes in gene regulation. Collectively, these processes may contribute to several biological features of ageing and increase the likelihood of cellular senescence. Figure 1 illustrates the proposed connections between persistent hyperglycaemia, cellular stress, and senescence-related changes.

4.1 Persistent Hyperglycaemia and Cellular Metabolic Disturbances

Sustained elevation of blood glucose changes the metabolic environment in which cells function. In susceptible tissues, excessive intracellular glucose availability can increase the activity of alternative glucose-processing pathways and disturb normal metabolic regulation. These changes include increased flux through the polyol and hexosamine pathways, activation of protein kinase C (PKC) signalling, and enhanced formation of advanced glycation end products (AGEs). The extent of these effects varies according to the tissue, its glucose-transport mechanisms, and the duration and severity of hyperglycaemia [11].

Although these pathways have distinct biochemical functions, their effects may overlap. They can influence redox balance, modify cellular proteins, alter gene expression, and promote inflammatory signalling. Persistent activation of these processes may therefore create an environment in which cellular damage accumulates and normal repair mechanisms become less effective.

4.2 Advanced Glycation End Products (AGEs)

Advanced glycation end products develop through chemical reactions involving sugars or reactive carbonyl compounds and biological molecules, including proteins, lipids, and nucleic acids. Their formation can occur under normal physiological conditions, but the process may become more pronounced during prolonged hyperglycaemia and oxidative stress [2, 12].

The biological consequences of AGE accumulation depend on the molecules affected and the tissues in which these compounds are deposited. Modification of long-lived structural proteins, including collagen, can alter tissue elasticity and contribute to vascular stiffness. In addition, AGEs can interact with the receptor for advanced glycation end products (RAGE), initiating intracellular signalling that may activate nuclear factor kappa B (NF-κB) and promote inflammatory responses. These interactions can influence oxidative stress and tissue function, thereby contributing to complications associated with diabetes [12].

Some AGE-modified proteins persist for extended periods, particularly in tissues containing slowly renewed structural components. Their gradual accumulation may help explain why prolonged exposure to elevated glucose can have lasting consequences. However, the contribution of individual AGE compounds to specific ageing-related outcomes depends on their chemical properties, distribution, and biological activity.

4.3 Oxidative Stress

Oxidative stress is an important mechanism connecting disturbed glucose metabolism with cellular injury. Under hyperglycaemic conditions, changes in mitochondrial metabolism and the activation of alternative glucose-processing pathways can increase the production of reactive oxygen species (ROS). The mitochondrial electron transport chain is one potential source of these molecules, while alterations in PKC signalling and other metabolic pathways may further disturb cellular redox balance [13].

Cells possess antioxidant defences that help regulate ROS concentrations and limit oxidative injury. These include superoxide dismutase (SOD), catalase, and glutathione peroxidase. When ROS production exceeds the capacity of antioxidant and repair systems, oxidative stress develops. This imbalance can modify DNA, damage membrane lipids, and alter protein structure and function. Persistent oxidative injury may also affect signalling pathways involved in inflammation, metabolism, and cellular survival [14].

In T2DM, oxidative stress may interact with other metabolic abnormalities rather than acting as an isolated process. Its potential contribution to biological ageing is particularly relevant because prolonged oxidative damage can interfere with cellular maintenance and activate stress-response pathways associated with senescence.

4.4 Mitochondrial Dysfunction

Mitochondria play a central role in cellular energy metabolism and the regulation of redox processes. They are also susceptible to damage caused by excessive ROS production. In T2DM, disturbances in glucose and lipid metabolism may alter mitochondrial activity, potentially creating a cycle in which metabolic stress contributes to mitochondrial injury and impaired mitochondrial function further disrupts cellular homeostasis [15].

Mitochondrial abnormalities may include reduced efficiency of energy production, altered ATP availability, changes in ROS generation, and disturbances in mitochondrial dynamics. These dynamics involve the coordinated processes of fission and fusion, which help maintain mitochondrial structure and function. An imbalance between these processes can affect the distribution and quality of mitochondria within cells.

The removal of damaged mitochondria through mitophagy is another important component of mitochondrial maintenance. Evidence suggests that impaired mitochondrial quality control may contribute to metabolic dysfunction in T2DM, although the extent of impairment varies among tissues and experimental settings [25]. When damaged mitochondria are not adequately removed, they may sustain oxidative stress and inflammatory signalling, potentially increasing cellular vulnerability to senescence.

4.5 DNA Damage and Cellular Stress Responses

DNA integrity can be compromised by oxidative stress and other metabolic disturbances associated with T2DM. One marker investigated in this context is 8-hydroxy-2′-deoxyguanosine (8-OHdG), which reflects oxidative modification of guanine in DNA. Studies have reported altered levels of this marker in people with diabetes, although findings can vary according to the biological sample, measurement method, and study population [16].

Cells respond to DNA lesions through a coordinated DNA damage response (DDR), which detects damage, regulates cell-cycle progression, and activates repair mechanisms. When damage is extensive or persistent, these responses may lead to temporary cell-cycle arrest, programmed cell death, or cellular senescence. The tumour suppressor protein p53 and its downstream effector p21 are important components of pathways that can establish and maintain cell-cycle arrest [17].

The outcome depends on the type of damage, the affected cell, and the effectiveness of repair mechanisms. If cellular stress remains unresolved, prolonged activation of these pathways may favour senescence rather than successful recovery. This provides a plausible mechanism through which chronic metabolic disturbances could contribute to the accumulation of senescent cells.

4.6 Chronic Inflammation and Inflammaging

Metabolic stress, AGE–RAGE interactions, and mitochondrial abnormalities can influence inflammatory signalling. One relevant pathway involves NF-κB, a transcriptional regulator that controls the expression of numerous genes associated with inflammation. Depending on the cellular context, activation of this pathway may increase the production

of mediators such as interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β). The NLRP3 inflammasome is another component of innate immune signalling that may respond to metabolic and cellular stress [18].

Inflammaging describes the persistent, low-grade inflammatory state associated with ageing. In T2DM, metabolic disturbances may interact with inflammatory responses, while inflammation may further impair insulin sensitivity and tissue function. This reciprocal relationship can sustain cellular stress and contribute to the progression of metabolic complications [19].

Nevertheless, inflammation is not uniform across all individuals or tissues. Its intensity, duration, and biological effects depend on several factors, including metabolic control, immune activity, and the presence of other diseases. The relationship between T2DM and inflammaging should therefore be understood as a complex interaction rather than a single, universal pathway.

4.7 Cellular Senescence

Cellular senescence is a state in which cells undergo a sustained withdrawal from the cell cycle in response to stress or damage. Persistent DNA lesions, oxidative injury, and inflammatory signals can contribute to the activation of senescence-associated pathways. Two major regulatory systems involved in this process are the p16INK4a–retinoblastoma protein (Rb) pathway and the p53–p21 pathway. Their activation can maintain cell-cycle arrest, although the relative contribution of each pathway differs among cell types and senescence-inducing conditions [20].

Senescent cells remain viable and can develop changes in metabolism, gene expression, and secretory activity. Many produce a senescence-associated secretory phenotype (SASP), consisting of varying combinations of inflammatory mediators, proteases, and growth factors. These secretions may influence neighbouring cells, modify the extracellular environment, and alter tissue repair. Their effects can be harmful or context-dependent, rather than uniformly damaging in every situation.

Research has examined senescence-associated markers in tissues relevant to T2DM, including adipose tissue, the kidneys, the liver, and the vasculature. Associations between these markers and metabolic dysfunction or diabetic complications have been investigated in experimental and clinical studies [21]. However, individual markers are not exclusive to senescent cells, and their presence alone cannot establish the total senescent-cell burden in a tissue. Further research using multiple complementary markers and appropriate functional assessments is needed to clarify the contribution of senescence to diabetes-related tissue damage.

4.8 Epigenetic Ageing

Epigenetic ageing research examines molecular changes associated with age-related alterations in gene regulation. DNA methylation-based epigenetic clocks use patterns of methylation at selected genomic sites to estimate aspects of biological age. Different models, including Horvath's clock and GrimAge, were developed using distinct approaches and biological information. Consequently, their estimates are not interchangeable, and their interpretation depends on the population, sample type, and research question [22]. T2DM has been investigated in relation to epigenetic changes involving DNA methylation and histone modifications. Metabolic disturbances may influence the enzymes and cellular processes responsible for maintaining these regulatory patterns. Such changes could affect the expression of genes involved in inflammation, glucose metabolism, and cellular stress responses. However, the direction and persistence of individual epigenetic alterations vary, and not every change necessarily indicates accelerated biological ageing.

The concept of metabolic memory is relevant to this relationship. It describes the persistence of certain adverse biological effects following previous exposure to hyperglycaemia, even after improved glucose control. Epigenetic regulation has been proposed as one mechanism contributing to this phenomenon, alongside other forms of lasting molecular and cellular change [23]. This concept supports the importance of early and sustained diabetes management, although the relative contribution of epigenetic mechanisms to metabolic memory remains an active area of investigation.

4.9 Telomere Shortening

Telomeres are specialised DNA–protein structures that protect chromosome ends from degradation and inappropriate DNA repair responses. Their length may decrease during successive cell divisions, although the

rate of shortening varies according to cell type, telomerase activity, and environmental influences. When telomeres become critically short or dysfunctional, they can activate DNA damage responses that promote cellular senescence or, in some circumstances, cell death [24].

Oxidative stress may influence telomere maintenance because telomeric DNA contains guanine-rich sequences that are susceptible to oxidative damage. Persistent metabolic stress associated with T2DM has therefore been investigated as a possible contributor to telomere dysfunction. Several studies have reported associations between diabetes and shorter leukocyte telomere length, but the magnitude and consistency of these findings vary across populations and research designs [24].

Telomere length is influenced by multiple factors, including chronological age, inherited characteristics, lifestyle, and cell composition. Accordingly, shorter leukocyte telomeres should not be interpreted as definitive evidence of accelerated ageing in every individual with T2DM. Current evidence also does not establish telomere shortening as the sole cause of specific diabetes complications.

4.10 Impaired Autophagy and Mitophagy

Autophagy is a cellular recycling process through which intracellular material is delivered for degradation and reuse. It contributes to the removal of damaged proteins, organelles, and other cellular components, helping preserve normal cellular function. Mitophagy is the selective removal of mitochondria that are damaged or no longer functioning appropriately. Both processes are relevant to metabolic regulation and the maintenance of cellular quality.

In T2DM, changes in nutrient-sensing and energy-signalling pathways may disrupt autophagic activity. The mechanistic target of rapamycin (mTOR) regulates cellular growth and nutrient responses and can suppress autophagy initiation when its activity is elevated. AMP-activated protein kinase (AMPK), which responds to cellular energy status, can promote autophagy under appropriate conditions. Disturbances in these regulatory networks may therefore alter the balance between cellular maintenance and metabolic demands [25].

If the removal of damaged components becomes insufficient, dysfunctional mitochondria and abnormal proteins may accumulate, potentially increasing oxidative stress and impairing cellular function. Altered autophagy has been investigated in relation to pancreatic β-cell dysfunction, insulin resistance, and inflammatory activity in T2DM [26]. However, its effects depend on the tissue, disease stage, and specific autophagic pathway involved. Clarifying these differences is important for determining whether interventions that modify autophagy could help preserve metabolic function or reduce age-related cellular damage.

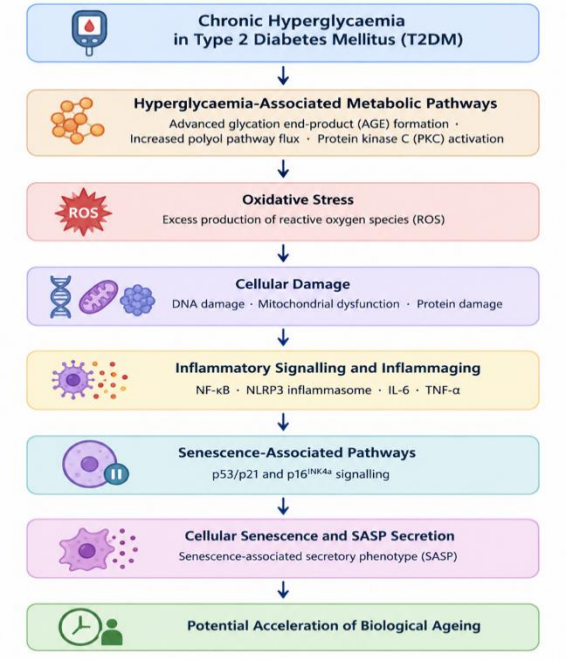


Fig 1- Proposed Mechanistic Pathway Linking Chronic Hyperglycaemia to Cellular Senescence and Accelerated Biological Ageing

V. ORGAN-SPECIFIC MANIFESTATIONS OF ACCELERATED BIOLOGICAL AGEING IN TYPE 2 DIABETES MELLITUS

Type 2 diabetes mellitus (T2DM) is associated with metabolic disturbances that can affect the structure and function of several organ systems. However, these effects are not uniform, as each tissue responds differently to prolonged glucose exposure, oxidative injury, inflammatory signalling, and disruptions in cellular maintenance. Advanced glycation end-products (AGEs), mitochondrial impairment, and cellular senescence are among the processes that may contribute to these changes. The resulting

manifestations range from neurological and cardiovascular dysfunction to impaired tissue repair and reduced physical capacity. Table 2 outlines selected organ-specific changes, their potential biological drivers, and their clinical relevance.

Organ or system	Principal ageing-associated changes	Potential underlying processes	Clinical relevance
Brain	Altered neuronal function, neuroinflammatory activity, and amyloid-β-associated changes	Glycation-related damage, oxidative imbalance, altered cerebral insulin signalling, and inflammatory responses	Cognitive impairment and increased susceptibility to dementia, including Alzheimer's disease
Heart	Reduced myocardial compliance, cardiac dysfunction, and senescence-related changes in cardiomyocytes	AGE-associated collagen cross-linking, mitochondrial injury, oxidative stress, and inflammatory signalling	Diastolic dysfunction, heart failure, and other cardiovascular complications
Kidney	Glomerular scarring, tubular damage, and cellular senescence-associated changes	Accumulation of AGEs, ROS-mediated injury, persistent inflammation, and cellular stress	Diabetic kidney disease, progression to chronic kidney disease (CKD), and potentially end-stage renal disease (ESRD)
Blood vessels	Impaired endothelial function, increased arterial stiffness, and atherosclerotic changes	Oxidative injury, AGE accumulation, disturbed endothelial nitric oxide synthase (eNOS) activity, and vascular inflammation	Peripheral artery disease, elevated stroke risk, and other vascular complications
Retina	Damage to retinal microvessels, loss of pericytes, and abnormal new-vessel formation in advanced disease	AGE-associated injury, oxidative stress, inflammatory processes, and altered vascular endothelial growth factor (VEGF) signalling	Diabetic retinopathy and possible loss of vision
Skeletal muscle	Deterioration in muscle quality, reduced strength, and mitochondrial abnormalities	Disrupted mitochondrial activity, altered autophagy, oxidative stress, and SASP-related signalling	Functional limitations, frailty, and greater susceptibility to falls and disability
Bone	Changes in bone remodelling and deterioration in bone material quality	Glycation-related modification of collagen, oxidative stress, and altered bone-cell activity	Compromised skeletal health and increased fracture susceptibility
Skin	Reduced extracellular-matrix remodelling and delayed tissue repair	AGE-mediated collagen cross-linking, oxidative stress, and altered dermal fibroblast function	Slow wound healing, persistent ulcers, and increased wound-related complications

Table 2. Organ-specific manifestations and potential mechanisms of ageing-associated dysfunction in T2DM

Abbreviations: AGE, advanced glycation end-product; CKD, chronic kidney disease; eNOS, endothelial nitric oxide synthase; ESRD, end-stage renal disease; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; T2DM, type 2 diabetes mellitus; VEGF, vascular endothelial growth factor.

5.1 Neurological manifestations

Neurological changes associated with T2DM include an increased likelihood of cognitive impairment and dementia. Observational evidence has linked the condition with Alzheimer's disease, although the strength of this association and the mechanisms involved differ across studies. Disturbances in insulin signalling, inflammatory activity, and cellular stress have been investigated as possible contributors. Some publications use the expression “type 3 diabetes” to discuss hypothesised connections between brain insulin resistance and Alzheimer's disease. This expression remains a research concept rather than a formally recognised diagnostic classification [27].

5.2 Cardiovascular manifestations

Diabetes-associated metabolic stress may affect both the myocardium and the vascular system. The accumulation of AGEs can modify collagen and increase tissue stiffness, while endothelial dysfunction can compromise normal vascular regulation. Mitochondrial disturbances, oxidative injury, and

persistent inflammatory signalling may also contribute to myocardial remodelling and fibrosis. Collectively, these processes may be involved in the development of impaired diastolic function and heart failure in individuals with T2DM [28].

5.3 Skeletal muscle changes

Skeletal muscle may also exhibit metabolic and functional abnormalities in T2DM. Impaired mitochondrial activity and alterations in cellular quality-control mechanisms can affect muscle energy metabolism and tissue maintenance. In some individuals, these changes may accompany reduced muscle strength, declining physical performance, and greater vulnerability to frailty. Nevertheless, the contribution of diabetes-related mechanisms to accelerated biological ageing must be distinguished from the effects of chronological ageing, physical inactivity, and coexisting conditions. The relative importance of these factors remains incompletely established [29].

VI. BIOMARKERS OF ACCELERATED AGEING IN TYPE 2 DIABETES MELLITUS

Several biomarkers have been investigated to understand the relationship between type 2 diabetes mellitus (T2DM), metabolic stress, cellular senescence, and biological ageing. These indicators reflect different biological processes, including long-term glycaemic exposure, AGE accumulation, systemic inflammation, mitochondrial status, and epigenetic changes. However, they differ in their biological specificity, measurement methods, and degree of clinical validation. No single biomarker currently provides a universally accepted, comprehensive measure of biological ageing in individuals with T2DM. Table 3 summarises selected biomarkers, their biological significance, commonly used assessment methods, and potential clinical applications.

Biomarker	Biological significance	Assessment method	Clinical application and limitations
Glycated haemoglobin (HbA1c)	Reflects average glycaemic exposure over approximately 2–3 months; it is not a direct marker of biological age.	Blood test	Routinely used to monitor glycaemic control in diabetes.
Serum or tissue AGEs	Indicate the accumulation of proteins and other molecules modified through glycation-related processes.	Enzyme-linked immunosorbent assay (ELISA), mass spectrometry, or other validated assays	Used primarily in research for assessing glycation-related changes; results depend on the assay and sample type.
Skin autofluorescence (SAF)	Provides a non-invasive estimate of the accumulation of selected fluorescent AGE-related compounds in the skin.	AGE Reader or a comparable validated device	Investigated in research and selected risk-assessment settings; it does not measure all AGEs or biological ageing comprehensively.
Telomere length	May provide information about replicative history and cellular stress, although measurements vary with tissue, cell composition, and methodology.	Quantitative polymerase chain reaction (qPCR), Southern blotting, or other validated methods	Primarily a research measure; unsuitable as a stand-alone indicator of biological age.
Epigenetic clocks (e.g., GrimAge)	Use DNA methylation patterns to estimate selected aspects of biological ageing and, depending on the clock, mortality-related risk.	DNA methylation profiling	Used mainly in research; interpretation depends on the clock, study population, and validation method.
p16^INK4a expression	Reflects the expression of a cell-cycle regulator associated with certain senescence-related processes.	Quantitative PCR (qPCR), immunohistochemistry, or other validated expression assays	Research use; expression is tissue-dependent and is not sufficient by itself to confirm cellular senescence.

p21 expression	Represents a cell-cycle inhibitor that may be induced by DNA damage and other cellular stress responses, including some senescence programmes.	qPCR, immunohistochemistry, or other validated expression assays	Primarily a research marker; not specific for senescence when assessed alone.
Senescence-associated β-galactosidase (SA-β-gal)	Enzymatic activity commonly used as one indicator of a senescence-associated cellular phenotype.	Histochemical or validated fluorometric assay	Used mainly in research; results should be interpreted alongside additional senescence markers.
Mitochondrial DNA (mtDNA) copy number	May provide information about mitochondrial content or status, but does not directly measure mitochondrial function.	qPCR or another validated molecular assay	Primarily a research measure; interpretation depends on tissue, sample characteristics, and analytical methods.
Interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), and C-reactive protein (CRP)	Reflect aspects of systemic inflammation that may overlap with pathways associated with inflammaging and the senescence-associated secretory phenotype (SASP).	Immunoassays, including ELISA, or routine blood testing for CRP	Useful for assessing inflammatory status in appropriate contexts, but these markers are not specific to cellular senescence or biological ageing.

Table 3. Selected Biomarkers Associated with Glycaemic Exposure, Advanced Glycation, Cellular Senescence, Inflammation, and Biological Ageing in Type 2 Diabetes Mellitus (T2DM): Biological Significance, Assessment Methods, Clinical Applications, and Limitations.

Abbreviations: AGE, advanced glycation end-product; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; HbA1c, glycated haemoglobin; IL-6, interleukin-6; mtDNA, mitochondrial DNA; qPCR, quantitative polymerase chain reaction; SAF, skin autofluorescence; SA-β-gal, senescence-associated β-galactosidase; SASP, senescence-associated secretory phenotype; T2DM, type 2 diabetes mellitus; TNF-α, tumour necrosis factor-alpha.

Skin autofluorescence has been investigated as a non-invasive indicator of accumulated fluorescent AGE-related compounds and as a potential marker associated with complications in selected populations. However, it should not be interpreted as a direct measurement of biological age because it captures only selected aspects of glycation-related changes [30].

Associations between epigenetic-clock estimates and T2DM should also be interpreted in relation to the specific clock, population characteristics, and study design. Similarly, changes in epigenetic-age estimates following an intervention do not necessarily demonstrate that the intervention has reversed biological ageing. Further validation is needed to establish how reliably these measures reflect ageing-related changes in people with T2DM [31].

VII. THERAPEUTIC STRATEGIES

If T2DM-related metabolic stress contributes to ageing-associated pathways, interventions targeting these pathways may have potential benefits. The current therapeutic landscape includes lifestyle measures, established glucose-lowering and cardiometabolic treatments, and experimental strategies informed by geroscience. Evidence that these approaches directly slow or reverse biological ageing in people with T2DM remains limited for several proposed therapies. Table 4 summarises these approaches, separating established management options from investigational strategies and not implying proven effects on biological ageing.

Lifestyle/weight management	Established diabetes therapies	Emerging / investigational approaches
Aerobic and resistance exercise [32]	Metformin: investigated for potential effects on ageing pathways; geroprotective benefit is unproven [34]	Dasatinib + quercetin: early human target-engagement evidence; not established T2DM treatment [36]

Weight management / bariatric surgery; AGE-related effects have been studied [33]	Empagliflozin / SGLT2 inhibitor: cardiometabolic benefit does not establish ageing modification [35]	NAD^+ precursors (NMN, NR): investigational for T2DM-associated ageing [37]

Table 4. Selected examples of lifestyle measures, established diabetes therapies, and investigational ageing-targeted approaches. The cited studies support the specific claims shown; inclusion does not establish that an intervention modifies biological ageing.

7.1 Lifestyle Interventions

Regular physical activity supports glycaemic control, cardiovascular health, physical function, and metabolic health. Aerobic and resistance exercise may influence oxidative stress, mitochondrial function, and inflammatory signalling, while resistance training helps preserve muscle strength. Evidence linking exercise to changes in specific ageing biomarkers varies by study and should be distinguished from established clinical benefits [32].

Balanced dietary patterns and weight management can improve metabolic risk factors in people with T2DM. Cooking methods may influence dietary AGE exposure, although the clinical significance of dietary AGE reduction remains under investigation. Claims that dietary restriction reverses epigenetic ageing or that bariatric surgery reduces senescent-cell burden should be stated cautiously and supported by directly relevant evidence [33].

7.2 Metformin

Metformin is widely used to manage T2DM and has been investigated for effects on pathways associated with ageing, including AMPK signalling and cellular metabolism. However, it has not been established as a geroprotective treatment, and evidence that it slows biological ageing in humans remains insufficient. The Targeting Ageing with Metformin (TAME) concept should not be described as an ongoing trial unless its current status has been verified from an authoritative source [34].

7.3 GLP-1 Receptor Agonists and SGLT2 Inhibitors

Glucagon-like peptide-1 (GLP-1) receptor agonists and sodium–glucose cotransporter-2 (SGLT2) inhibitors are used to manage T2DM. Selected agents have demonstrated cardiovascular or renal benefits in defined patient groups; for example, cardiovascular outcome trials have reported benefits for liraglutide and empagliflozin [35, 38]. These clinical benefits should not be interpreted as proof that either class directly slows biological ageing.

7.4 Senolytics and Senomorphics

Senolytics are investigational agents intended to selectively remove senescent cells. Dasatinib, a tyrosine kinase inhibitor, and quercetin, a flavonoid, have been studied in early clinical research. Findings from small or preliminary studies should not be interpreted as evidence of established efficacy or safety for routine T2DM treatment [36].

Senomorphic approaches aim to modify the activity of senescent cells, including components of the senescence-associated secretory phenotype (SASP), rather than eliminate the cells. Agents such as rapamycin and navitoclax have distinct mechanisms and safety profiles; their roles in ageing-related disease remain investigational.

7.5 NAD^+ Precursors

NAD^+ metabolism is involved in cellular energy balance, DNA repair, and signalling pathways, and changes in NAD^+ availability have been studied in ageing and metabolic disease. Nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR) are being investigated as NAD^+ precursors. Their clinical benefits for T2DM-associated ageing have not been established, and findings from early studies require cautious interpretation [37].

VIII. RESEARCH GAPS AND FUTURE DIRECTIONS

Important gaps remain in understanding the relationship between T2DM and biological ageing. Addressing these questions is necessary before mechanistic findings can be translated into clinical recommendations.

Longitudinal human studies: Most mechanistic evidence comes from animal models or cross-sectional human studies. Long-term prospective cohorts tracking biological age markers from pre-diabetes through established T2DM and its complications are urgently needed.

Biomarker validation: Epigenetic clocks and senescence biomarkers have largely been developed in European populations. Validation across diverse ethnic groups including South Asian populations, who bear a disproportionate burden of T2DM is critically needed.

Clinical testing of senolytics: The safety and efficacy of senolytic regimens in people with T2DM have not been established in large, adequately powered randomised controlled trials. Future studies should report trial registration, recruitment status, prespecified metabolic outcomes, and adverse events.

Multi-omics integration: Combining genomics, proteomics, metabolomics, and epigenomics in single cohorts will allow a far more comprehensive picture of how T2DM accelerates ageing at the systems level and which interventions can reverse it.

Reversibility of biological ageing: It remains uncertain whether metabolic control combined with targeted interventions can reverse, rather than slow, specific measures of biological ageing. Reports of changes in epigenetic-age estimates after weight-loss interventions require further investigation and should not be equated with reversal of organism-wide ageing.

IX. CONCLUSION

Chronic hyperglycaemia in T2DM contributes to a network of processes that includes advanced glycation end-product accumulation, oxidative stress, mitochondrial dysfunction, DNA damage, and inflammatory signalling. These pathways overlap with mechanisms implicated in cellular senescence and biological ageing. The strength of evidence differs across pathways, tissues, and clinical outcomes.

T2DM is associated with complications across multiple organ systems, including cognitive impairment, cardiovascular disease, chronic kidney disease, skeletal-muscle dysfunction, and impaired wound healing. These outcomes overlap with conditions commonly seen in later life, but they should not automatically be attributed to accelerated biological ageing. The relative contributions of hyperglycaemia, vascular risk factors, inflammation, senescence, and chronological ageing differ by tissue and patient.

Several established interventions reduce diabetes-related risk and complications, including appropriate glucose management, physical activity, and evidence-based cardiometabolic therapies. Other approaches, including senolytics and interventions intended to modify epigenetic-age measures, remain experimental. Further studies are needed to determine whether these strategies can safely and meaningfully alter biological ageing in people with T2DM.

Geroscience investigates whether shared biological processes contribute to multiple age-related diseases. T2DM provides an important context in which to study the interaction between metabolic dysfunction and ageing-associated pathways. Glycaemic management remains essential, while the potential value of directly targeting ageing-related mechanisms requires rigorous clinical evaluation.

REFERENCES

[1] International Diabetes Federation, *IDF Diabetes Atlas*, 10th ed. Brussels, Belgium: International Diabetes Federation, 2021.

[2] M. Brownlee, “The pathobiology of diabetic complications: A unifying mechanism,” *Diabetes*, vol. 54, no. 6, pp. 1615–1625, 2005, doi: 10.2337/diabetes.54.6.1615.

[3] R. Syed, R. A. Aloti, B. J. Awad, W. I. Alghoul, M. A. M. S. A. Hassan, A. Kharoufeh, *et al*., “Cellular senescence and metabolic aging in type 2 diabetes: Mechanistic insights and translational implications,” *Frontiers in Endocrinology*, vol. 17, Art. no. 1799261, 2026, doi: 10.3389/fendo.2026.1799261.

[4] López-Otín, M. A. Blasco, L. Partridge, M. Serrano, and G. Kroemer, “The hallmarks of aging,” *Cell*, vol. 153, no. 6, pp. 1194–1217, 2013, doi: 10.1016/j.cell.2013.05.039.

[5] López-Otín, M. A. Blasco, L. Partridge, M. Serrano, and G. Kroemer, “Hallmarks of aging: An expanding universe,” *Cell*, vol. 186, no. 2, pp. 243–278, 2023, doi: 10.1016/j.cell.2022.11.001.

[6] J. P. Coppé, P. Y. Desprez, A. Krtolica, and J. Campisi, “The senescence-associated secretory phenotype: The dark side of tumor suppression,” *Annual Review of Pathology*, vol. 5, pp. 99–118, 2010, doi: 10.1146/annurev-pathol-121808-102144.

[7] C. Franceschi, P. Garagnani, P. Parini, C. Giuliani, and A. Santoro, “Inflammaging: A new immune-metabolic viewpoint for age-

related diseases," *Nature Reviews Endocrinology*, vol. 14, no. 10, pp. 576–590, 2018, doi: 10.1038/s41574-018-0059-4.

[8] R. A. DeFronzo, E. Ferrannini, L. Groop, R. R. Henry, W. H. Herman, J. J. Holst, *et al*., "Type 2 diabetes mellitus," *Nature Reviews Disease Primers*, vol. 1, Art. no. 15019, 2015, doi: 10.1038/nrdp.2015.19.

[9] R. H. Unger, G. O. Clark, P. E. Scherer, and L. Orci, "Lipid homeostasis, lipotoxicity and the metabolic syndrome," *Biochimica et Biophysica Acta*, vol. 1801, no. 3, pp. 209–214, 2010, doi: 10.1016/j.bbalip.2009.10.006.

[10] G. S. Hotamisligil, "Inflammation, metaflammation and immunometabolic disorders," *Nature*, vol. 542, no. 7640, pp. 177–185, 2017, doi: 10.1038/nature21363.

[11] T. Nishikawa, D. Edelstein, X. L. Du, S. Yamagishi, T. Matsumura, Y. Kaneda, *et al*., "Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage," *Nature*, vol. 404, no. 6779, pp. 787–790, 2000, doi: 10.1038/35008121.

[12] R. Ramasamy, S. F. Yan, and A. M. Schmidt, "RAGE: Therapeutic target and biomarker of the inflammatory response—the evidence mounts," *Journal of Leukocyte Biology*, vol. 86, no. 3, pp. 505–512, 2009, doi: 10.1189/jlb.0409230.

[13] F. Giacco and M. Brownlee, "Oxidative stress and diabetic complications," *Circulation Research*, vol. 107, no. 9, pp. 1058–1070, 2010.

[14] P. Newsholme, V. F. Cruzat, K. N. Keane, R. Carlessi, and P. I. de Bittencourt Jr., "Molecular mechanisms of ROS production and oxidative stress in diabetes," *Biochemical Journal*, vol. 473, no. 24, pp. 4527–4550, 2016, doi: 10.1042/BCJ20160503C.

[15] J. S. Bhatti, G. K. Bhatti, and P. H. Reddy, "Mitochondrial dysfunction and oxidative stress in metabolic disorders—a step towards mitochondria-based therapeutic strategies," *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, vol. 1863, no. 5, pp. 1066–1077, 2017.

[16] J. Leinonen, T. Lehtimäki, S. Toyokuni, *et al*., "New biomarker evidence of oxidative DNA damage in patients with non-insulin-dependent diabetes mellitus," *FEBS Letters*, vol. 417, no. 1, pp. 150–152, 1997, doi: 10.1016/S0014-5793(97)01273-8.

[17] B. G. Childs, M. Durik, D. J. Baker, and J. M. van Deursen, "Cellular senescence in aging and age-related disease: From mechanisms to therapy," *Nature Medicine*, vol. 21, no. 12, pp. 1424–1435, 2015, doi: 10.1038/nm.4000.

[18] K. Schroder and J. Tschopp, "The inflammasomes," *Cell*, vol. 140, no. 6, pp. 821–832, 2010, doi: 10.1016/j.cell.2010.01.040.

[19] F. Prattichizzo, V. De Nigris, L. La Sala, A. D. Procopio, F. Olivieri, and A. Ceriello, "Inflammaging as a druggable target: A senescence-associated secretory phenotype-centered view of type 2 diabetes," *Oxidative Medicine and Cellular Longevity*, vol. 2016, Art. no. 1810327, 2016, doi: 10.1155/2016/1810327.

[20] T. Tchkonia, Y. Zhu, J. van Deursen, J. Campisi, and J. L. Kirkland, "Cellular senescence and the senescent secretory phenotype," *Journal of Clinical Investigation*, vol. 123, no. 3, pp. 966–972, 2013, doi: 10.1172/JCI64098.

[21] K. Palmer, B. Gustafson, J. L. Kirkland, and U. Smith, "Cellular senescence: At the nexus between ageing and diabetes," *Diabetologia*, vol. 62, no. 10, pp. 1835–1841, 2019, doi: 10.1007/s00125-019-4934-x.

[22] S. Horvath and K. Raj, "DNA methylation-based biomarkers and the epigenetic clock theory of ageing," *Nature Reviews Genetics*, vol. 19, no. 6, pp. 371–384, 2018, doi: 10.1038/s41576-018-0004-3.

[23] El-Osta, D. Brasacchio, D. Yao, A. Pocai, P. L. Jones, R. G. Roeder, *et al*., "Transient high glucose causes persistent epigenetic changes and altered gene expression during subsequent normoglycemia," *Journal of Experimental Medicine*, vol. 205, no. 10, pp. 2409–2417, 2008, doi: 10.1084/jem.20081188.

[24] F. Monickaraj, S. Aravind, K. Gokulakrishnan, C. Sathishkumar, P. Prabu, D. Prabu, *et al*., "Accelerated aging as evidenced by increased telomere shortening and mitochondrial DNA depletion in patients with type 2 diabetes,"

Molecular and Cellular Biochemistry, vol. 365, nos. 1–2, pp. 343–350, 2012, doi: 10.1007/s11010-012-1276-0.

[25] S. Bhansali, A. Bhansali, R. Walia, U. N. Saikia, and V. Dhawan, "Alterations in mitochondrial oxidative stress and mitophagy in subjects with prediabetes and type 2 diabetes mellitus," *Frontiers in Endocrinology*, vol. 8, Art. no. 347, 2017, doi: 10.3389/fendo.2017.00347.

[26] W. Quan, K. Y. Hur, Y. Lim, S. H. Oh, J. C. Lee, K. H. Kim, *et al*., "Autophagy deficiency in beta cells leads to compromised unfolded protein response and progression from obesity to diabetes in mice," *Diabetologia*, vol. 55, no. 2, pp. 392–403, 2012, doi: 10.1007/s00125-011-2350-y.

[27] S. M. de la Monte and J. R. Wands, "Alzheimer's disease is type 3 diabetes—evidence reviewed," *Journal of Diabetes Science and Technology*, vol. 2, no. 6, pp. 1101–1113, 2008, doi: 10.1177/193229680800200619.

[28] G. Jia, A. Whaley-Connell, and J. R. Sowers, "Diabetic cardiomyopathy: A hyperglycaemia- and insulin-resistance-induced cardiac metabolic, structural and functional abnormality," *Diabetologia*, vol. 61, no. 1, pp. 21–28, 2018, doi: 10.1007/s00125-017-4390-4.

[29] S. W. Park, B. H. Goodpaster, E. S. Strotmeyer, *et al*., "Decreased muscle strength and quality in older adults with type 2 diabetes," *Diabetes*, vol. 55, no. 6, pp. 1813–1818, 2006, doi: 10.2337/db05-1183.

[30] R. Meerwaldt, R. Graaff, P. H. Oomen, *et al*., "Simple non-invasive assessment of advanced glycation endproduct accumulation," *Diabetologia*, vol. 47, no. 7, pp. 1324–1330, 2004, doi: 10.1007/s00125-004-1451-2.

[31] T. Lu, A. Quach, J. G. Wilson, *et al*., "DNA methylation GrimAge strongly predicts lifespan and healthspan," *Aging*, vol. 11, no. 2, pp. 303–327, 2019, doi: 10.18632/aging.101684.

[32] L. B. Borghouts and H. A. Keizer, "Exercise and insulin sensitivity: A review," *International Journal of Sports Medicine*, vol. 21, no. 1, pp. 1–12, 2000, doi: 10.1055/s-2000-8847.

[33] W. Sturm, G. Engl, S. Mair, *et al*., "Effect of bariatric surgery on advanced glycation endproducts and soluble forms of their receptor in morbidly obese patients," *Obesity Surgery*, vol. 21, no. 2, pp. 170–176, 2011.

[34] N. Barzilai, J. P. Crandall, S. B. Kritchevsky, and M. A. Espeland, "Metformin as a tool to target aging," *Cell Metabolism*, vol. 23, no. 6, pp. 1060–1065, 2016, doi: 10.1016/j.cmet.2016.05.011.

[35] B. Zinman, C. Wanner, J. M. Lachin, *et al*., "Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes," *New England Journal of Medicine*, vol. 373, no. 22, pp. 2117–2128, 2015, doi: 10.1056/NEJMoa1504720.

[36] L. J. Hickson, L. G. P. Langhi Prata, S. A. Bobart, *et al*., "Senolytics decrease senescent cells in humans: Preliminary report from a clinical trial of dasatinib plus quercetin in individuals with diabetic kidney disease," *EBioMedicine*, vol. 47, pp. 446–456, 2019, doi: 10.1016/j.ebiom.2019.08.069.

[37] J. Yoshino, J. A. Baur, and S. I. Imai, "NAD+ intermediates: The biology and therapeutic potential of NMN and NR," *Cell Metabolism*, vol. 27, no. 3, pp. 513–528, 2018, doi: 10.1016/j.cmet.2017.11.002.

[38] S. P. Marso, G. H. Daniels, K. Brown-Frandsen, P. Kristensen, J. F. E. Mann, M. A. Nauck, *et al*., "Liraglutide and cardiovascular outcomes in type 2 diabetes," *New England Journal of Medicine*, vol. 375, no. 4, pp. 311–322, 2016, doi: 10.1056/NEJMoa1603827.