REVIEW

Accelerated biological aging in type 2 diabetes mellitus: mechanistic, cellular, and systemic perspectives

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Abstract

Type 2 diabetes mellitus (T2DM), a common chronic metabolic disease that affects multiple organ systems, is still a major global public health concern. Long-term diabetes is linked to cardiovascular disease, renal impairment, neurotoxicity, musculoskeletal weakness, and progressive pancreatic β-cell loss in addition to disruptions in glucose metabolism. These issues frequently start earlier and worsen faster than one may anticipate given one's age. According to recent research, T2DM may be considered a disorder of accelerated biological aging. Diabetes patients exhibit early activation of aging-related processes, including cellular senescence, oxidative stress, chronic low-grade inflammation, genomic instability, mitochondrial dysfunction, and epigenetic changes. Persistent hyperglycemia, insulin resistance, and metabolic stress intensify these pathways, which are similar to those seen during physiological aging. The main molecular and cellular processes such as dysregulated nutrient-sensing pathways, poor mitochondrial energy metabolism, inflammation, telomere shortening, and loss of tissue regeneration capacity that connect diabetes and aging are outlined in this study. The cardiovascular, renal, neurological, musculoskeletal, and endocrine systems are among the organ-specific signs of accelerated aging in T2DM that are highlighted. Knowing that T2DM is a condition of accelerated aging offers crucial information for managing and preventing the illness. In addition to good glycemic management and lifestyle change, targeting aging-related pathways may help prevent complications, maintain organ function, and enhance long-term health outcomes in people with T2DM.

Keywords: Insulin resistance, mitochondrial dysfunction, inflammation, type 2 diabetes mellitus, accelerated aging

Introduction

One of the biggest worldwide health issues of the twenty-first century is type 2 diabetes mellitus (T2DM). According to the International Diabetes Federation (IDF), there are currently over 530 million people with diabetes globally, and by 2045, that number is predicted to rise to over 700 million [1]. Known as the "diabetes capital of the world," India alone contributes significantly to this worldwide burden. Rapid urbanization, sedentary lifestyles, poor eating habits, and genetic predispositions are all blamed for this concerning trend [2]. Because T2DM is linked to cardiovascular disease, renal failure, and neurological problems, its socioeconomic effects extend beyond individuals to families and healthcare systems [3].

Traditionally, insulin resistance, β-cell dysfunction, and persistent hyperglycemia have been identified as the main characteristics of T2DM. Its pathogenesis has been closely associated with reduced physical activity, obesity, and excessive calorie consumption. Both macrovascular problems like atherosclerosis and coronary artery disease as well as microvascular problems like neuropathy, nephropathy, and retinopathy are brought on by prolonged exposure to hyperglycemia. Diabetic complications continue to appear earlier and more aggressively despite advancements in glucose control and medication, indicating that the disease process involves more than just metabolic dysregulation [4, 5].

A paradigm shift is supported by recent scientific data: T2DM is a condition of accelerated biological aging as well as a metabolic problem. Numerous studies have

shown that people with T2DM exhibit early cellular and tissue aging, including telomere shortening, oxidative stress, mitochondrial dysfunction, and persistent low-grade inflammation [6]. These processes coincide with the signs of aging, such as loss of proteostasis, chromosomal instability, and epigenetic changes. As a result, early-onset vascular stiffness, frailty, and cognitive decline—conditions usually associated with old age—are frequently seen in diabetic patients. be a result, T2DM is now referred to be a "metabolic disease of accelerated aging"[7].

The goal of this review is to investigate the complex biological and molecular connections between accelerated aging and T2DM. It aims to address the basic characteristics of aging and how they directly relate to the pathophysiology processes that underlie T2DM. The review continues to elucidate the molecular relationships between the two conditions, emphasizing oxidative stress, mitochondrial dysfunction, chronic inflammation, insulin resistance, telomere shortening, and epigenetic modifications. It also examines the organ-specific signs of accelerated aging seen in diabetic patients, such as early aging of the neurological, renal, and cardiovascular systems. Additionally, the review seeks to assess new therapeutic approaches that target aging-related pathways in diabetes

management and to highlight recent developments in the identification of biomarkers of biological aging.

This study offers a thorough and cohesive framework for understanding T2DM as both a metabolic problem and an aging disease, with important implications for personalized medication and public health initiatives. It does this by combining viewpoints from metabolic research and geroscience.

Conceptual framework for aging and metabolic dysfunction

Aging is a progressive and irreversible biological process characterized by the cumulative accumulation of molecular and cellular damage, leading to functional decline and increased vulnerability to disease. Contemporary geroscience frameworks describe aging as a regulated process driven by conserved biological mechanisms collectively termed the hallmarks of aging. Updated models identify twelve interconnected hallmarks, including genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, dysregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, al-

Table 1. Types of stem cells in anemones.

No	Hallmark of aging	Mechanistic description	Relevance to metabolic aging / T2DM	References
1	Genomic instability	Accumulation of DNA damage, mutations, and chromosomal aberrations with age.	Hyperglycemia-induced oxidative stress accelerates DNA damage in pancreatic β-cells and vascular endothelium.	[8]
2	Telomere attrition	Shortening of telomeres limits cellular replication capacity.	Shortened telomeres in diabetic patients correlate with insulin resistance and vascular aging.	[9]
3	Epigenetic alterations	DNA methylation and histone modification changes affecting gene expression.	Accelerated "epigenetic clock" observed in T2DM suggests faster biological aging.	[10]
4	Loss of proteostasis	Decline in chaperone activity and autophagy causing protein aggregation.	Hyperglycemia and lipid peroxidation promote misfolded protein accumulation in diabetic tissues.	[11]
5	Deregulated nutrient sensing	Disruption of the sirtuin, mTOR, AMPK, and insulin/IGF-1 signaling pathways.	Insulin resistance and mTOR overactivation are central to both aging and diabetes.	[12]
6	Mitochondrial dysfunction	Impaired mitochondrial biogenesis and increased ROS generation.	Diabetic tissues show defective ATP production and enhanced oxidative stress.	[13]
7	Cellular senescence	Irreversible growth arrest and SASP-mediated inflammation.	Senescent adipocytes and endothelial cells impair insulin signaling and tissue repair.	[12]
8	Stem cell exhaustion	Decline in regenerative potential of progenitor cells.	Reduced β-cell and muscle stem cell renewal in T2DM parallels premature aging.	[14]
9	Altered intercellular communication	Chronic low-grade inflammation and disrupted signaling.	Inflammatory cytokines (IL-6, TNF-α) drive "inflammaging" and insulin resistance.	[15]
10	Chronic inflammation	Persistent systemic inflammation from immune dysregulation.	Overlaps with diabetic inflammation, worsening vascular and metabolic dysfunction.	[16]
11	Disabled macroautophagy	Impaired removal of damaged organelles.	Reduced autophagy in diabetic muscle and liver contributes to metabolic stress.	[17]
12	Dysbiosis of gut microbiota	Imbalance of gut microorganisms affecting metabolism.	Alters glucose metabolism and insulin sensitivity in aging and diabetes.	[8]

tered intercellular communication, chronic inflammation, impaired autophagy, and gut microbiome dysbiosis (Table 1).

Importantly, many of these hallmarks are now measurable through established and emerging biological aging biomarkers, such as telomere length, DNA methylation clocks, mitochondrial DNA integrity, inflammatory mediators, proteomic and metabolomic signatures, and senescence-associated factors. In T2DM, these biomarkers consistently demonstrate premature activation and accelerated progression of aging pathways, indicating that diabetes represents a state of accelerated biological aging rather than normal chronological aging. Hyperglycemia, insulin resistance, oxidative stress, and chronic inflammation act as upstream drivers that amplify aging hallmarks, resulting in earlier onset of age-related phenotypes across multiple organs.

Thus, integrating aging biomarkers within this conceptual framework provides a comprehensive perspective for understanding metabolic dysfunction in T2DM and highlights accelerated aging biomarkers as both indicators of disease severity and potential targets for therapeutic intervention.

Metabolic aging and its acceleration in T2DM

Normal aging is accompanied by a gradual decline in metabolic flexibility—the capacity to efficiently switch between glucose and lipid utilization—resulting in impaired energy homeostasis and reduced cellular resilience. Age-related increases in oxidative stress, mitochondrial inefficiency, chronic inflammation, and diminished insulin responsiveness collectively predispose older individuals to insulin resistance and metabolic disease. These metabolic alterations closely resemble the pathophysiology of T2DM, supporting the concept that diabetes represents a state of accelerated metabolic aging, in which aging-related mechanisms are activated earlier and progress more rapidly.

Glucose homeostasis and mitochondrial energy dysfunction

During physiological aging, insulin sensitivity progressively declines in skeletal muscle, liver, and adipose tissue due to impaired insulin receptor signaling and reduced GLUT4 (glucose transporter type 4) translocation. Concurrently, pancreatic β-cell mass and secretory capacity decrease as a result of cumulative oxidative damage and mitochondrial stress [18]. Mitochondrial DNA mutations, impaired oxidative phosphorylation, defective mitophagy, and downregulation of proliferator–activated receptor gamma coactivator-1α (PGC-1α) further reduce ATP production and increase reactive oxygen species (ROS) generation [19]. In T2DM, chronic hyperglycemia and insulin resistance markedly intensify these processes. Hypergly-
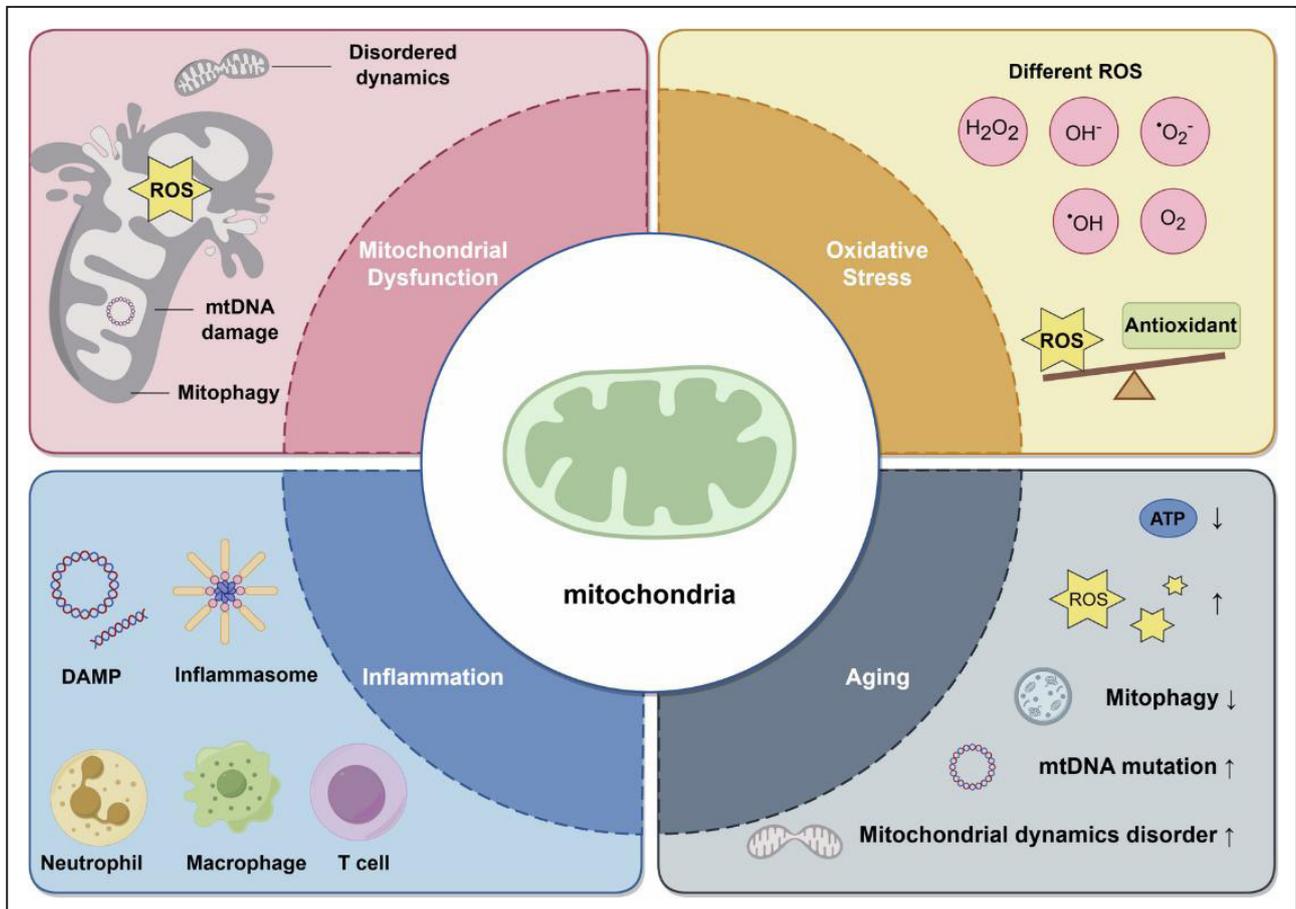

Figure 1. Mitochondrial dysfunction's crucial role in oxidative stress, inflammation, and aging.

cemia-induced oxidative stress accelerates mitochondrial damage, impairs lipid oxidation, promotes ectopic lipid accumulation, and hastens β-cell exhaustion. This convergence amplifies insulin resistance and reinforces accelerated metabolic aging [20].

Adipose tissue remodeling, protein metabolism, and sarcopenia

Aging is associated with redistribution of adipose tissue from subcutaneous to visceral depots, promoting systemic inflammation and insulin resistance. This shift is accompanied by adipokine imbalance, characterized by elevated leptin and reduced adiponectin levels, contributing to inflammaging and lipotoxicity in muscle and liver tissues [21]. Simultaneously, reduced muscle protein synthesis and anabolic resistance—driven by impaired mTORC1 signaling and decreased essential amino acid utilization—lead to sarcopenia, decreased energy expenditure, and frailty [22]. In T2DM, insulin resistance and mitochondrial dysfunction further suppress protein synthesis and muscle regeneration, accelerating muscle loss and functional decline beyond that expected with chronological aging.

Immune–metabolic inflammation and cellular senescence

Aging is characterized by persistent immune activation and increased production of pro-inflammatory cytokines such as TNF-α and IL-6, which interfere with insulin signaling and increase oxidative stress, forming a metabolic–aging axis [23]. In T2DM, chronic exposure to hyperglycemia and elevated free fatty acids sustains activation of inflammatory pathways such as NF-κB, intensifying inflammaging, endothelial dysfunction, and tissue fibrosis [24]. The accumulation of senescent cells further links aging and diabetes. Senescent cells in pancreatic β-cells, liver, and adipose tissue adopt a senescence-associated secretory phenotype (SASP), releasing pro-inflammatory cytokines and matrix-degrading enzymes. Hyperglycemia accelerates this senescent burden, leading to premature β-cell dysfunction and tissue deterioration [25].

Epigenetic alterations and nutrient-sensing dysregulation

Epigenetic alterations and telomere shortening are central markers of biological aging and are significantly accelerated in T2DM. Chronic metabolic stress induces oxidative DNA damage, telomere attrition, and aberrant DNA methylation patterns that advance epigenetic aging clocks and alter gene expression related to glucose metabolism and

inflammation [26]. Parallel to these changes, dysregulation of nutrient-sensing pathways—including insulin/IGF-1 signaling, AMP-activated protein kinase (AMPK), and mechanistic target of rapamycin (mTOR)—is observed in both aging and T2DM. Chronic nutrient excess promotes sustained mTORC1 activation, suppresses autophagy, and accelerates cellular damage, while reduced AMPK activity impairs metabolic adaptation, reinforcing metabolic inflexibility and cellular senescence [27].

Stem cell exhaustion and integrated acceleration of aging

Stem cell exhaustion limits tissue regeneration during aging and is further exacerbated in T2DM. Metabolic stress and chronic inflammation impair pancreatic progenitor cells, skeletal muscle satellite cells, and bone marrow–derived stem cells. Hyperglycemia-induced oxidative damage reduces self-renewal capacity, accelerating β-cell failure, sarcopenia, and vascular complications [28]. Taken together, normal aging and T2DM share deeply overlapping metabolic mechanisms; however, in diabetes these processes are prematurely activated and pathologically intensified. T2DM therefore represents a model of accelerated metabolic aging, in which age-related molecular and cellular dysfunctions converge to drive early-onset organ decline and increased disease burden.

Mechanistic links between T2DM and accelerated aging

Oxidative stress and mitochondrial dysfunction

Chronic hyperglycemia in T2DM markedly increases the production of ROS within cellular mitochondria, thereby accelerating molecular and cellular processes typically associated with biological aging [29]. Persistently elevated glucose levels overload the mitochondrial electron transport chain, leading to electron leakage and excessive ROS generation [30]. This oxidative burden causes mitochondrial DNA (mtDNA) damage, lipid peroxidation, impaired oxidative phosphorylation, and reduced adenosine triphosphate (ATP) production, culminating in diminished cellular energy reserves and early tissue dysfunction [31].

Notably, these mitochondrial alterations mirror hallmark features of physiological aging, in which antioxidant defense systems—such as superoxide dismutase (SOD), catalase, and glutathione peroxidase—progressively decline, mitochondrial biogenesis is reduced (via downregulation

Table 2. Pro-inflammatory cytokines and their roles.

Cytokine	Principal source	Role in aging	Role in T2DM	References
IL-6	Adipose tissue/macrophages	Promotes inflammaging, muscle wasting	Insulin resistance, β-cell dysfunction	[36]
TNF-α	Activated macrophages	Inhibits cell repair, promotes senescence	Impairs insulin receptor signaling, endothelial damage	[37]
IL-1β	Inflammasome activation	Contributes to age-related immune dysregulation	β-cell apoptosis, adipose inflammation	[38]

of regulators including PGC-1α and NRF1), and mitochondrial fusion–fission dynamics become dysregulated [32]. In T2DM, however, these aging-associated mitochondrial defects emerge earlier and with greater severity, supporting the concept that diabetes represents a state of accelerated mitochondrial aging rather than merely metabolic dysfunction [33] (Figure 1).

Chronic inflammation

Aging is characterized by a persistent, low-grade inflammatory state termed inflammaging, which contributes to functional decline and age-related diseases. In T2DM, chronic metabolic stress—driven by hyperglycemia, elevated free fatty acids, and advanced glycation end products (AGEs)—sustains aberrant activation of pro-inflammatory pathways, including NF-κB signaling and the NLRP3 inflammasome. This results in persistently elevated levels of inflammatory mediators such as IL-6, TNF-α, and C-reactive protein (CRP), which impair insulin signaling, promote endothelial dysfunction, and accelerate tissue senescence [34].

While inflammaging also develops in non-diabetic aging, the inflammatory milieu in T2DM closely mimics—and markedly intensifies—this process, leading to premature immune dysregulation, impaired tissue repair, and cumulative organ damage. Thus, diabetes amplifies age-related inflammatory pathways, accelerating metabolic and vascular aging beyond what is observed in chronological aging alone (Table 2) [35].

Advanced glycation end products

AGEs accumulate through the non-enzymatic glycation of proteins, lipids, and nucleic acids—a process that occurs slowly during normal aging but is substantially accelerated under hyperglycemic conditions. In T2DM, elevated glucose levels and reactive dicarbonyls such as methylglyoxal drive excessive AGE formation. Binding of AGEs to their receptor (RAGE) on endothelial cells, macrophages, and other tissues triggers ROS generation, NF-κB activation, pro-inflammatory cytokine release, and cellular senescence.

AGE-mediated cross-linking of collagen and extracellular matrix proteins reduces tissue elasticity, contributing to vascular stiffness and impaired organ function—phenotypes classically associated with advanced aging. Similarly, AGE accumulation during normal aging is linked to reduced cellular turnover, loss of proteostasis, and progressive tissue rigidity in organs such as the skin, kidneys, and vasculature. Therefore, the AGE–RAGE axis represents a critical mechanistic bridge between diabetes and aging, whereby metabolic dysregulation in T2DM accelerates molecular aging processes [39].
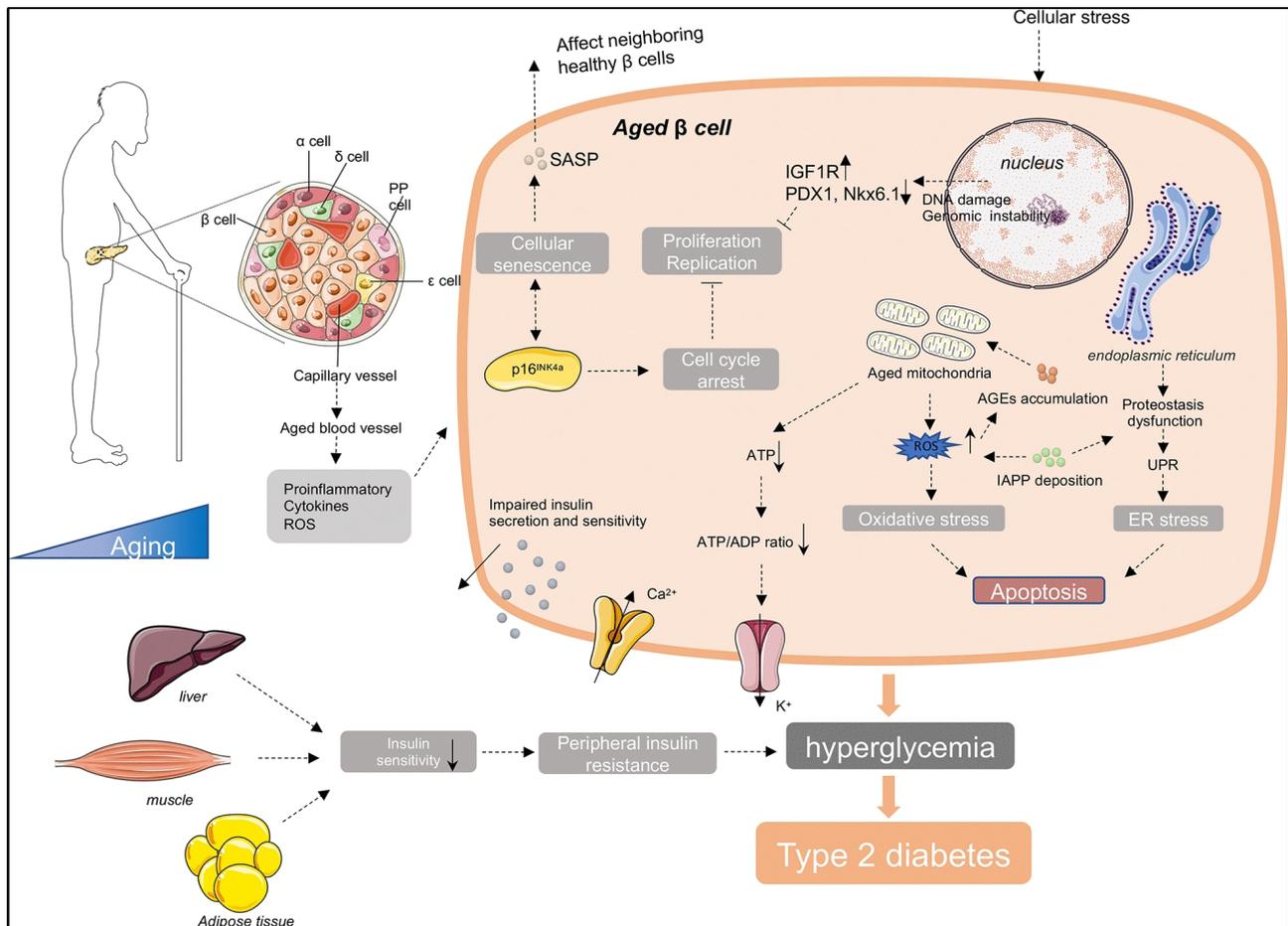

Figure 2. **Aging-associated cellular stress and senescence in β-cell dysfunction leading to type 2 diabetes.** Age-related mitochondrial dysfunction, oxidative and endoplasmic reticulum stress, impaired proteostasis, and SASP compromise insulin secretion and sensitivity, promoting hyperglycemia and systemic insulin resistance.

Insulin resistance and cellular senescence

Persistent insulin resistance is a defining feature of T2DM and a hallmark of metabolic aging. In both contexts, oxidative stress, chronic inflammation, and sustained nutrient excess impair insulin receptor signaling, particularly along the PI3K–Akt–mTOR pathway, leading to reduced glucose uptake and dysregulated lipid metabolism. These metabolic insults simultaneously promote cellular senescence, an irreversible state of cell-cycle arrest accompanied by the SASP.

Senescent adipocytes, hepatocytes, and pancreatic β-cells secrete pro-inflammatory cytokines (including IL-6, IL-8, and TNF-α), reinforcing local inflammation and further worsening insulin resistance. This establishes a self-perpetuating cycle in which diabetes accelerates aging-related senescence, while senescence exacerbates diabetic pathology. Consistent with accelerated aging, diabetic tissues exhibit increased expression of senescence markers such as p16^{INK4a}, p21^{Cip1}, and SA-β-galactosidase activity—patterns also observed in aged organs. Importantly, experimental clearance of senescent cells via senolytic therapies improves insulin sensitivity in diabetic models, underscoring senescence as a key mediator of diabetes-driven accelerated aging [40] (Figure 2).

Genomic instability and telomere shortening

Telomeres, the repetitive DNA sequences that protect chromosome ends, progressively shorten with each cell division and are widely recognized as biomarkers of cellular aging. In T2DM, heightened oxidative stress and poor glycemic control are associated with accelerated telomere attrition, reflecting premature cellular aging. Hyperglycemia-induced ROS directly damage both genomic DNA and telomeric regions, while chronic inflammatory signaling further exacerbates telomere erosion.

Activation of DNA damage response (DDR) pathways, including p53, promotes senescence and apoptosis in vascular cells and pancreatic β-cells, contributing to early tissue dysfunction in diabetes [41]. These processes closely resemble those observed in natural aging, where accumulated DNA lesions, impaired repair mechanisms (*e.g.*, PARP and ATM dysfunction), and telomere failure drive progressive cellular decline (Table 3). Thus, T2DM accelerates genomic aging by intensifying mechanisms normally associated with chronological aging.

Epigenetic changes

Epigenetic alterations—including DNA methylation, histone modifications, and non-coding RNA regulation—are fundamental mechanisms underlying physiological aging, contributing to progressive cellular dysfunction over time. Normal aging is characterized by a gradual acceleration of the epigenetic clock, marked by global DNA hypomethylation alongside site-specific hypermethylation of stress-response and metabolic genes, leading to altered gene expression, mitochondrial decline, and increased inflammatory signaling.

In T2DM, these same epigenetic aging mechanisms are prematurely activated and intensified by chronic hyperglycemia. Aberrant DNA methylation of key metabolic and mitochondrial regulators—such as PPARGC1A, INS, and SIRT1—drives insulin resistance and mitochondrial dysfunction and gives rise to the phenomenon of "metabolic memory," whereby aging-like cellular phenotypes persist even after glycemic normalization. Consistent with accelerated aging, individuals with T2DM exhibit epigenetic ages that are approximately 3–5 years older than age-matched non-diabetic controls, indicating advanced biological aging.

Additional epigenetic dysregulation further reinforces this acceleration. Altered histone acetylation due to reduced SIRT1 activity and increased HDAC signaling exacerbates oxidative stress and inflammation, while diabetes- and aging-associated non-coding RNAs—particularly miR-34a and miR-146a—promote cellular senescence, apoptosis, and chronic inflammatory responses. Collectively, these findings demonstrate that T2DM does not merely coexist with epigenetic aging but actively accelerates epigenetic aging trajectories, contributing to premature metabolic and organ dysfunction [45].

Organ-specific signs of T2DM-related accelerated aging

T2DM is increasingly recognized as a systemic disorder that accelerates aging-like changes across multiple organ systems. Chronic hyperglycemia, oxidative stress, mitochondrial dysfunction, and sustained inflammatory signaling converge to drive premature cellular senescence, fibrosis, and functional decline, recapitulating the molecular and structural features of physiological aging but occurring earlier and with greater severity. Thus, diabetes can be conceptualized as a model of accelerated biological aging rather than isolated metabolic disease.

In the cardiovascular system, T2DM induces premature vascular aging, characterized by endothelial dysfunction, arterial stiffness, and accelerated atherosclerosis. Chronic hyperglycemia promotes excessive formation of AGEs,

Table 3. Comparative overview of telomere dynamics in aging and T2DM.

Parameter	Normal aging	Type 2 diabetes mellitus	References
Telomere length	Gradual shortening over decades	Rapid shortening due to chronic oxidative stress	[41]
DDR activation	Moderate, progressive	Persistent, exaggerated	[42]
Consequence	Slow cellular senescence	Premature senescence and apoptosis	[43]
Clinical impact	Age-related organ decline	Early vascular aging, neuropathy, β-cell loss	[44]

Table 4. Comparative markers of renal aging and diabetic nephropathy.

Parameter	Aging kidney	Diabetic kidney	References
Glomerular morphology	Mild sclerosis	Nodular (Kimmelstiel–Wilson) sclerosis	[48]
Oxidative stress	Moderate	Markedly elevated	[49]
Mitochondrial function	Reduced ATP production	Severe mitochondrial loss	[50]
Senescence markers (p16, p21)	Increased	Strongly overexpressed	[51]
Repair capacity	Gradual decline	Early exhaustion of progenitor cells	[52]

which cross-link collagen and elastin within the vascular wall, reducing elasticity in a manner analogous to age-related arterial stiffening. Concurrently, reduced endothelial nitric oxide synthase (eNOS) activity limits nitric oxide (NO) bioavailability, impairing vasodilation and promoting vascular aging [46].

Oxidative stress and pro-inflammatory signaling (TNF-α, IL-6, NF-κB) further accelerate endothelial senescence and vascular smooth muscle cell proliferation, hastening plaque formation and arterial rigidity. These changes closely resemble those observed in aged vasculature but emerge decades earlier in individuals with diabetes, underscoring the concept of diabetes-driven cardiovascular aging.

Similarly, the kidneys of patients with T2DM display structural and functional alterations that parallel age-related nephrosclerosis. Chronic hyperglycemia induces glomerular basement membrane thickening, podocyte loss, and tubulointerstitial fibrosis—hallmark features of renal aging. Accelerated telomere shortening, mitochondrial dysfunction, and accumulation of senescent glomerular and tubular cells further impair renal repair capacity. Activation of senescence pathways, particularly the p16^{INK4a}–p21^{Cip1} axis, enforces permanent cell-cycle arrest, limiting regeneration and promoting early decline in renal function [47] (Table 4). Collectively, these findings indicate that diabetic nephropathy represents a form of premature renal aging.

Neurodegeneration in T2DM likewise reflects accelerated neuronal aging. Insulin resistance within the brain, coupled with microvascular dysfunction, disrupts neuronal metabolism and synaptic plasticity. Glucose toxicity, mitochondrial failure, and chronic neuroinflammation (IL-1β, TNF-α) promote neuronal loss and cognitive impairment. Clinical and imaging studies reveal increased tau hyperphosphorylation, amyloid-β accumulation, and faster cognitive decline in individuals with diabetes—features characteristic of Alzheimer's disease, often described as "type 3 diabetes". Chronic inflammatory exposure and oxidative mitochondrial DNA damage drive astrocyte and microglial senescence, further advancing neurodegenerative aging processes.

Skeletal muscle aging is also markedly accelerated in T2DM. Sarcopenia, a classical hallmark of aging, develops earlier and progresses more rapidly in diabetic individuals. Persistent inflammation, impaired insulin–Akt–mTOR signaling, and mitochondrial dysfunction reduce protein synthesis and muscle regeneration. Insulin resistance in skeletal muscle diminishes glucose uptake and ATP production, leading to muscle fatigue and atrophy. Diabetic neuropathy further exacerbates muscle loss by reducing motor unit activation. Combined with reduced physical activity and heightened oxidative stress, these mechanisms substantially increase frailty risk in diabetes, mirroring advanced biological aging [53] (Table 5).

Within the endocrine pancreas, pancreatic β-cells exhibit hallmarks of accelerated cellular aging in T2DM. Prolonged exposure to glucotoxicity and lipotoxicity induces oxidative DNA damage, mitochondrial dysfunction, and activation of senescence pathways involving p53, p21, and p16. Senescent β-cells demonstrate impaired insulin secretion, increased release of SASP factors (including IL-6 and MCP-1), and diminished regenerative capacity. Experimental studies show that selective elimination of senescent β-cells via senolytic therapies restores insulin secretion and improves glucose homeostasis in diabetic models, highlighting β-cell aging as a central driver of metabolic dysfunction in T2DM [59].

Biological aging biomarkers in T2DM

Biological aging in T2DM is reflected by molecular biomarkers that indicate premature cellular and genomic

Table 5. Mechanistic comparison of age-related and diabetic sarcopenia.

Mechanism	Normal aging	T2DM-associated	References
Insulin signaling	Gradual decline	Strong inhibition	[54]
Mitochondrial ROS	Moderate	Severe	[55]
Muscle stem cell activity	Reduced	Early depletion	[56]
Protein synthesis	Decreased	Impaired (via mTOR/AMPK imbalance)	[57]
Clinical effect	Sarcopenia	Sarcopenic obesity & frailty	[58]

Table 6. Telomere Biomarkers in Aging *vs.* T2DM.

Parameter	Normal Aging	T2DM Aging	References
Telomere length	Slow decline	Rapid shortening	[62]
Oxidative stress effect	Moderate	Severe, linked with hyperglycaemia	[63]
DDR activation	Low–moderate	High (↑p53, ↑γ-H2AX)	[64]
Functional outcome	Gradual senescence	Premature senescence, organ dysfunction	[65]

decline. These aging signatures correlate strongly with vascular complications, cognitive impairment, frailty, and β-cell dysfunction, demonstrating that diabetes is associated with accelerated biological aging rather than normal chronological aging [60].

Telomere-based biomarkers

Telomeres shorten naturally with age, but in T2DM this process is markedly accelerated due to chronic hyperglycemia, oxidative stress, and persistent inflammation. Leukocyte telomere length (LTL) is significantly shorter in individuals with T2DM compared with age-matched non-diabetic controls, indicating an advanced biological age. Accelerated telomere attrition is closely linked to poor glycemic control (HbA1c) and activates DNA damage response pathways (p53/p21), promoting early cellular senescence in β-cells, endothelial cells, and renal cells. Reduced telomerase (hTERT) activity further limits telomere repair, reinforcing genomic instability and premature aging in diabetes [61] (Table 6).

Epigenetic biomarkers

Epigenetic dysregulation in T2DM reflects accelerated biological aging, driven by chronic hyperglycemia and metabolic stress. Aberrant DNA methylation of key aging- and metabolism-related genes (*SIRT1*, *PPARGC1A*, *INS*, *GLUT4*) and persistent "metabolic memory" promote inflammation, mitochondrial dysfunction, and premature cellular senescence [66]. DNA methylation clocks consistently show an epigenetic age acceleration of ~3–6 years in individuals with T2DM, strongly linking diabetes to accelerated aging [67, 68].

Mitochondrial Biomarkers

Mitochondrial biomarkers provide direct evidence of accelerated mitochondrial aging in T2DM. Reduced mtDNA copy number, increased oxidative mtDNA damage, impaired mitochondrial dynamics (↓MFN1/2, ↑DRP1), and electron transport chain dysfunction lead to reduced ATP production and early metabolic failure [69, 70]. These changes parallel age-related mitochondrial decline but occur earlier and more severely in diabetes, contributing to sarcopenia, fatigue, and β-cell dysfunction (Table 7).

Biomarkers of oxidative stress and inflammation

Chronic low-grade inflammation (inflammaging) is a shared hallmark of physiological aging and T2DM, but in diabetes this process is accelerated and amplified, driving premature tissue dysfunction. Elevated circulating inflammatory markers—including IL-6, TNF-α, and CRP/hs-CRP—are strongly associated with diabetic vascular aging, endothelial dysfunction, and insulin resistance, indicating advanced biological age. Increased levels of MCP-1, ICAM-1, and VCAM-1 further reflect premature endothelial activation and immune cell recruitment, key features of vascular aging.

Oxidative stress biomarkers provide complementary evidence of accelerated molecular aging in T2DM. Elevated 8-hydroxy-2′-deoxyguanosine (8-OHdG), malondialdehyde (MDA), and 8-iso-prostaglandin F2α (8-iso-PGF2α) indicate excessive oxidative DNA and lipid damage, while reduced antioxidant enzyme activity (GPx, catalase, SOD) reflects diminished stress resilience—hallmarks of advanced biological aging [76].

Proteomic and metabolomic biomarkers of accelerated aging

Metabolomic and proteomic profiling provides strong molecular evidence that T2DM is associated with premature biological aging.

Metabolomic biomarkers in T2DM mirror aging-related metabolic decline, including accumulation of branched-chain amino acids (BCAAs), excessive AGEs, and reduced NAD$^+$ availability. Elevated BCAAs activate mTOR signaling, promote insulin resistance, and accelerate cellular senescence, while AGE accumulation drives vascular stiffness and chronic inflammation via RAGE–NF-κB signaling. A reduced NAD$^+$/NADH ratio impairs

Table 7. Mitochondrial aging markers in T2DM.

Mitochondrial marker	Aging	T2DM	References
mtDNA copy number	Mild decline	Strongly reduced	[71]
Mitochondrial ROS	Moderate	High	[72]
ATP output	Lower	Severely impaired	[73]
Fusion / fission	Dysregulated	Markedly disrupted	[74]
OXPHOS activity	Reduced	Major reduction	[75]

sirtuin activity, mitochondrial biogenesis, and DNA repair, reinforcing metabolic and cellular aging pathways [77]. Proteomic biomarkers reveal a pro-senescent systemic environment in T2DM. Increased expression of SASP proteins (IL-6, IL-8, MMP-3, PAI-1) sustains inflammaging and accelerates vascular aging. Concurrent reductions in anti-aging proteins such as Klotho, SIRT1, and FGF21 reflect impaired stress resistance, mitochondrial dysfunction, and metabolic inflexibility—features characteristic of advanced biological aging. Increased glycated albumin further indicates cumulative metabolic damage and loss of proteostasis, closely paralleling age-related protein dysfunction [78].

Therapeutic implications include

Calorie restriction and intermittent fasting

Calorie restriction (CR) and intermittent fasting are among the most extensively studied non-pharmacological interventions targeting conserved aging pathways and metabolic health. At the molecular level, CR suppresses mTOR signaling, enhances autophagy, and reduces oxidative stress and chronic inflammation while activating key energy-sensing pathways such as AMPK and sirtuins. These adaptations collectively lower nutrient-sensing signals, including insulin and insulin-like growth factor-1 (IGF-1), thereby promoting cellular maintenance and stress resistance. In the context of T2DM, CR improves insulin sensitivity, reduces ectopic lipid accumulation, attenuates adipose tissue inflammation, and mitigates metabolic dysfunctions associated with accelerated biological aging. Robust evidence from animal models demonstrates significant lifespan and healthspan extension with CR, whereas human clinical trials consistently report improvements in metabolic parameters and aging-related biomarkers. However, despite these promising findings, the long-term impact of CR and intermittent fasting on human longevity remains to be fully established, underscoring the need for large-scale, long-duration intervention studies [79].

Organized training

Organized or structured physical training represents a cornerstone intervention for targeting both metabolic dysfunction and biological aging in T2DM. At the molecular level, regular exercise enhances insulin signaling efficiency, promotes skeletal muscle hypertrophy, and stimulates mitochondrial biogenesis and function through upregulation of peroxisome PGC-1α. These adaptations improve oxidative capacity, reduce ROS production, and preserve proteostasis, thereby counteracting sarcopenia and age-related mitochondrial decline. Clinically, organized training significantly reduces insulin resistance, improves glycemic control, and attenuates frailty, directly addressing two fundamental hallmarks of aging—loss of proteostasis and mitochondrial dysfunction. Owing to its robust and reproducible benefits, structured exercise training is strongly recommended in clinical guidelines for the management of T2DM, with additional potential to slow metabolic aging and extend healthspan [80].

Circadian synchronization (time-restricted feeding, sleep scheduling)

Circadian synchronization through time-restricted feeding and sleep scheduling improves metabolic health by aligning the body's peripheral clocks—such as those in the liver and adipose tissue—with the central clock in the

Table 8. Pharmacological agents and their potential benefits in T2DM aging.

Intervention	Mechanism(s) relevant to aging	Potential benefits in T2DM aging	References
Metformin	Activates AMPK, inhibits mTOR signaling, reduces mitochondrial ROS, modulates epigenetic marks, promotes autophagy.	May reduce inflammaging, vascular aging, cancer risk signals; improves metabolic profile.	[85, 86]
SGLT2 inhibitors	Lowers glucotoxicity; improves cardiac/renal energetics; emerging data suggest reduced cellular senescence markers.	Reduces HF, CKD progression — major contributors to age-related morbidity; may attenuate senescence pathways.	[87, 88]
GLP-1 receptor agonists (GLP-1 RAs)	Weight loss, improved insulin sensitivity, anti-inflammatory effects; possible direct neuroprotective and multi-organ benefits.	By reducing obesity, inflammation and metabolic stress, may slow aging phenotypes; potential cognitive benefits reported.	[87, 89]
Senolytics (*e.g.*, dasatinib + quercetin)	Selectively eliminate senescent cells → reduce SASP; lower tissue inflammation.	Direct targeting of fundamental aging mechanism (cellular senescence) — could mitigate organ-level aging (kidney, vasculature) in T2DM.	[90, 91]
mTOR inhibitors / rapalogs (sirolimus / everolimus)	mTOR inhibition → promotes autophagy, cellular stress resistance.	Could attenuate nutrient-signaling driven aging processes; theoretical metabolic benefit if dosed carefully.	[92, 93]
NAD⁺ precursors (NR, NMN)	Restore NAD⁺ levels → support sirtuin activity, mitochondrial function, DNA repair.	Potential to improve mitochondrial dysfunction and metabolic resilience in T2DM.	[94]
Epigenetic therapies (HDAC/DNMT modulators, reprogramming approaches)	Reverse maladaptive epigenetic marks (age-related methylation), partial cellular reprogramming may reset aging signatures.	Could theoretically reverse aging signatures in metabolic tissues (pancreas, liver) — promising but experimental.	[95, 96]

brain [81]. This alignment enhances glucose homeostasis by optimizing insulin sensitivity and glucose metabolism, while also reducing metabolic inflammation by regulating inflammatory pathways that are sensitive to circadian timing [82]. By restricting food intake to the active phase and maintaining regular sleep patterns, these behaviors act as strong time cues that coordinate metabolic processes across tissues, promoting more efficient energy utilization and glycemic control. This synchronization not only supports better management of blood glucose levels but also helps mitigate the physiological stresses associated with aging [83]. In contrast, when circadian rhythms are misaligned—due to irregular eating schedules, late-night feeding, or disrupted sleep—there is a breakdown in this coordination, leading to impaired glucose tolerance, increased inflammation, and accelerated metabolic dysfunction. Thus, aligning feeding and activity windows with the body's natural circadian rhythm is a vital strategy to enhance metabolic health, prevent disease progression, and reduce age-related metabolic stress, as highlighted in studies summarized in Table 8 [84].

Future prospective

The focus of future research on T2DM must change from treating it as a metabolic disease to comprehending its intricate relationship to biological aging. According to geroscience-based models, metabolic degradation and aging are caused by processes such oxidative stress, cellular senescence, chronic inflammation, and mitochondrial malfunction. Thus, comprehensive strategies that incorporate lifestyle medicine, molecular aging biology, and endocrinology are crucial. Using indicators like mitochondrial indices, inflammatory signals, and epigenetic clocks, these models would enable the early identification of "accelerated aging phenotypes" in diabetic patients. Interventions that simultaneously enhance glycemic management and reduce the underlying aging process will be found thanks to this convergence of fields will improve the basis for gerotherapeutics in diabetes to be approved by regulators.

Conclusions

It is becoming more well acknowledged that T2DM is both a metabolic disease and a syndrome marked by accelerated biological aging. Evidence from molecular biology, clinical research, and biomarker studies has come together to show that pathways like oxidative stress, cellular senescence, mitochondrial failure, and chronic inflammation are common mechanisms that drive the course of diabetes and aging. A more thorough framework for explaining the early onset of problems, decreased physiological resilience, and increased vulnerability seen in diabetics is provided by an understanding of this reciprocal interaction. The management of diabetes in the future will be significantly impacted by this aging-centric viewpoint. Therapeutic approaches must address the deeper

biological mechanisms controlling aging itself rather than concentrating only on glycemic management. Metformin, GLP-1 agonists, SGLT2 inhibitors, senolytics, and NAD^+-enhancing agents are among the pharmacological strategies that have the potential to slow both metabolic decline and the aging trajectory when paired with lifestyle interventions like structured exercise, calorie restriction, and circadian alignment. Clinicians may be able to customize treatments based on biological age rather than chronological age by incorporating aging biomarkers into routine evaluation. All things considered, redefining T2DM as a metabolic disease of accelerated aging creates new opportunities for clinical translation and innovation in public health. Healthcare systems can transition from reactive disease control to proactive healthspan extension by connecting geroscience and diabetology. In addition to lowering long-term problems, this strategy may enhance the general quality of life and functional ability of people with T2DM.

In the end, this integrated approach might turn diabetes care into a field that emphasizes longevity, resilience, and prevention.

Declarations

Conflict of interest: The authors confirm that there are no known conflicts of interest.

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

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