

## Review Article

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# Senescent adipocytes and type 2 diabetes – current knowledge and perspective concepts

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**Abstract:** Among civilization diseases, the number of individuals suffering from type 2 diabetes (T2DM) is expected to increase to more than a billion in less than 20 years, which is associated with, e.g., populational aging, poor diet, sedentary lifestyle, genetic predispositions, and immunological factors. T2DM affects many organs and is characterized by insulin resistance, high glucose levels, and adipocyte dysfunction, which are related to senescence. Although this type of cellular aging has beneficial biological functions, it can also act unfavorable since senescent adipocytes resist

apoptosis, enhance cytokine secretion, downregulate cell identity genes, and acquire the senescence-associated secretory phenotype that renders a more oxidative environment. Opposing T2DM is possible via a wide variety of senotherapies, including senolytics and senomorphics; nevertheless, further research is advised to expand therapeutic possibilities and benefits. Consequences that ought to be deeply researched include secretory phenotype, chronic inflammation, increasing insulin resistance, as well as impairment of adipogenesis and functioning of adipocyte cells. Herein, despite reviewing T2DM and fat tissue senescence, we summarized the latest adipocyte-related anti-diabetes solutions and suggested further research directions.

**Keywords:** diabetes, T2DM, insulin resistance, senescence, adipocytes

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## Introduction

Global Burden of Diseases (GBD) reports that about 529 million people have diabetes, which is expected to increase to 1.3 billion by 2050 [1]. This conforms with the 10th Diabetes Atlas of the International Diabetes Federation (IDF), which indicated that 537 million people had diabetes in 2021, and the number might reach 643 million by 2030 or 783 million by 2045 [2]. Relative to IDF data from 2021, the comparative prevalence of diabetes in adults (20–79 years) for the year 2045 is expected to reach 20.4% (from 18.1%) in the Middle East and North Africa, 14.2% (from 11.9%) in North America and Caribbean region, 11.5% (from 9.9%) in Western Pacific region, 11.3% (from 10.0%) in South-East Asia, 9.8% (from 8.2%) in South and Central America, 8.7% (from 7.0%) in Europe, and 5.6% (from 5.3%) in Sub-Saharan Africa [3]. Diabetes is characterized by chronically elevated blood glucose levels (hyperglycemia) due to insulin resistance (type 2) or insufficient insulin production via auto-immune response directed at  $\beta$ -cells of the pancreas (type 1). Type 1 accounts only for 5–10% of all diabetic cases, whereas type 2 for 90–95% of them. Other types are gestational diabetes and maturity-onset diabetes of the young (MODY).

The former occurs during pregnancy and disappears after childbirth; however, developing type 2 diabetes (T2DM) later in life is forecasted. MODY is a rare form of disease that stems from hereditary factors or genetic variations and develops before the age of 25 among non-obese patients [4]. T2DM progresses very slowly, with symptoms being mild and delaying diagnosis. Patients with T2DM are more prone to blindness, kidney failure, heart attacks, stroke, and lower limb amputation [4–7]. The number of individuals affected by diabetes is still rising, which is associated with, e.g., populational aging, poor diet, lack of physical activity, as well as some genetic predispositions such as ones in gene *FTO* related to obesity or *IRS1* related to insulin resistance [6]. More factors are still being discovered; the awareness of various complex mechanisms at the root of diabetes would improve diagnosis and treatment to ensure a healthier life for patients.

A plethora of diabetes research has been performed and discussed, yielding various pharmacological and non-pharmacological treatment approaches. The latter considers caloric restriction and physical exercise to improve mitochondrial function and insulin efficacy [8,9]. Antihyperglycemic drugs can differ according to an individual's needs and have diverse mechanisms of action, enabling the division into classes such as biguanides, sulfonylureas, glinides, glitazones, dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter-2 inhibitors,  $\alpha$ -glucosidase inhibitors, or glucagon-like peptide-1 receptor agonists [5,8]. Current research provides insight into how premature senescence and dysfunction of mature adipocytes impact the human body or how it corresponds to T2DM. However, up to now, no experiments have compared the senescence of fat cells in multiple organs and how removing them may impact various patients. Although the studies are performed thoroughly and incorporate animal models or mature human adipose cells, they are mainly limited to the pancreas and liver [10,11]. There are still many questions to be asked. What are the differences between senescence in various tissues affected by T2DM? Do some medications work better than others in controlling senescence? How can removing senescent adipocytes from different organs impact diabetes? This review aims to provide current knowledge on T2DM and senescent fat cells; it also intends to summarize the latest adipocyte-related anti-diabetes solutions and suggest further research directions.

## General knowledge about T2DM

T2DM, previously referred to as adult-onset diabetes, is one of the most common chronic and heterogeneous metabolic

disorders and the most common type of diabetes in the general population [12]. The correlation between aging and T2DM is supported by various statistical data [13,14]. The GBD study from 2021 established that diabetes is particularly prevalent among adults aged 65 and older, with a global prevalence of about 20% or even 24.4% among those aged 75–79. In contrast, total diabetes prevalence was less than 1% among those younger than 20 years [1]. Aging increases the risk of metabolic disorders such as obesity and cardiovascular disease due to hormonal changes, sedentary habits, lifelong exposure to environmental factors, and genetics that influence fat metabolism, insulin sensitivity, and energy expenditure [15,16]. Unfortunately, around 46% of people suffering from T2DM are undiagnosed due to the difficulty in identifying early mild symptoms linked with this disease [17]. When left untreated or as a result of chronic hyperglycemia, patients diagnosed with T2DM can suffer from several secondary diseases that are seemingly unrelated to insulin resistance and pancreas impairment. Examples include coronary and vascular diseases (strokes and heart failure), lung diseases, depression, epilepsy, kidney failure, neuropathies, and diabetic foot, with the last three being the most common comorbidities [18]. Kidney failure is caused by uncontrolled glycemia levels, reduced estimated glomerular filtration rate, and albuminuria (high albumin level in urine). It can lead to death if left untreated, emphasizing the need for a kidney transplant [19]. Diabetic neuropathy is a long-term comorbidity caused by chronically high blood sugar levels and affects more than 25% of the T2DM patients. The main issues of this condition are pricking sensations, numbness, and the presence of neuropathic ulcers [20]. The most common type of neuropathy in T2DM is the so-called diabetic foot that is manifested by infection and tissue destruction, with the presence of pus, ulcers, swelling, and redness of the skin of the lower limbs. Unfortunately, most diabetic foot cases end up with limb amputation to ensure the patient's survival [21].

Several lifestyle factors can contribute to the development of T2DM. Factors such as high body mass (and consequently a high body mass index), active smoking, poor diet, lack of sleep, and a sedentary lifestyle can have a significant impact on the instability of blood sugar levels, leading to the development of T2DM [17]. Affected individuals suffer from insulin resistance or intolerance, meaning that there is a lack of response to this hormone from tissues or even the whole organism [12,22]. It is essential to distinguish diabetes from prediabetes. The latter describes a high glucose level, but not as high as in diabetes – dysfunction in the action of both fasting glucose ( $>100$  mg/dL) and glucose tolerance ( $>140$  mg/dL) is noted. In diabetes, values exceed  $>126$  and  $>200$  mg/dL, respectively [17]. The glucose level

should be adjusted to its homeostatic state by insulin, but since the body becomes resistant to it, the presence of glucose in the bloodstream persistently signals pancreatic  $\beta$ -cells to produce more insulin, weakening them and rendering the inability to produce enough insulin [12,22]. T2DM not only impacts the pancreas but also has repercussions on the liver, kidneys, small intestine, and adipose tissue (AT), all of which play a role in glucose metabolism [12]. The basics of T2DM are presented in Figure 1.

## Molecular and genetic basis of T2DM

T2DM is characterized by the deterioration of pancreatic  $\beta$ -cells, which are responsible for the synthesis of insulin from proinsulin originating from preproinsulin. Alongside the alterations within the pancreatic islets, the leading causes of insulin resistance are chronic inflammation (via elevated levels of immune factors such as IL-6, C-reactive protein, plasminogen activator inhibitor, and tumor necrosis factor) and obesity that lead to AT dysfunction. Due to insulin resistance, cells are in a permanent gluconeogenesis state even when the insulin level is high. Followingly, impaired insulin secretion results in elevated blood glucose levels (hyperglycemia), peripheral glucose uptake, and increased hepatic glucose production [23–25]. Some studies showed the correlation between T2DM and heritability. The set of T2DM-related genes is dependent on population or family disease history [26]. During various genome-wide association studies, a few candidate genes were identified to have a role in T2DM development. These include genes such as fat mass and obesity-associated (*FTO*), peroxisome proliferator-activated receptor gamma (*PPARG*), and insulin receptor substrate 1 (*IRS1*) [26,27].

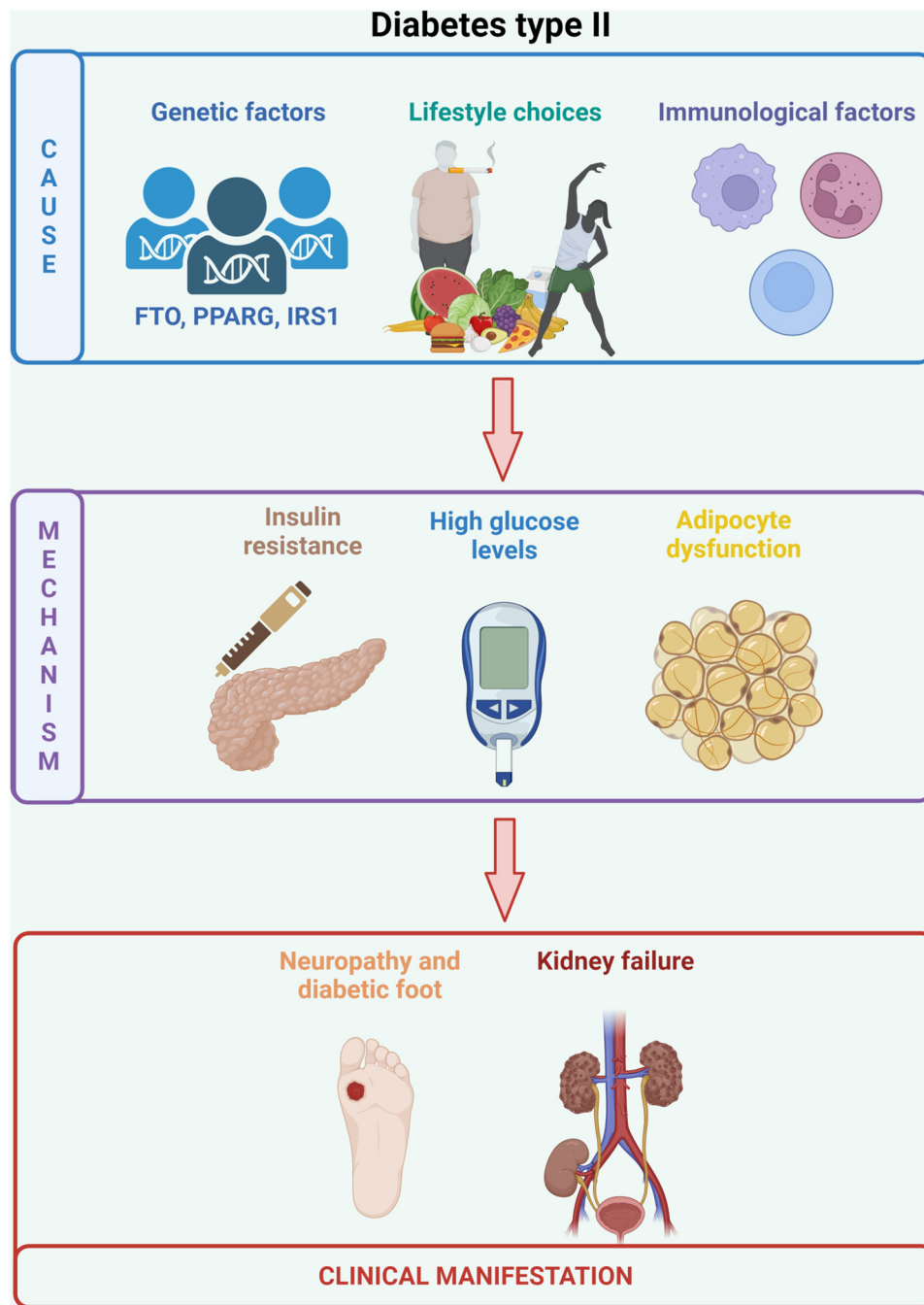
*FTO* is strongly connected with obesity and high body mass index [28,29]. It is responsible for regulating lipolysis, demethylation of nucleic acids, and regulation of energy deposit. Unfortunately, the molecular mechanism of the impact of *FTO* in T2DM is still unknown. However, the presence of polymorphisms such as rs9940128 and rs8050136 can increase the morbidity of diabetes [28,30]. *PPARG* was extensively investigated in T2DM; this gene is widely expressed in adipocyte cells and regulates glucose regulation, lipid metabolism, proliferation, and cellular differentiation [31]. Elevated risk of T2DM is associated with polymorphisms such as rs17036160, rs1797912, and rs1801282, the presence of which varies in population [26,27]. *IRS1* participates in intracellular signaling pathways related to insulin, regulating the

level of this hormone. It is also partially responsible for the proper functioning of the digestive system [27,32]. T2DM-related polymorphisms identified globally are rs4675095 and rs2943634 [27].

Other examples of genes linked with the genetic predisposition to T2DM are *TCF7L2*, *ABCC8*, and *HNF1A* [27,33]. Research shows that they have a great impact on the pancreas and insulin sensitivity of  $\beta$ -cells, which is the most important aspect for maintaining proper glucose levels [33]. *TCF7L2* encodes the transcription factor crucial for the correct functioning of signaling pathways, mainly the Wnt/ $\beta$ -catenin pathway. Polymorphisms such as rs7903146 and rs12255372 have a documented influence on T2DM morbidity [34]. *ABCC8* encodes the receptor responsible for the regulation of insulin secretion. Polymorphisms rs757110 and rs1799854 were linked with changes in receptor sensitivity to insulin, which impaired the mechanism of lowering blood glucose [35]. Finally, *HNF1A* is involved in pancreatic  $\beta$ -cell maturation; its polymorphisms rs1169288 and rs2464196 were associated with dysregulation of glucose homeostasis, which may entail T2DM [36]. It should be noted that the above-mentioned genes are not disease markers diagnostically utilized on a daily basis.

## Adipocytes in T2DM

Made up of fat cells known as adipocytes, the AT functions as a metabolic, immune, and endocrine organ. Depending on the mitochondria density and lipid droplet size, AT can be classified as white (WAT) or brown (BAT). The third type is beige adipose tissue (BeAT) which poses characteristics of WAT and BAT, which can be a result of *de novo* differentiation of specific precursor cells or white-to-brown transdifferentiation [37,38]. The point of adipogenesis (the development of adipocytes from fibroblast-like progenitor cells) is the production of adipocytes in a two-stage manner: creating preadipocytes and then functional mature adipocytes. This process is conducted in the presence of PPAR $\gamma$ , bone morphogenetic proteins 2 and 4 (BMP2 and BMP4), and hormones such as insulin, glucagon, cortisol, and growth hormone. AT is responsible for maintaining proper glucose levels and storing energy through triacylglycerides and glycogen. Those mechanisms are regulated mainly by glucose transporters (GLUT), especially GLUT4, and to a lesser extent by GLUT1, GLUT8, and GLUT10 [39,40]. The underexpression of GLUT4 in T2DM renders hyperglycemia, which is a main symptom of this disease [39]. GLUT1 stays unaffected in diabetes, and there is no scientific data proving the correlation between the impairment of GLUT8, GLUT10, and T2DM [40].



**Figure 1:** Causes of T2DM and some of the consequences connected to the disease. T2DM causation is an overlap of genetic predispositions (related to genes such as *FTO*, *IRS1*, and *PPARG*, but also *TCF7L2*, *ABCC8*, and *HNF1A*), lifestyle (e.g., high body mass index, active smoking, poor diet, and lack of sleep), and immunological factors (e.g., interleukin-6 [IL-6], C-reactive protein, plasminogen activator inhibitor, and tumor necrosis factor). T2DM is characterized by insulin resistance, high glucose levels (fasting glucose >126 mg/dL and glucose tolerance >200 mg/dL), and adipocyte dysfunction (related to extensive hypertrophy, hyperplasia, inflammation, and senescence). The most common clinical manifestations include neuropathies and kidney failure, but patients may also suffer from coronary and vascular diseases, lung diseases, depression, or epilepsy. Figure created using BioRender.

Glucose transporters are also expressed in other T2DM-associated organs, such as the liver or muscles.

Not only does fat tissue produce and secrete hormones termed adipokines (e.g., leptin, adiponectin, acylation-stimulating

protein, and resistin), but it is also responsive to hormones and metabolic compounds such as cortisol, growth hormone, and insulin [41,42]. When the functioning of adipokines is impaired, it can cause disruptions in fat storage and energy metabolism,



which are connected to the development of metabolic dysfunction and T2DM. In addition, changes in adipokine production and secretion from AT have been linked to the development of insulin resistance, a hallmark of T2DM [43]. The latest data show that AT contributes to immune response since it can release immune system modulators such as cytokines and blood clotting factors [44]. Dysregulation of cytokine signaling and the presence of chronic inflammation due to impaired immune cell release may lead to the onset of metabolic dysfunctions such as insulin resistance and decreased glucose tolerance [45]. In T2DM, fat tissue develops insulin resistance, which means it is no longer as sensitive to the insulin signal to store rather than release energy.

Considering the development of AT, it is also crucial to mention the vascularization process, which is controlled by vascular endothelial growth factor that regulates oxygen levels and the transport of nutrients or hormones [46,47]. In addition, the nutrition state dictates AT remodeling that can be both correct and pathological. For the latter, during conditions such as obesity, adipocytes adapt to different metabolic states and change their morphology, with major changes considering their increased size (hypertrophy) or number (hyperplasia). When these changes are critically prevalent and intolerable, the dysfunction may lead to insulin resistance within AT but also in the liver, muscles, and pancreas. The so-called AT overflow hypothesis suggests that when adipocytes enlarge, they may eventually be unable to store lipids as effectively, which causes fatty acid leakage into tissues such as the liver or muscle and promotes insulin resistance [48]. Moreover, Monickaraj et al. observed that adipocyte hypertrophy in visceral and subcutaneous AT is related to shortened telomeres, oxidative stress, hypoadiponectinemia, as well as poor glycemic and lipid control among obese individuals and T2DM patients [49]. Dysfunctional adipocytes secrete and synthesize cytokines, such as IL-6, tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), and monocyte chemoattractant protein 1 (MCP-1), that cause inflammation of AT, ultimately contributing to cellular aging, known as cell senescence [39,49,50]. Senescent cells release chemicals that can cause neighboring cells to follow the cell cycle arrest, inducing a chain reaction during which the available adipocytes undergo hypertrophy if there is an insufficient amount of preadipocytes to make new fat cells [7,51].

## Senescence of adipocytes

Senescence is a topic initially described by Hayflick and Moorhead in 1961 [52]. This irreversible cell cycle arrest can be triggered by excessive intracellular or extracellular

events such as mitotic stress, DNA damage, telomere erosion, mitochondrial dysfunction, oxidative stress, inflammation, mechanical stress, or carcinogens [53]. Senescence intends to limit the proliferation of damaged cells, eliminate harmful factors, and prevent potential malignant transformation [54]. Senescent cells are characterized by changes in nuclear structure, enlargement with flattened morphology, formation of foci expressing histone H2A $\gamma$ , and increased levels of cell cycle inhibitors such as p16Ink4 and p21Cip1 [54,55]. Another feature is the increased activity of senescence-associated beta-galactosidase (SA- $\beta$ -gal) responsible for breaking beta-galactosides. This hydrolase is typically active at pH 4, but its functionality in senescent cells at pH 6 renders cell cycle arrest and lysosomal mass increase. Traditional SA- $\beta$ -gal staining cannot distinguish between cell types in complex tissues. To confidently identify senescent cells, it is recommended to combine SA- $\beta$ -gal staining with additional indicators such as  $\gamma$ H2AX, p16, p53, p21, and senescence-associated heterochromatin foci [56,57].

Although not entirely unraveled, one can presume that the senescence of a specific type of AT may be a result of different molecular phenomena that reflect its main biological function, i.e., energy storage in WAT or non-shivering thermogenesis in BAT and BeAT. One of the key regulators of cellular senescence is the mitochondrion, of which dysfunction entails reduced respiratory capacity and membrane potential, mitochondrial DNA depletion, as well as increased production of reactive oxygen species. Interestingly, loss of mitochondrial homeostasis can both trigger and result from cellular senescence [58,59]. However, it is worth noting that white, brown, and beige adipocytes have distinct mitochondrial plasticity, function, and abundance, with the latter being lower in white fat cells relative to the other two types [60,61]. Mitochondria in WAT induce lipogenesis, lipolysis, adipocyte differentiation, and fatty acid oxidation. The same organelles in BAT have increased density of cristae, i.e., folds within the inner mitochondrial membrane and uniquely express UCP1 protein that uncouples oxidative phosphorylation from adenosine triphosphate production, rendering considerable thermogenic power [58,62]. Beige adipocytes have mitochondria similar to those of brown adipocytes as they express UCP1 and utilize substrates such as lipids and carbohydrates [63]. Comparably important regulators appear to be lipid droplets that are large unilocular in adipocytes of WAT or small multilocular in those of BAT and BeAT. Not only lipids are known regulators of senescence [64] but also aging induces lipid accumulation that differs between aged WAT and aged BAT, with the former presenting global accumulation of lipids while the latter accumulating only bis(monoacylglycerol)phosphate and diacylglycerol [65]. Ectopic lipid accumulation in hypertrophic adipocytes entails the recruitment

of immune cells such as M1 macrophages, rendering AT inflammation. This dysregulates adipokine production, e.g., there is an overproduction of pro-inflammatory cytokines such as TNF $\alpha$  and MCP-1, as well as a reduction of anti-inflammatory factors such as adiponectin [66]. BAT is characterized by lower levels of pro-inflammatory cytokines than WAT, which presumably reflects a more anti-inflammatory phenotype of immune cells residing in brown AT [67]. Coupled with the intrinsic ability of brown adipocytes to diminish the inflammatory profile of macrophages, it appears that BAT may be less prone to inflammation [68]. As the body ages, the number and volume of adipocytes decrease in BAT but increase in WAT, with the latter undergoing redistribution in favor of visceral rather than subcutaneous fat mass [69]. It has been suggested that aging-related metabolic dysfunction presumably originates from a deficiency of subcutaneous AT [70], which is complemented by the fact that this tissue is beneficial for metabolism, unlike visceral AT expansion, which is considered detrimental [71]. Even though it appears that redistribution of depots in inflammable WAT precedes changes in less prevalent BAT, their multifaceted and intertwined relation cannot be omitted, e.g., individuals with lower BAT levels are prone to excessive WAT accumulation [72], as well as increased levels of pro-inflammatory cytokines suppress UCP1 expression and repress BAT thermogenesis in the aging process [73].

Adipocytes are highly susceptible to cellular aging that is accompanied by the development of low-grade systemic inflammation, so-called inflammaging, rendering a situation where senescent cells promote inflammation in the environment, and at the same time, pro-inflammatory cytokines can further promote the same phenomenon in previously unaffected surrounding cells [7,70,74,75]. When the extent becomes intolerable, the chain reaction involving cellular dysfunction, DNA damage, chronic inflammation, and adipogenesis impairment leads to insulin resistance [76]. Impairment of adipogenesis has consequences in high levels of zinc finger matrin-type 3, p53, and p16, inhibiting cell division and inducing senescence. Moreover, low levels of PPAR $\gamma$  and stemness are observed among immature fat cells [7,77]. All of the aspects discussed in this paragraph have been confirmed using murine models of obesity [76,78].

## Senescence and its role in T2DM

Although senescence is predominantly considered beneficial, it can act unfavorable since senescent cells are resistant

to apoptosis due to the upregulation of signaling pathways such as BCL-2/BCL-XL, HIF-1 $\alpha$ , PI3K/AKT, and p53/p21/serpins [10,57]. In addition to downregulating cell identity genes [10], senescent cells can enhance the secretion of pro-inflammatory cytokines (such as IL-6 or 8) and activate the nuclear factor-kappa B (NF- $\kappa$ B), acquiring the senescence-associated secretory phenotype (SASP) and rendering a more oxidative cellular environment [11,55,79]. SASP is characterized by the secretion of soluble pro-inflammatory factors such as ILs and chemokines, growth factors, soluble or shed receptors and ligands, nonprotein factors such as prostaglandin E2 and nitric oxide, as well as extracellular matrix components such as fibronectin and collagens [80]. Their secretion causes cell death, production of reactive oxygen species, immune cell infiltration, and tissue remodeling [81,82]. Interestingly, various stressors or time course of senescence progression may elicit a different secretory profile even in the same cell type [83,84], although some pro-inflammatory cytokines (IL-1, IL-6, and IL-8) and chemokines (CCL2) are common SASP factors [76]. In general, the accumulation of senescent cells represents a favorable environment for the development of inflammatory diseases associated with aging [85].

Of the foremost issues related to senescence is the lack of a singular marker that recognizes this state in an unequivocal manner. Typically, multiple biomarkers are used in the analysis of senescence-related hallmarks such as cell cycle arrest (p16Ink4a, p21Cip1, p53, and Rb), secretory phenotype factors (PAI-1, IL-6, IL-1 $\alpha$ , TNF $\alpha$ , and CCL3-5), nuclear reorganization or DNA damage (P53BP1, LMNB1, and  $\gamma$ H2AX), or changes in lysosomal compartment (SA- $\beta$ -gal and lipofuscin) [10,86]. Characteristics of senescent cells allow them to promote diabetes and metabolic diseases. They promote T2DM by impacting pancreatic  $\beta$ -cells, SASP-mediated tissue damage, and their involvement in AT dysfunction [87,88]. Moreover, fat accumulation in hepatocytes can promote telomere shortening and DNA damage, which in turn can induce hepatocyte senescence that is correlated with liver fibrosis and diabetes [89,90]. Cellular senescence has been noted in the pancreatic cells as well as adipocytes. For the latter, the senescence may occur in preadipocytes or mature cells, and it is associated with SA- $\beta$ -gal staining, enlargement of nucleus and cell, loss of nuclear high mobility group box 1 protein, as well as high expression of cyclin D1, p21Cip1, and p16Ink4a [91,92]. Moreover, the secretion of SASP-related markers by adipocytes inhibited adipogenesis and induced insulin resistance [85]. On the other hand, senescence in pancreatic  $\beta$ -cells was reported in a high-fat diet model, suggesting its influence on T2DM pathogenesis [93,94].

Interestingly, while cellular senescence is reported to contribute to the pathogenesis of T2DM, the microenvironment

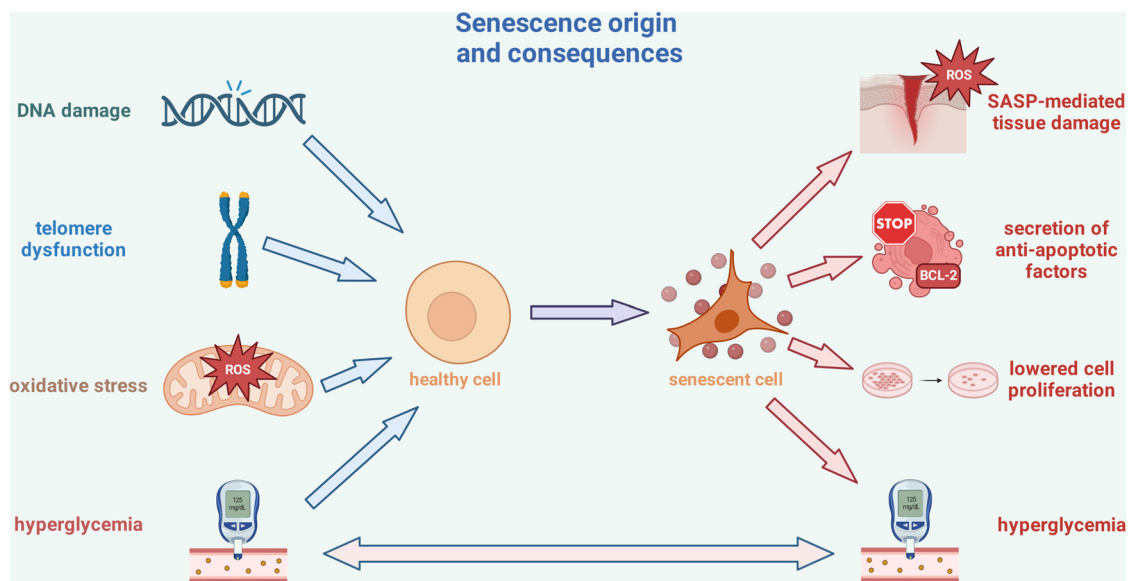
also plays a role in senescence induction, which can be perceived as a positive pathogenic loop [78,87]. One of the examples of how a diabetic environment promotes senescence concerns high glucose levels that are able to push premature senescence in different cells, e.g., endothelial cells, fibroblasts, or adipose-derived stem cells. The exact mechanism is not fully understood, but mitochondrial dysfunctions are pointed out [95,96]. Hyperglycemia and hyperinsulinemia (two characteristic aspects of T2DM) lead to cellular aging in the pancreas and other essential tissues (e.g., the liver), contributing to the further progression of the disease and related complications [10]. Equally critical are the advanced glycation end-products (AGEs), which are lipids or proteins that end up glycated when combined with sugars. AGEs alter protein structures and functions within the extracellular matrix, affecting matrix–matrix and matrix–cell interactions, thus causing various microvascular and macrovascular complications. In T2DM, the expanded arrangement of AGEs stimulates endothelial cell senescence [97,98]. Finally, alterations in the cellular pathway incorporating growth hormone and insulin-like growth factor (particularly IGF-1 and IGF binding protein-3 or -5) might propagate the senescent signals to other cells [87]. The above aspects prove that ongoing efforts to provide

anti-senescence treatment for T2DM patients are valid and should be further pursued. Senescence causes and consequences are summarized in Figure 2.

## Crucial discoveries and aspects yet to be investigated

Studies conducted over the years have shown that hyperglycemia can cause senescence through several phenomena, such as fibrosis, inflammation, and p53/p21 signaling [99,100]. Opposing T2DM and its consequences is possible via a wide variety of senotherapies, including senolytics that selectively kill the senescent cells and senomorphics that are able to impact SASP pathways without killing these cells [10,101,102]. Research on humans and utilizing animal models provided more insights regarding the aforementioned therapeutic possibilities in T2DM and related senescent fat cells.

Animal model-based experiments revealed that removing senescent cells improves blood glucose levels and decreases diabetic complications [94,103,104]. One of the medications that have been used in T2DM for decades is metformin, which



**Figure 2:** Causes of senescence and its consequences. Excessive intracellular and extracellular phenomena such as DNA damage, telomere erosion, mitotic or mechanical stress, mitochondrial dysfunction, oxidative stress, and inflammation can trigger irreversible cycle arrest of healthy cells. Senescent cells are characterized by, e.g., morphological changes, increased levels of cell cycle inhibitors (e.g., p16Ink4 and p21Cip1), upregulation of anti-apoptotic signaling pathways (e.g., BCL-2/BCL-XL and PI3K/AKT), overactivity of SA- $\beta$ -gal, and acquisition of senescence-associated secretory phenotype that render more oxidative cellular environment. The senescence of adipocytes is accompanied by an inflammatory environment that further promotes cellular aging in previously unaffected surrounding cells. When the extent becomes intolerable, the chain reaction involving cellular dysfunction, DNA damage, chronic inflammation, and adipogenesis impairment leads to insulin resistance. Interestingly, while cellular senescence is reported to contribute to the pathogenesis of T2DM, hyperglycemia also plays a role in senescence induction, which can be perceived as a positive pathogenic loop. Figure created using BioRender. ROS – Reactive oxygen species. BCL-2 – B-cell lymphoma 2.

works by inhibiting hepatic gluconeogenesis but may possess anti-aging properties and senomorphic effects [105,106]. Experiments conducted on mice showed that the said drug reduces senescence initiation and inhibits acute state in mesenchymal stem cells [107,108]. The murine model of T2DM led to the discovery that consuming too many calories causes oxidative stress in the AT, which in turn contributed to the emergence of senescence-related markers such as p53, SA- $\beta$ -gal, and elevated levels of pro-inflammatory cytokines [109]. Another experiment proved that elevated DNA damage and cellular senescence in AT contribute to the development of diabetes or glucose intolerance [110]. Finally, the degree of adipose cell senescence was positively correlated with whole-body insulin resistance and adipose cell size [11].

Considering human clinical trials, they have been carried out on both diabetics and non-diabetics. In addition to senolytics and senomorphics, patients are offered bariatric surgery that is classified as one of the caloric restriction mimetics [111,112], which are known to limit senoinflammation and extend lifespan via aging-related pathways [113,114]. One example of *ex vivo* research focused on AT in which macrophage infiltration and phenotype were estimated [115], whereas a different study described fibrosis as a new pathological factor in AT [116]. Another clinical trial evaluated the adaptation of human gut microbiota to energetic restriction in obesity and related comorbidities [117]. Chronic exposure to hyperinsulinemia can lead to cell cycle progression, increase in DNA content, activation of senescence, and inflammatory SASPs, which trigger human AT inflammation [10,92]. Senolytics such as dasatinib and quercetin are known to reduce the quantity of human senescent cells; in one study, they significantly decreased senescent cell burden, whereas, in the second, they alleviated physical dysfunction in idiopathic pulmonary fibrosis [91,118]. The activity of SA- $\beta$ -gal in AT was positively correlated

with serum leptin, insulin resistance markers, and increased abdominal fat [116], all of which were reduced following the metformin treatment [94,119,120].

Some clinical trials utilizing senotherapy are ongoing. One such study investigates how a senotherapeutic agent known as fisetin affects AT-derived mesenchymal stem/stromal cell function, kidney function, inflammation markers, and physical function of patients with advanced chronic kidney disease, particularly diabetic kidney disease [121]. Another trial evaluates the safety, tolerance, and pharmacokinetics of a single intravitreal injection of foselutoclax (also known as UBX1325, a potent Bcl-xL inhibitor that promotes apoptosis in senescent cells) in patients with diabetic macular edema or neovascular age-related macular degeneration [122]. There are also clinical trials on senotherapeutics outside the scope of diabetes, e.g., investigating Alzheimer's disease (AD) or bone metabolism. For example, a phase II clinical trial assesses the safety, feasibility, and effectiveness of dasatinib and quercetin in AD. It is a multi-site, randomized, double-blind, placebo-controlled study focusing on older adults with amnesic mild cognitive impairment and early-stage AD patients who have neurofibrillary tangles confirmed by positron emission tomography [123]. Another study determines whether fisetin, dasatinib, and quercetin can decrease senescent cell burden and alter markers of bone resorption or formation among elderly women [124].

Further research is still advised to expand therapeutic possibilities and benefits. First, although metformin has senomorphic activity, there was no research focused on circulating SASP before and after administration, which could predict who would benefit the most from therapy and constitute a groundwork for personalized care among patients [10,125]. Furthermore, although plenty of studies show the impact of cell culture in high glucose levels on promoting senescence, no unifying model explains all

**Table 1:** Key findings on senescence and type 2 diabetes with aspects worth investigating in the future

Crucial discoveries	Aspects worth investigating in the future
1. A diabetic environment can promote cellular senescence, e.g., via high glucose levels [95,96], AGEs [97,98], and growth hormone/IGF signaling pathway [87].	1. Measurement of circulating SASP before and after administration to ensure the best therapy [10,125].
2. Cellular senescence in adipose tissue has been implicated in developing diabetes and glucose intolerance [11,110].	2. Research on a unifying model explaining all forms of hyperglycemia-associated senescence [126–129].
3. Chronic exposure to hyperinsulinemia induces cell cycle progression but not mitosis, leading to senescence [10,92].	3. Senescence differences in individual tissues among diabetics [10].
4. SA- $\beta$ -gal activity in adipose tissue positively correlates with serum leptin, markers for insulin resistance, and increased abdominal fat [116]. Other senescence markers than SA- $\beta$ -gal are also known, e.g., p53 [109].	4. The outcome of removing senescent cells from individual organs [10].
5. Several senotherapies can be divided into senolytics and senomorphics [10,101,102]. Metformin is a well-known example of the latter [106,107,119].	5. In-depth analysis of exercise and Mediterranean diet regarding senotherapies in T2DM [130,131].



forms of hyperglycemia-associated senescence. It is due to the fact that hyperglycemia can promote senescence through multiple pathways [126–129]. Future actions should evaluate the difference in senescence between tissues among diabetics and the outcome of removing senescent cells from specific organs [10]. Altering the lifestyle also plays a crucial role in T2DM and senescence; exercise proves to be an effective way of reducing the risks of cellular aging. Moreover, the Mediterranean diet has been associated with a decrease in senescence hallmarks and should be further analyzed in terms of T2DM-related senotherapy (Table 1) [130,131]. Further delineating the pathological effects of senescence is of paramount importance [132]. Crucial discoveries made over the years and aspects yet to be investigated are collected in Table 1.

## Summary

T2DM is one of the major metabolic diseases of the general population, necessitating the expansion of therapeutic possibilities. The impairment of pancreatic  $\beta$ -cells, hyperglycemia, and systemic inflammation preventing insulin signaling are essential aspects that should be considered in T2DM therapy. Insulin resistance and adipocyte remodeling due to overnutrition can lead to the senescence of adipocytes. Consequences that ought to be deeply researched include SASP phenotype, chronic inflammation, increasing insulin resistance, as well as impairment of adipogenesis and functioning of adipocyte cells.

The primary approach to opposing senescent adipocytes is senotherapy, which includes senolytics and SASP-inhibiting medications. Current therapeutic methods concentrating on glucose level, insulin resistance, and senescence should be complemented with approaches focusing on immunological, adipocytic, and signaling aspects. There is still a lot to uncover in this field, especially regarding senescence and elimination of adipocytes with SASP phenotype, as well as their correlation with T2DM. The course of treatment involving senolytics and SASP inhibitors needs a personalized approach.

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