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Review

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Adenosine Monophosphate-Activated Protein Kinase Activation and Mammalian Target of Rapamycin Complex 1 Inhibition: A Mechanistic Rationale for Anti-Aging Therapy in Type 2 Diabetes

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Abstract

Aging is a complicated biological process that induces a decline in the human organs' structure and function and elevates the risks of aging-related diseases such as Alzheimer's disease (AD) and type 2 diabetes. Type 2 diabetes accelerates all clinical manifestations of aging. Metabolic disorders in type 2 diabetes are unfavorably associated with all hallmarks of aging, such as inflammation and mitochondrial dysfunction. Adenosine monophosphate-activated protein kinase (AMPK) and the mammalian target of rapamycin complex 1 (mTORC1) are key players in cellular metabolism, and AMPK activation and mTORC1 inhibition improve all hallmarks of aging. AMPK activation and mTORC1 inhibition are favorably associated with diabetic complications. Nutritional interventions, such as caloric restriction, resveratrol, and astaxanthin, have AMPK-activating and mTORC1-inhibitory effects and improve metabolic abnormalities in type 2 diabetes. Anti-diabetic drugs, metformin, sodium-glucose cotransporter-2 inhibitors, and glucagon-like peptide 1 receptor agonists have been reported to have AMPK-activating and mTORC1-inhibiting effects and show prevention of aging-related diseases such as cardiovascular disease. The therapeutic interventions that activate AMPK and inhibit mTORC1 may be optimal treatments for type 2 diabetes from the perspective of anti-aging medicine. Furthermore, senolytics may be a promising, direct anti-aging therapeutic strategy specifically for type 2 diabetes and its complications.

Keywords: Aging; AMP-activated protein kinase; Mammalian target of rapamycin complex 1; Metformin; Type 2 diabetes

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Introduction

Aging is a complicated biological process involving the deterioration of the structure and function of human organs, which increases the risks of aging-related diseases, such as Alzheimer's disease (AD), cardiovascular diseases (CVDs), and type 2 diabetes [1]. Recent studies have identified several key hallmarks of aging [2, 3]. These include oxidative stress [4], inflammation [5], advanced glycation end products (AGEs) [6], dysbiosis [7, 8], DNA damage [9, 10], telomere shortening [11], epigenetic alterations [12, 13], loss of protein balance [14], deregulated nutrient-sensing [15], altered intercellular communication [16, 17], mitochondrial dysfunction [18, 19], loss of nicotinamide adenine dinucleotide (NAD^+) [20, 21], cellular senescence [22], stem cell exhaustion [23, 24], and impaired macroautophagy [25, 26].

Type 2 diabetes [27], aging [28], and related conditions such as frailty [29] and sarcopenia [30] are characterized by chronic inflammation. Hence, reviewing the treatment options and mechanisms between aging and type 2 diabetes is reasonable. Here, we will report the influence of type 2 diabetes on the clinical manifestations and hallmarks of aging. Adenosine monophosphate-activated protein kinase (AMPK) controls intracellular energy balance and regulates cellular metabolism. AMPK signaling declines with aging, enhancing the aging process [31]. AMPK activity is reduced in type 2 diabetes [32]. Therefore, a great number of studies have highlighted that AMPK and its activators may have significant benefits in the treatment of type 2 diabetes. The mammalian target of rapamycin complex 1 (mTORC1) is a key component of cellular metabolism, and inhibition of mTORC1 with therapeutic rapamycin promotes health and longevity in diverse model organisms [33]. Overactivity of mTORC1 has been proposed to provide a new perspective on type 2 diabetes in terms of pathogenesis, clinical focus, and therapeutic strategies [34].

We will provide insights into the effects of AMPK activation and mTORC1 inhibition on hallmarks of aging, type 2 diabetes, and diabetic complications. We searched for the effects of nutritional interventions that have AMPK-activating and mTORC1-inhibitory effects on type 2 diabetes. Further-

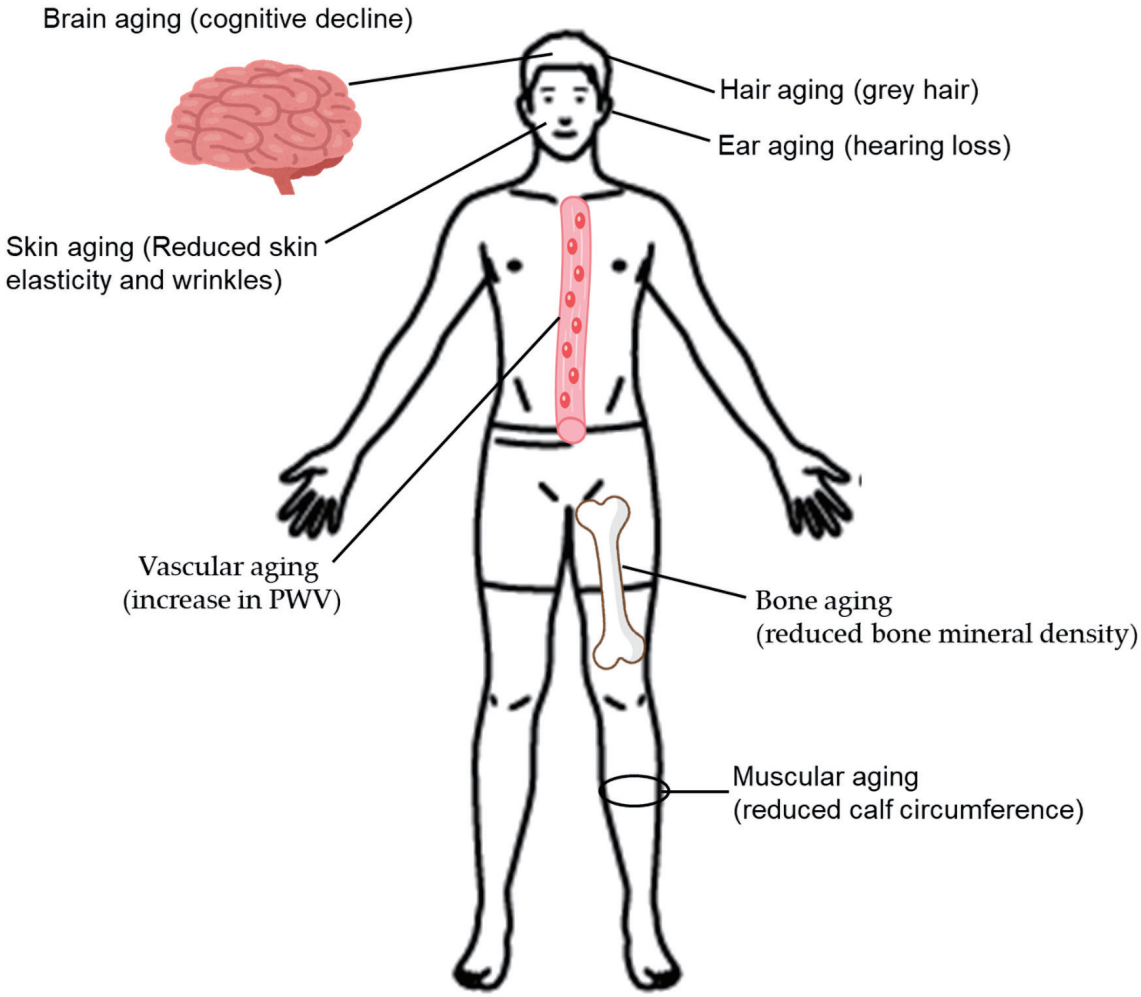

Figure 1. The clinical manifestations of aging. PWV, pulse wave velocity.

more, we investigated whether type 2 diabetes medications, which have been reported to be effective in preventing the onset of complications such as CVD, have AMPK-activating and mTORC1-inhibitory effects. We would like to provide the mechanistic rationale for anti-aging therapy in type 2 diabetes.

The Influence of Type 2 Diabetes on the Clinical Manifestations of Aging

The clinical manifestations of aging are shown in Figure 1.

Hair aging

Dysregulation of the spectral balance of melanocytes in the hair follicle is the fundamental cause of pathological hair greying [35]. As we age, tyrosinase activity decreases, inhibiting melanin synthesis [36]. Premature grey hair is usually accompanied by type 2 diabetes [37].

Skin aging

Diabetes causes increased production of AGEs, which may induce damage to collagen fibers and accelerate skin aging [38]. Diabetic patients had greater epidermal water loss, less elastic skin, and deeper, larger wrinkles [38]. In addition, diabetic patients presented with polycyclic papillae and distorted amorphous collagen fibers [38].

Ear aging

Diabetic patients are twice as likely to experience hearing loss compared to people without diabetes, and people with prediabetes are 30% more likely to experience hearing loss [39].

Brain aging

In a meta-analysis, type 2 diabetic patients were found to have

significant impairment in cognition, executive function, and processing speed [40]. Type 2 diabetes was significantly related to the atrophy of gray matter [40].

Bone aging

The meta-analysis revealed that bone mineral density (BMD) was significantly lower in patients with type 2 diabetes than in nondiabetic individuals at the lumbar vertebrae (mean difference (MD): -0.14; 95% confidence interval (CI): -0.22 to -0.06; P = 0.0009), and at femoral neck (MD: -0.11; 95% CI: -0.18 to -0.04; P = 0.002) [41].

Vascular aging

Increased arterial stiffness has been suggested to be a predictor of CVD and all-cause mortality [42-44]. Arterial stiffness increases with age. In postmenopausal women with obesity and diabetes, arterial stiffness is accelerated, leading to increased CVD events compared with lean, non-diabetic premenopausal women [45-47]. The carotid-femoral pulse wave velocity (PWV) is the current standard for assessing arterial stiffness [48, 49]. The meta-analysis showed that PWV was a useful noninvasive early marker for vascular dysfunction in patients with type 2 diabetes [50].

Muscular aging

Insulin resistance is closely associated with increased muscle protein degradation [51]. AGEs accumulation induces skeletal muscle atrophy and dysfunction, and oxidative stress and mitochondrial dysfunction due to type 2 diabetes can induce myocyte apoptosis. Patients with type 2 diabetes are at high risk of developing sarcopenia [52]. Calf circumference measurement was the most effective tool to screen for sarcopenia in patients with type 2 diabetes [53].

Effect of type 2 diabetes on the clinical manifestations of aging

Type 2 diabetes accelerates all clinical manifestations of aging.

The Hallmarks of Aging and Their Association With Type 2 Diabetes

Oxidative stress

Oxidative stress is caused by an imbalance between the generation of reactive oxygen species (ROS) and antioxidant capacity and is closely linked to aging and aging-related diseases [54]. Mitochondrial dysfunction due to ROS induces aging [55]. Oxidative damage affects mitochondrial DNA replication and transcription, leading to mitochondrial dysfunction and resulting in increased production of ROS [55]. ROS are highly reactive and can damage cellular components such as DNA, proteins, and lipids, leading to aging [56]. ROS induce mutations and breaks in DNA strands, leading to genomic instability, and DNA damage increases the risk of age-related diseases [57]. Oxidative stress can trigger inflammation and accelerate the shortening of telomeres, which are associated with cellular aging and senescence [58].

Oxidative stress is thought to be involved in the progression of prediabetes to type 2 diabetes [59]. Oxidative stress contributes to insulin resistance, beta-cell dysfunction, and diabetic complications. The levels of glutathione, a major antioxidant, are notably low in patients with type 2 diabetes, exacerbating oxidative stress and inflammation [60]. Elevated interleukin-6 (IL-6) levels further intensify inflammation and oxidative stress, disrupt insulin signaling, and exacerbate diabetic complications. Patients with type 2 diabetes are prone to inflammation and oxidative stress [61, 62], and hyperglycemia, hyperglycemia-induced oxidative stress and inflammation are closely related to the development and progression of type 2 diabetes and its complications.

Inflammation

Aging is associated with increased blood levels of inflammatory markers, a condition termed “inflammaging” [63]. The inflammaging contributes to many aging-related pathologies. Inflammation is a major cause of type 2 diabetes and CVD [64]. Inflammatory markers predict the development of type 2 diabetes and diabetic complications. Overnutrition, unhealthy diets, lack of exercise, obesity, and aging are all known to increase inflammation, promote insulin resistance, and perpetuate the development of type 2 diabetes. The proinflammatory cells infiltration into adipose tissue is associated with an increased production of inflammatory chemokines and a reduced adiponectin [65]. Inflammation in adipose tissue induces insulin resistance and type 2 diabetes in obesity. In addition to adipose tissue, liver, muscle, and pancreas are the sites of inflammation in the presence of obesity [66], inducing insulin resistance and beta-cell dysfunction. Furthermore, the nuclear factor kappa B (NF-κB) and the nod-like receptor pyrin 3 (NLRP3) inflammasome axis leads to pancreatic beta-cell dysfunction and the development of type 2 diabetes [67].

AGEs

AGEs are formed by non-enzymatic glycation of proteins and lipids [68]. AGEs accumulation in tissues is significantly correlated with blood glucose levels [69]. The accumulation of AGEs in nucleotides, lipids, and proteins is a crucial factor in aging [70]. AGEs are associated with changes seen during the aging process and the development of age-related diseases. Even after an improvement in hyperglycemia, AGE levels in diabetic tissues often do not return to normal, which may indicate “metabolic memory” [71]. AGEs are implicated in the

development of diabetes [72]. AGEs bind to the receptor for AGEs (RAGE), thereby activating proinflammatory signaling pathways [73]. AGEs bind RAGE, triggering multiple intracellular signaling pathways, including the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase that leads to increased production of ROS, thus contributing to generating a pro-oxidant environment [74], contributing to the development of diabetic microvascular complications [75].

Dysbiosis

The gut microbiome plays a key role in regulating health and disease. With aging, profound changes in the composition and function of the gut microbiome can lead to gut dysbiosis, increased inflammation, weakened immunity, and metabolic disorders [76]. Inflammaging is significantly associated with gut microbial alterations and contributes to the development and progression of AD, CVD, obesity, and diabetes [76]. A systematic review has reported that a major change in the gut microbiota in obesity is characterized by a specific decrease in butyrate-producing bacteria and the production of metabolites and components that lead to insulin resistance, type 2 diabetes, and CVD [77]. Inflammation plays a major role as a link between gut microbiota dysbiosis and obesity-associated metabolic complications. Dysbiosis may contribute to the development of type 2 diabetes [78]. Individuals with type 2 diabetes exhibit a notable reduction in butyrate-producing bacteria [78]. Gut dysbiosis can cause inflammation and induce peripheral and brain insulin resistance, potentially amplifying processes that promote the progression of AD. Furthermore, gut dysbiosis has been shown to increase the risk of developing AD [79].

DNA damage

The accumulation of DNA damage contributes to cell death, senescence, and tissue dysfunction [9]. DNA damage induces inflammation through the activation of the interferon gene axis and NF-κB [9]. Loss of efficient repair of DNA can lead to accelerated aging [10]. High levels of mutations in DNA induce excessive cell death and stem cell exhaustion [10]. Accumulated DNA damage and mutation are the hallmarks of aging. DNA damage induces a senescence-associated secretory phenotype (SASP), such as increased secretion of inflammatory cytokines [80]. SASP may also play important roles in diabetes. White adipose tissue (WAT) cells are prone to senescence due to obesity and type 2 diabetes. The senescence of WAT induces hypertrophy of adipocytes, insulin resistance, and dyslipidemia [80]. The meta-analysis showed that significantly elevated rates of chromosomal aberrations have been observed in type 2 diabetic subjects [81].

Telomere shortening

Telomere is a part of a chromosome that prevents the tangling of the chromosome during DNA replication. When a cell divides, the telomere gets shorter each time, and this process continues until the telomere becomes too short, at which point the cell cannot divide anymore, and the cell dies [82]. Oxidative stress and incomplete DNA replication play a major role in telomere shortening [83]. When telomeres shorten and reach a critical length, apoptosis is initiated, which contributes to cellular senescence [84].

In patients with diabetes, excessive oxidative stress damages telomeres, shortening their length [85]. Telomere length is a good surrogate marker for mortality and diabetic complications in diabetic patients. Telomere length in pancreatic beta-cells is also shortened in diabetic patients, which induces impaired proliferation and insulin secretion [85]. Telomere attrition in adipose tissue induces insulin resistance. Excessive oxidative DNA damage and telomere shortening in type 2 diabetes have been suggested to lead to senescent retinal, renal, and vascular phenotypes [86].

Epigenetic alterations

Among epigenetic alterations, DNA methylation, the involvement of noncoding RNAs, and histone modifications play important roles in aging [87]. Aberrant DNA methylation influences cellular functions and may lead to CVD, metabolic diseases, and cancer. Long noncoding RNAs are increasingly recognized as key regulators in cellular senescence and various age-related pathologies [88]. In general, histones are decreased, and aberrant nucleosome occupancies occur during aging. The accumulation of histone variants is another common feature in the aging process [89]. Methylation and acetylation of histone play an important role in regulating the chromatin structure [90], and such changes influence the senescence-associated gene expression [91]. Unhealthy eating habits and lack of exercise increase the risk of obesity and can affect gene expression through epigenetic alterations [92]. Epigenetic alterations occur early in obesity and may contribute to obesity-related complications [92]. Patients with type 2 diabetes exhibit epigenetic alterations associated with mitochondrial dysfunction in pancreatic islets [93]. DNA methylation, histone modifications, and regulation by noncoding RNAs are epigenetic alterations observed in type 2 diabetes [94]. Oxidative stress can induce abnormal DNA methylation in beta cells, leading to altered gene expression related to insulin secretion [95]. In type 2 diabetes, hyperglycemia induces DNA methyltransferase 1-dependent epigenetic reprogramming of the endothelial exosome proteome [96]. In middle-aged and older Australians, epigenetic age was positively associated with the prevalence and incidence of type 2 diabetes [97].

Loss of protein balance

Aging is associated with a decline in muscle mass, strength, and function, a process known as sarcopenia, which is largely attributed to an imbalance between muscle protein synthesis and breakdown [98]. This imbalance is influenced by factors like reduced anabolic response to stimuli like food intake and

exercise, as well as changes in protein absorption. The muscle protein synthetic response to the major anabolic stimuli, such as food intake and exercise, tends to be blunted in elderly people [99-101]. This anabolic resistance is now considered to be a key factor contributing to progressive loss of skeletal muscle mass. Diabetes can lead to pronounced physiological and cellular adaptations in protein regulation [102], and such pathological conditions can result in a net loss of muscle mass [103]. Muscle strength is reduced in individuals with insulin resistance and type 2 diabetes [104, 105].

Deregulated nutrient sensing

Deregulated nutrient sensing is a key hallmark of aging, where cellular and organismal processes become less effective at responding to nutrient availability. This dysregulation, particularly in pathways like mTORC1 signaling, contributes to the aging process [106]. The nutrient-sensing network (NSN) is an interconnected network of signaling pathways centered on insulin, insulin-like growth factor-1 (IGF-1), mTORC1, AMPK, and sirtuins (SIRTs), the disruption of which promotes aging [3]. Lifestyle factors such as diet may modulate the NSN [107, 108].

Altered intercellular communication

Age-related changes in intercellular communication include SASP, direct intercellular communication via gap junctions or tubular structures, and long-distance communication via extracellular vesicles, and paracrine communication via hemichannels, including connexins [109]. Extracellular vesicles (EVs) are lipid membranes that are produced and released from parent cells and taken up by recipient cells [110]. EV-mediated communication between adipocytes, blood vessels, and immune cells may play an important role in the development of type 2 diabetes [110]. Impaired Ca^{2+} uptake into mitochondria, or impaired interconnected mitochondrial network, is associated with defective insulin secretion [111]. Altered mitochondrial metabolism may also impair beta-cell-beta-cell communication.

Mitochondrial dysfunction

Mitochondrial dysfunction is a hallmark of aging, significantly impacting cellular energy, oxidative balance, and calcium levels [112]. Mitochondrial dysfunction can trigger cellular senescence [112]. Hyperglycemia, hyperlipidemia, and insulin resistance contribute to mitochondrial dysfunction in every organ system [113]. Mitochondria are at the crossroads of important intracellular pathways, such as energy substrate metabolism, ROS production, and apoptosis. Mitochondrial dysfunction induces impaired oxidative phosphorylation, increases ROS generation, mitochondrial DNA damage, and altered mitochondrial dynamics, which contribute to the development of diabetic complications [114]. Mitochondrial dysfunction induces dysfunction of the liver, heart, skeletal muscle, beta-cells, and nervous system in type 2 diabetes [113]. Furthermore, the accumulation of mitochondrial DNA mutations and mitochondrial DNA copy number depletion, as well as epigenetic modification of the mitochondrial genome, are associated with the development of type 2 diabetes.

A decline in NAD^+

NAD^+ is a crucial coenzyme involved in numerous cellular processes, including energy production and DNA repair. Most of the cellular NAD^+ is generated through nicotinamide phosphoribosyl transferase (NAMPT) activation, a key rate-limiting enzyme that is involved in the salvage pathway. NAD^+ is essential for mitochondrial function, and NAD^+ acts as a cofactor for enzymes involved in the electron transport chain [115]. Furthermore, NAD^+ is known to benefit and restore DNA replication, chromatin, epigenetic modifications, and gene expression. A decline in NAD^+ is strongly linked to the aging process and the development of aging-related diseases [116]. As we age, NAD^+ levels naturally decrease, potentially impairing these vital cellular functions and contributing to aging-related decline and disease [117]. NAD^+ is depleted in diabetes, CVD, and neurodegenerative diseases, and in aging [118]. An important hallmark of dysfunctional obese adipose tissue is impaired NAD^+/SIRT signaling [119].

Cellular senescence

Cellular senescence, a state of irreversible cell cycle arrest, is a key hallmark of aging. It is a cellular response to stress and damage that can contribute to age-related diseases and the overall aging process [120]. Cell senescence accumulation with age can be detrimental, driving chronic inflammation and tissue dysfunction [121]. Senescence of islet beta-cells induces the pathogenesis of type 2 diabetes. Senescence-associated beta-galactosidase activity is increased in pancreatic islet beta cells isolated from aged and type 2 diabetic mice [122]. Furthermore, the expression level of IGF-1 receptor (IGF-1R) in beta cells of type 2 diabetes model mice was higher than that of control mice, suggesting a significant association between beta-cell senescence and type 2 diabetes [123]. Aging pancreatic islet beta cells have a reduced insulin secretory capacity and are less sensitive to high glucose stimulation [124]. A high-calorie diet can promote adipocyte senescence and cause insulin resistance [125], and insulin resistance can further induce pancreatic beta-cell senescence [126].

Stem cell exhaustion

Stem cell exhaustion is a significant factor in aging, characterized by a decline in the ability of stem cells to regenerate and maintain tissue homeostasis [127]. Patients with type 2 diabetes may have a reduced ability to revascularize ischemic tissues due to abnormal production of circulating pro-vascular

progenitor cells [128]. Increasing oxidative stress and inflammation intensify this regenerative cell exhaustion process. Diabetes reduces circulating stem/progenitor cells and impairs their function [129]. Diabetes inhibits bone marrow stem/progenitor cell mobilization, adversely affecting physiological hematopoiesis, immunoregulation, and tissue regeneration.

Impaired macroautophagy

Autophagy is a fundamental cellular process that removes molecules and intracellular elements, such as nucleic acids, proteins, lipids, and organelles, through lysosome-mediated degradation, promoting homeostasis, differentiation, development, and survival [130]. Although autophagy declines with age, it is a key determinant of cellular health and organismal longevity, and impaired or imbalanced autophagy promotes pathological aging and disease [130]. The decline in macroautophagy with age has been implicated in aging-related diseases such as Parkinson's disease and AD, cancer, and CVD [131]. Autophagy-deficient mice exhibit hypoinsulinemia and hyperglycemia, suggesting that autophagy is required for maintaining pancreatic beta-cell structure, mass, and function [132]. In diabetes, the accumulation of AGEs, excess oxidative stress, endoplasmic reticulum stress, hypoxia, and the activation of the renin-angiotensin system regulate autophagy activity, which contributes to the development of diabetic nephropathy [133]. Enhanced macroautophagy is important for maintaining the fidelity of the secretory apparatus under conditions of high insulin demand, and failure of these adaptive mechanisms likely contributes to beta-cell dysfunction [134]. Islet macroautophagic impairment was found in human type 1 diabetes [135]. Endothelial dysfunction is a key determinant in the pathogenesis of diabetes. Autophagy appears to play an important role in endothelial cells, ensuring endothelial homeostasis and functions. Autophagic flux impairment has been observed in patients with type 1 or type 2 diabetes [136]. Diabetes causes impaired autophagy in endothelial cells, contributing to diabetes-mediated endothelial dysfunction.

The association between hallmarks of aging and type 2 diabetes

Metabolic disorders such as hyperglycemia and insulin resistance observed in type 2 diabetes induce harmful factors such as oxidative stress, inflammation, AGEs, and dysbiosis. Such harmful factors induce impaired maintenance of healthy cells by inducing DNA damage, epigenetic alteration, mitochondrial dysfunction, worsening type 2 diabetes, and developing diabetic complications. Impaired maintenance of healthy cells is induced by an impaired clearance of senescent cells due to stem cell exhaustion and impaired macroautophagy. Impaired clearance of senescent cells is unfavorably associated with metabolic disorders and diabetic complications. Thus, type 2 diabetes and aging form a vicious cycle, exacerbating each other's pathology.

The Significance of AMPK Activation and mTORC1 Inhibition for Anti-Aging Medicine

AMPK activation is strongly linked to anti-aging mechanisms, as it acts as a cellular energy sensor and regulator that maintains cellular homeostasis, metabolism, stress resistance, and promotes processes like autophagy, all of which are crucial for healthy aging and extended lifespan [137]. mTORC1 and AMPK signaling play a crucial role in biological networks involved in cellular senescence [138]. AMPK activation and mTORC1 inhibition are closely linked mechanisms involved in the aging process and are expected to have the effect of extending lifespan and reducing diseases associated with aging. AMPK is activated under low ATP levels, leading to the inhibition of mTORC1, a key pathway involved in cell growth and metabolism that is often dysregulated with age [138].

In acute energy-deficient status, AMPK activation is protective to restore cellular energy by stimulating catabolism and inhibiting anabolism [139]. However, in chronic conditions, overactivation of AMPK can be detrimental. Chronic activation has been proposed to inhibit overall energy metabolism by shifting processes toward energy-dissipating states in the heart [140].

mTORC1 activation induces muscle growth (hypertrophy) by increasing protein synthesis [141]. Complete and chronic inhibition can lead to muscle atrophy and dysfunction [141]. Chronic mTOR inhibition by rapamycin induces muscle insulin resistance [142]. mTORC1 activity is important for immune cell function, and pharmacological inhibition of mTORC1 can significantly alter or eliminate immune responses [143]. Over-inhibition can impair lipid metabolism, mitochondrial function, and autophagy [144, 145]. mTOR signaling is necessary for rapid wound healing, and mTOR signaling enables an increase in cell volume that facilitates wound repair [146]. Therefore, restoring balance and regulation of mTORC1 is key to anti-aging.

Effects of AMPK activation and mTOR inhibition on aging-related molecules and aging hallmarks were shown in Figure 2. Nuclear factor E2-related factor 2 (Nrf2) is activated under oxidative stress conditions, which promotes antioxidant gene expression [147]. Peroxisome proliferator-activated receptor-γ coactivator 1α (PGC1α) and Nrf2 have been shown to promote each other and regulate the expression of antioxidant genes. Nrf2 is a downstream target of AMPK, and activation of the AMPK/Nrf2 signaling pathway is important for preventing aging-related diseases.

Chronic inflammation associated with increased NF-κB signaling is a typical feature of several age-related metabolic disorders [148]. Activators of AMPK have anti-inflammatory properties. AMPK activation can inhibit NF-κB signaling [149]. AMPK activation can also inhibit the NLRP3 inflammasome pathway [150].

AMPK activation mitigates AGEs by reducing inflammation and cellular damage [70]. The inhibition of mTORC1 has been suggested to diminish the accumulation of AGEs, possibly due to a protective role of autophagy in the clearance of AGEs [151]. AMPK inactivation is an etiological factor in

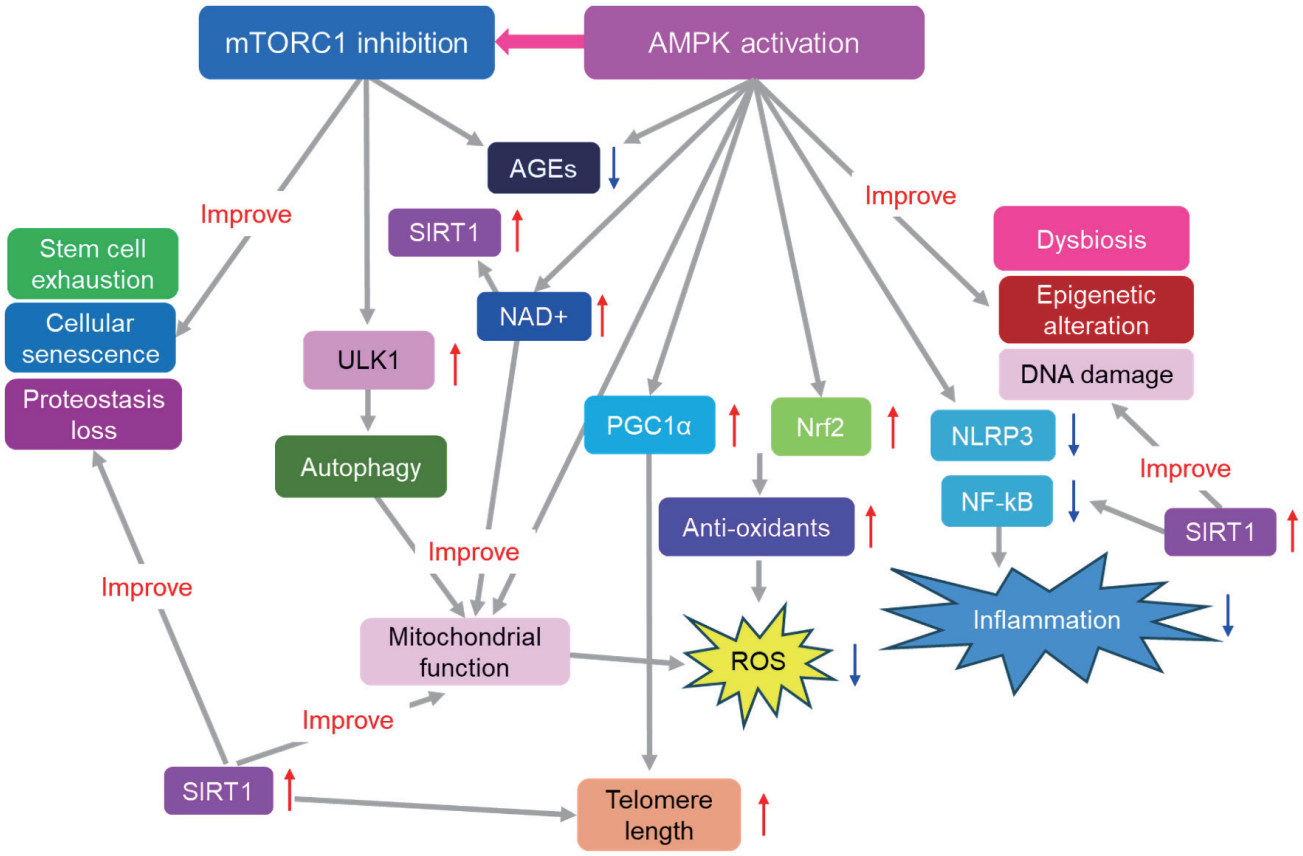

Figure 2. Effects of AMPK activation and mTOR inhibition on aging-related molecules and aging hallmarks. Thick gray arrows indicate effects, and red upward arrows indicate the increase, and blue downward arrows indicate the decrease. AGEs: advanced glycation end products; AMPK: adenosine monophosphate-activated protein kinase; mTORC1: mammalian target of rapamycin complex 1; NAD^+: nicotinamide adenine dinucleotide; NLRP3: nod-like receptor pyrin 3 inflammasome; Nrf2: nuclear factor E2-related factor 2; NF-κB: nuclear factor-kappa B; PGC1α: peroxisome proliferator-activated receptor-γ coactivator 1α; ROS: reactive oxygen species; SIRT1: sirtuin 1; ULK1: unc-51-like autophagy activating kinase 1.

intestinal dysfunction, and AMPK activation favorably influences intestinal health [152].

AMPK acts as a central regulator of epigenetic processes by phosphorylating histones, DNA methyltransferases, and histone modifiers [153]. Epigenetic modifications play an important role in the management of DNA damage, influencing both the detection and repair of DNA damage and leading to long-term alterations in gene expression [154]. Telomerase reverse transcriptase (TERT) has a telomere-lengthening effect [155]. AMPK-dependent PGC1α upregulation is required for the metformin-induced upregulation of TERT and telomere activity and length [156].

AMPK controls autophagy through mTORC1 and unc-51-like autophagy activating kinase 1 (ULK1) signaling, which augments the quality of cellular housekeeping. The ULK1 complex plays a central role in the initiation stage of autophagy [157]. mTORC1 inhibits the activity of the ULK1 complex by phosphorylating ULK1 and Atg13 [158].

AMPK is promptly activated after mitochondrial stress [159]. AMPK regulates autophagy and mitophagy by activating the kinase ULK1 [160]. AMPK phosphorylates mitochondrial fission factors to promote mitochondrial fission under energy stress. By simultaneously regulating mitochondrial fission, mitophagy, and the transcriptional regulation of mitochondrial biogenesis, AMPK functions as a signal integration platform to maintain mitochondrial function.

NAD^+ is a vital coenzyme crucial for maintaining mitochondrial function, directly participating in key energy-producing pathways like the tricarboxylic acid cycle and oxidative phosphorylation, and playing a role in cellular signaling and overall homeostasis [161]. Declining NAD^+ levels are associated with aging and various chronic diseases, often accompanied by mitochondrial dysfunction [161]. AMPK cooperates with another metabolic sensor, the NAD^+-dependent type III deacetylase SIRT1, to regulate the expression of genes involved in energy metabolism [162]. AMPK increases the activity of SIRT1 by increasing intracellular NAD^+ levels.

The anti-aging effects of SIRT1 have been widely studied [163, 164]. SIRT1 regulates inflammation and stress resistance and suppresses various effects associated with aging, including genomic instability, stem cell depletion, mitochondrial dysfunction, and telomere shortening. Activating SIRT1 inhibits inflammation by deacetylating NF-κB [165]. AMPK activation and mTORC1 inhibition improve all hallmarks of aging.

Effects of AMPK Activation and mTORC1 Inhibition on Diabetic Complications

Diabetic complications include microangiopathy, such as neuropathy, retinopathy, and nephropathy, and macroangiopathy, such as CVD. Research is increasingly highlighting the link between AD and type 2 diabetes, showing that the risk of developing both increases exponentially with age, and that type 2 diabetes predisposes to AD [166]. What about the effects of AMPK activation and mTOR inhibition on these diabetic complications and AD?

Diabetic neuropathy

Increased ROS, amplified apoptosis, decreased insulin secretion, neuroinflammation, and decreased autophagy induce the development of diabetic neuropathy [167]. Impaired AMPK signaling in neurons is associated with mitochondrial dysfunction and peripheral neuropathy in diabetic models [168]. Activation of AMPK has been shown to improve heat sensitivity and reduce epidermal innervation density in streptozotocin-treated rodents [168].

Tang Bi formula (TBF) has been proven effective for diabetic polyneuropathy. Very recently, TBF ameliorated diabetic polyneuropathy by rectifying mitochondrial dynamic imbalance and modulating the activation of the AMPK-PGC-1α-mitochondrial fusion protein pathway [169].

The altered mTORC1 activity can impair nerve function by affecting brain-derived neurotrophic factor (BDNF) in Schwann cells, increasing ROS and AGEs, and suppressing autophagy [170]. Targeting the mTOR pathway with inhibitors or natural compounds shows promise for novel regenerative therapeutic strategies against diabetic complications like neuropathy [171].

Diabetic retinopathy (DR)

C1q/tumor necrosis factor-related protein-3 (CTRP3), a newly discovered adipokine, prevents diabetes-induced retinal vascular permeability by activating AMPK [172]. Recently, mTORC1 inhibition has been reported as a novel gene therapeutic strategy for DR [173].

Diabetic nephropathy

Renal tubulointerstitial fibrosis is a key pathological feature of diabetic nephropathy, and renal tubular damage may be associated with abnormal mitophagy. The AMPK agonist improved renal oxidative stress and tubulointerstitial fibrosis in high-fat diet- and streptozotocin-induced type 2 diabetic mice by activating the AMPK signaling pathway [174].

It has been observed that mTORC1 is involved in the progression of diabetic nephropathy by inhibiting autophagy, promoting inflammation, and increasing oxidative stress [175]. The inhibitory effect of rapamycin on the development and progression of diabetic kidney disease (DKD) was observed in diabetic animal models [176].

CVD

Emerging evidence suggests that naturally occurring AMPK activators may have significant cardiovascular (CV) benefits [177]. AMPK activators prevent CVD by reducing blood pressure, plasma glucose, serum lipids, and ROS production, and by increasing NO bioavailability.

The mTORC1 pathway plays a crucial role in CVD, promoting processes like atherosclerosis, myocardial infarction, and heart failure through effects on cell growth, metabolism, and inflammation [178]. Inhibiting mTORC1 can offer cardioprotective effects, reducing infarct size and slowing disease progression [179].

AD

AMPK reduces tau phosphorylation and improves brain function in an AD-like model [180]. Aberrant mTORC1 signaling is associated with AD pathogenesis, contributing to hallmark pathologies like amyloid beta plaques and tau neurofibrillary tangles through increased production and decreased clearance [181, 182]. mTORC1 activation also promotes neuroinflammation, oxidative stress, and cognitive decline, while its inhibition, particularly with drugs like rapamycin, has shown promise in preclinical models for clearing amyloid and tau aggregates and improving cognitive function [181, 182].

Sex Differences in the Anti-Aging Medicine

The gradual decline in hormone production and action with aging has detrimental effects on human health, including an increased risk of chronic diseases and a shortened lifespan [183]. Hormonal changes contribute to a variety of chronic diseases, including frailty, diabetes, CVD, and dementia.

Osteoarthritis (OA) affects women more frequently than men, especially after menopause [184, 185]. Cartilage undergoes various changes with aging, including a decrease in cell density and extracellular matrix content, followed by thinning and fragility [186]. The significant increase in the prevalence of OA in postmenopausal women suggests a link between OA and a decrease in estrogen [184].

The biological actions of estrogen are mediated by the estrogen receptor α or β (ERα or ERβ), which are members of a broad nuclear receptor superfamily. The reduction in circulating estrogen, regulated by classical ERα and ERβ, led to rapid changes in pancreatic beta-cell and islet function, glucose transporter 4 (GLUT4) expression, insulin sensitivity and glucose tolerance, lipid homeostasis dysfunction, oxidative stress, and inflammatory cascades [187]. Clinical trials have shown that hormone replacement therapy has a protective effect on glucose metabolism and may be useful for treating type 2 diabetes in menopausal women [187].

Table 1. Effects of Nutritional Interventions That Improve Aging Hallmarks by AMPK Activation and mTORC1 Inhibition on Type 2 Diabetes

Therapeutic interventions	AMPK activation	mTORC1 inhibition	Effects on type 2 diabetes
Calorie restriction	(+) [201]	(+) [202]	The meta-analysis showed that calorie-restricted diets were an effective intervention for type 2 diabetes remission in comparison to a usual diet or usual care [203].
Vitamin E	(+) [204]	(+) [205]	The meta-analysis showed that vitamin E intake has a beneficial role in improving HbA1c and insulin resistance in a population with diabetes [206].
Vitamin C	(+) [207]	(+) [208]	The meta-analysis showed that long-term (≥ 12 weeks) and high-dose vitamin C supplementation (≥ 1,000 mg/d) ameliorated glycemic profile in patients with type 2 diabetes [209].
Resveratrol	(+) [210]	(+) [211]	In the meta-analysis, there was a significant effect on the reduction of insulin resistance and glycated hemoglobin. For fasting blood glucose, the results were significant for individuals with diabetes [212].
Astaxanthin	(+) [213]	(+) [213]	Astaxanthin showed preventive effects against diabetes and atherosclerosis and may be a novel complementary treatment option for the prevention of diabetes in healthy volunteers, including subjects with prediabetes, without adverse effects [214].
n3-PUFA	(+) [215]	(+) [216]	An individual participant-level pooling project of 20 prospective cohort studies showed that higher circulating biomarkers of seafood-derived n-3 PUFA were associated with lower risk of type 2 diabetes in a global consortium of prospective studies [217].

AMPK: adenosine monophosphate-activated protein kinase; mTORC1: mammalian target of rapamycin complex 1; PUFA: polyunsaturated fatty acids; TG: triglyceride; HbA1c: glycated hemoglobin.

Early menopause and premature ovarian failure are independent risk factors for type 2 diabetes [188]. Patients with type 1 diabetes enter menopause earlier than controls [189]. Follicular development and growth are adversely affected by chronic hyperglycemia, which may lead to ovarian failure in type 1 diabetes. AGEs may contribute to ovarian aging [190].

Testosterone levels in men begin to decline between the ages of 30 and 40 and continue to decline until death [191]. Local and systemic illness, prescription medications, lung tumors, excessive smoking or alcohol, obesity, and untreated diabetes were correlated with a decrease in testosterone [192]. Testosterone levels have been reported in untreated elderly diabetic males to be approximately 15% lower compared to their non-diabetic counterparts [193]. Low testosterone levels are closely associated with visceral obesity, insulin resistance, poor glycemic control, and prolonged diabetes duration [194]. Low testosterone levels are associated with CVD, metabolic syndrome, insulin resistance, type 2 diabetes [192], psychological status [191], reduced muscle and bone mass, and sexual dysfunction [195].

Effects of Exercise on AMPK Activation, mTORC1 Inhibition, Type 2 Diabetes, and Aging-Related Diseases

During exercise, AMPK is activated in skeletal muscles in humans, and exercise may be the most powerful physiological activator of AMPK [196]. mTORC1 is inhibited in liver and fat by exercise, which may underlie some of the health benefits in these tissues [197].

A recent meta-analysis showed that combined resistance and aerobic exercise intervention significantly improved fasting blood glucose and serum lipids in patients with type 2 diabetes, especially in terms of blood glucose control and CV risk, demonstrating better outcomes than aerobic exercise alone [198].

The meta-analysis provides strong evidence that structured exercise-based programs significantly reduce the risk of major adverse cardiovascular events (MACE) in patients with CVD [199].

A meta-analysis showed that the Mini-Mental State Examination (MMSE) scores of the exercise group were higher than those of the control group (MD: 2.24; P = 0.002) [200]. Low-intensity aerobic exercise improved cognitive and motor function in patients with AD, while strength training and high-intensity exercise had little effect. This may be related to AMPK activation and mTORC1 inhibition caused by exercise intensity.

Effects of Nutritional Interventions That Have AMPK-Activating and mTORC1-Inhibitory Effects on Type 2 Diabetes

Effects of nutritional interventions that have AMPK-activating and mTORC1-inhibitory effects on type 2 diabetes are shown in Table 1 [201-217].

Calorie restriction has both AMPK-activating and mTORC1-inhibitory effects [201, 202]. At 6 months, each 500-kcal/day decrease in energy intake resulted in clinically meaningful reductions in body weight (MD: -6.33 kg; 95% CI: -7.76 to -4.9) and glycated hemoglobin (HbA1c, MD: -0.82%; 95% CI: -1.05 to -0.59) [203]. However, caloric restriction can be harmful for frail elderly individuals, increasing the risk of sarcopenia, functional decline, and weakened immune function. Frail older adults have a lower threshold for functional

Table 2. Effects of Anti-Diabetic Drugs That Have AMPK-Activating and mTORC1-Inhibitory Effects on Aging-Related Diseases

Anti-diabetic drugs	Effects on CVD	Effects on AD
Metformin	A meta-analysis showed that the risk of CVD mortality in metformin patients was lower than in the other two groups (placebo and other anti-diabetic drugs) (OR: 0.771; 95% CI: 0.688 to 0.853), and the risk of CVD in metformin users was also lower than in the other two groups (OR: 0.828; 95% CI: 0.781 to 0.785) [221].	A meta-analysis of 10 clinical observational studies showed no significant association between AD incidence and metformin exposure (OR: 1.17; 95% CI: 0.88 to 1.56) [222]. Three relevant clinical trials, Metformin in Alzheimer's Dementia Prevention (MAP), MET-FINGER, MET-MEMORY, are currently underway to understand the effect of metformin on the prevention of AD [223].
SGLT2is	The EMPA-REG OUTCOME showed that empagliflozin reduced 3P-MACE by 14% as compared with placebo [224]. The CANVAS program showed that the rate of 3P-MACE was lower with canagliflozin as compared with placebo by 14% [225].	A retrospective examination of data from a cohort of 1,348,362 participants with type 2 diabetes showed that SGLT2is use was associated with reduced risks of AD (aHR: 0.81; 95% CI: 0.76 to 0.87) [226].
GLP-1RAs	The LEADER showed that 3P-MACE occurred in significantly fewer patients in the liraglutide group than in the placebo group (HR: 0.87; 95% CI: 0.78 to 0.97) [227]. The SUSTAIN-6 trial showed that 3P-MACE occurred in 108 of 1,648 patients (6.6%) in the semaglutide group and in 146 of 1,649 patients (8.9%) in the placebo group (HR: 0.74; 95% CI: 0.58 to 0.95) [228].	The meta-analysis of pre-clinical studies showed that GLP-1RAs improved the learning and memory abilities of AD rodents; GLP-1RAs reduced amyloid beta deposition and phosphorylated tau levels in the brains of AD rodents [229]. A meta-analysis of human studies also showed that GLP-1RAs effectively improved cognitive function in patients with AD [230].

AMPK: adenosine monophosphate-activated protein kinase; mTORC1: mammalian target of rapamycin complex 1; AD: Alzheimer's disease; aHR: adjusted hazard ratio; CI: confidence interval; CVD: cardiovascular disease; GLP-1RAs: glucagon-like peptide-1 receptor agonists; OR: odds ratio; SGLT2is: sodium-glucose cotransporter 2 inhibitors; 3P-MACE: 3-point major cardiovascular event.

impairment, and weight loss from calorie restriction can lead to significant risks and lower quality of life [218]. Calorie restriction can induce diabetic ketoacidosis, which is life-threatening, in patients with poorly controlled diabetes [219].

Vitamin E shows AMPK-activating and mTORC1-inhibitory effects [204, 205]. In studies with an intervention period of less than 10 weeks, vitamin E supplementation significantly reduced fasting blood glucose levels [206]. Nonlinear dose-response analysis showed that the most effective dose range of vitamin E for lowering HbA1c in diabetic patients was 400 - 1,300 mg/day, with the highest effect observed at a dose of 1,000 mg/day [206]. Vitamin C also has AMPK-activating and mTORC1-inhibitory effects [208,208]. The long-term (≥ 12 weeks) and high-dose vitamin C supplementation (≥ 1,000 mg/day) may ameliorate glycemic profile in type 2 diabetic patients [209]. However, additional high-quality randomized controlled trials (RCTs) are necessary to validate these results.

Resveratrol has both AMPK-activating and mTORC1-inhibitory effects [210, 211]. A meta-analysis of 17 RCTs in 871 patients with type 2 diabetes found that ≥ 500 mg of resveratrol was superior to placebo in improving fasting plasma glucose (MD: -13.34 mg/dL; 95% CI: -22.73 to -3.95, P = 0.005) and HbA1c (MD: -0.41%; 95% CI: -0.65 to -0.16, P = 0.001) at 3 months [212]. Astaxanthin has both AMPK-activating and mTORC1-inhibitory effects [213]. After 12 weeks of supplementation with 12 mg of astaxanthin, blood glucose levels at 120 min after a 75 g oral glucose tolerance test were significantly reduced compared to baseline; furthermore, HbA1c levels decreased from 5.64±0.33% to 5.57±0.39% (P < 0.05) [214]. The Matsuda index, an indicator of insulin resistance, also improved in the astaxanthin group compared to baseline [214]. The n3-polyunsaturated fatty acids (PUFA) have been reported to have both AMPK-activating and mTORC1-inhibitory effects [215, 216]. In an individual participant-level pooling project of 20 prospective cohort studies, a total of 16,693 incident type 2 diabetes cases were identified during follow-up (median follow-up ranging from 2.5 to 21.2 years). In pooled multivariable analysis, eicosapentaenoic acid (EPA) (-8%) and docosahexaenoic acid (DHA) (-18%) were associated with a lower incidence of type 2 diabetes [217]. In a population pharmacokinetic-pharmacodynamic modelling and intake threshold study, a daily intake of n3-PUFA at 0.4 g was sufficient to achieve an HbA1c level of 7% in more than 95% of patients [220].

However, we should mention that the evidence for many of these (resveratrol, astaxanthin) in human diabetes is often from small studies, and meta-analyses show mixed or minimal clinical effects compared to pharmaceuticals. We should acknowledge the limitations of the human evidence for these supplements, including bioavailability issues and the magnitude of effect compared to standard pharmacotherapy.

Effects of Anti-Diabetic Drugs That Have AMPK-Activating and mTORC1-Inhibitory Effects on Aging-Related Diseases

Effects of anti-diabetic drugs that have AMPK-activating and mTORC1-inhibitory effects on aging-related diseases are shown in Table 2 [221-230].

Metformin has been reported to have both AMPK-acti-

vating and mTORC1-inhibitory effects [231, 232]. The UK Prospective Diabetes Study (UKPDS) demonstrated a legacy effect of early, intensive metformin therapy for type 2 diabetes in overweight patients, where the reduction in myocardial infarction and death from any cause persisted even after the trial concluded and glycemic differences were lost [233]. This "legacy effect" showed that early and thorough treatment of type 2 diabetes is crucial, as a period of intensive blood glucose control with metformin provided long-term health benefits that continued to show up years later. AMPK activation by metformin may counteract detrimental metabolic memory by restoring cellular energy balance, improving insulin sensitivity, and reducing fibrosis and inflammation, which are hallmarks of metabolic memory [234]. Such a mechanism restores cellular function, mitigates age-related damage, and prevents the establishment of aging-related diseases such as CVD and AD.

A recent umbrella review of systematic reviews with meta-analysis showed that the risk of CVD mortality in metformin patients was lower than in the other two groups (placebo and other anti-diabetic drugs) (odds ratio (OR): 0.771; 95% CI: 0.688 to 0.853), and the risk of CVD in metformin users was also lower than in the other two groups (OR: 0.828; 95% CI: 0.781 to 0.785) [221]. A meta-analysis of 10 clinical observational studies showed no significant association between AD incidence and metformin exposure (OR: 1.17; 95% CI: 0.88 to 1.56; P = 0.291) [222]. Further well-designed RCTs are required to understand the significance of metformin in the prevention of AD. Three clinical trials, Metformin in Alzheimer's Dementia Prevention (MAP), MET-FINGER, MET-MEMORY, are currently underway to understand the effect of metformin on the prevention of AD [223].

Sodium-glucose cotransporter-2 inhibitors (SGLT2is) have both AMPK-activating and mTORC1-inhibitory effects [235, 236]. The EMPA-REG OUTCOME demonstrated that empagliflozin reduced the incidence of the 3-point MACE (death from CV causes, nonfatal myocardial infarction, or nonfatal stroke) by 14% as compared with placebo [224]. The CANVAS program also demonstrated that the incidence of the 3-point MACE was lower with canagliflozin as compared with placebo by 14% [225]. A retrospective cohort study including 1,348,362 patients with type 2 diabetes showed that SGLT2i use was associated with a lower risk of AD (adjusted hazard ratio (aHR): 0.81; 95% CI: 0.76 to 0.87) [226].

Glucagon-like peptide 1 receptor agonists (GLP-1RAs) have been reported to have both AMPK-activating and mTORC1-inhibitory effects [237, 238]. The LEADER showed that the 3-point MACE occurred in significantly fewer patients in the liraglutide group than in the placebo group (hazard ratio (HR): 0.87; 95% CI: 0.78 to 0.97; P < 0.001) [227]. The SUSTAIN-6 trial showed that the incidence of the 3-point MACE in the semaglutide group (6.6%) was lower than in the placebo group (6.6%) (HR: 0.74; 95% CI: 0.58 to 0.95; P < 0.001) [228]. A meta-analysis of preclinical studies showed that GLP-1RAs improved learning and memory abilities and reduced brain amyloid beta and phosphorylated tau levels in rodents with AD [229]. A meta-analysis of human studies also showed that GLP-1RAs effectively improved cognitive function in AD [230].

SGLT2is and GLP-1RAs effectively lower HbA1c, but the mechanisms by which they do so are quite different, making them a compelling combination. Recently, both antidiabetic drugs have been shown to reduce MACE, although likely through various mechanisms. The combination therapy with SGLT2is and GLP-1RAs on aging-related diseases in patients with type 2 diabetes mellitus may be potentially beneficial [239]. A meta-analysis showed that in real-life conditions, the combination therapy with SGLT2is and GLP-1RAs reduced CVD compared with both GLP-1RA monotherapy and SGLT2i monotherapy [240].

Dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1RAs have been reported to have both AMPK-activating and mTORC1-inhibitory effects [241, 242]. Further research is needed to understand the impact of GIP/GLP-1RAs on age-related diseases such as CVD and AD.

Mitochondrial dysfunction and oxidative stress are important factors for aging. Imeglimin improves mitochondrial function and reduces reactive oxygen species [243]. Imeglimin has also been reported to enhance AMPK activity [244]; however, the effect of imeglimin on mTORC1 has not yet been reported. Further research is warranted to understand the impact of imeglimin on age-related diseases.

Future Directions for Application to Aging-Related Diseases

Cellular senescence is a direct cause of age-related diseases, and senescent cells have been recognized as potential therapeutic targets [245, 246]. Eradication of senescent cells appears to be an excellent way to reduce age-related changes such as inflammation [247]. A promising anti-aging drug cocktail consists of dasatinib (a tyrosine kinase inhibitor) and quercetin (a natural flavonoid) [248]. This cocktail has been examined in animal models of age-related diseases such as atherosclerosis, type 2 diabetes, and AD [247]. The first human study showed a reduction in the number of senescent cells in the adipose tissue of patients with DKD [249]. Recently, the combination of fisetin (a flavonoid) and metformin demonstrated superior anti-aging effects on type 2 diabetes-associated aortic aging compared to metformin monotherapy [250]. Senolytics may be a promising, direct anti-aging therapeutic strategy specifically for diabetes and its complications.

Limitations of This Review

The biological links between aging and type 2 diabetes may vary by genetics, ethnicity, lifestyle, and comorbidities, which could not be evaluated in this review. This review does not discuss whether findings are equally applicable across different populations, such as different races. Furthermore, this review could not identify the most susceptible age group for the anti-aging medicine, nor the best time to start anti-aging medicine.

Conclusions

Metabolic abnormalities in type 2 diabetes increase factors that

accelerate aging, such as inflammation and oxidative stress, and such factors exacerbate metabolic abnormalities and complications of type 2 diabetes. Therefore, it is important to consider the treatment options and mechanisms between aging and type 2 diabetes. A common feature observed in type 2 diabetes and aging is reduced AMPK activity and increased mTORC1 activity, and it is meaningful to focus on this phenomenon in treatments for type 2 diabetes. Exercise has both AMPK-activating and mTORC1-inhibitory effects and has been reported to improve type 2 diabetes and prevent aging-related disease. Nutritional interventions that have both AMPK-activating and mTORC1-inhibitory effects are beneficially associated with type 2 diabetes. Metformin, SGLT2is, and GLP-1RAs, which are anti-diabetic drugs with accumulated evidence of their effectiveness in preventing CV events, also contain both AMPK-activating and mTORC1-inhibitory effects, and are expected to be used in the treatment of AD. Furthermore, senolytics may be a promising, direct anti-aging therapeutic strategy specifically for type 2 diabetes and its complications.

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Conflict of Interest

The authors declare that they have no conflict of interest concerning this article.

Author Contributions

HY contributed to conceptualization, supervision, writing - original draft, review and editing. MH, HK, and HA contributed to formal analysis and data curation. HK contributed to conceptualization and data curation. All authors have read and agreed to the published version of the manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations

AD: Alzheimer's disease; AGEs: advanced glycation end products; AMPK: adenosine monophosphate-activated protein kinase; BDNF: brain-derived neurotrophic factor; BMD: bone mineral density; CTRP3: C1q/tumor necrosis factor-related protein-3; CI: confidence interval; CVD: cardiovascular diseases; DR: diabetic retinopathy; DKD: diabetic kidney disease; EVs: extracellular vesicles; GIP: glucose-dependent insulinotropic polypeptide; GLP-1RAs: glucagon-like peptide 1 receptor agonists; HFD: high-fat diet; IL-6: interleukin-6; IGF-1: insulin-like growth factor 1; MACE: major adverse cardiovascular events; MD: mean difference; NSN: nutrient-sensing network; mTORC1: mammalian target of rapamycin complex 1; NAD^+: nicotinamide adenine dinucleotide; NADPH: nicotinamide adenine dinucleotide phosphate; NAMPT: nicotinamide phosphoribosyl transferase; NF-κB: nuclear factor-kappa B; NLRP3: nod-like receptor pyrin 3; Nrf2: nuclear factor E2-related factor 2; PGC1α: peroxisome proliferator-activated receptor-γ coactivator 1α; PWV: pulse wave velocity; PUFA: polyunsaturated fatty acids; RAGE: receptors for advanced glycation end products; ROS: reactive oxygen species; SASP: senescence-associated secretory phenotype; SGLT2: sodium glucose cotransporter-2; SIRT: sirtuin; TBF: Tang Bi formula; TERT: telomerase reverse transcriptase; ULK1: unc-51-like autophagy activating kinase 1; WAT: white adipose tissue

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