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Review Article

Extending Healthspan via GLP-1 Receptor Agonist: Insights and Perspectives

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Abstract

Aging is characterized by a progressive decline in physiological function, an increased risk of chronic diseases, and multiple molecular and cellular alterations, including inflammation, oxidative stress, and mitochondrial dysfunction. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), initially developed for the treatment of type 2 diabetes and obesity, may modulate pathways associated with the hallmarks of aging. This review aims to summarize the mechanistic and therapeutic evidence for GLP-1 RAs in targeting key aging processes and their potential to restore cellular homeostasis and enhance healthspan. A comprehensive literature search was conducted in PubMed, Scopus, and Web of Science up to August 2025. Both preclinical and clinical studies were included if they evaluated the effects of GLP-1 RAs on the major biological processes encompassed by the 12 hallmarks of aging, such as mitochondrial dysfunction, insulin resistance, dysbiosis, inflammaging, autophagy, proteostasis, and genomic stability. Data were analyzed narratively to elucidate potential mechanisms and translational relevance. Evidence from animal and human studies demonstrates that GLP-1 RAs improve mitochondrial function, reduce oxidative stress, attenuate chronic inflammation, and enhance autophagic activity. Additionally, they modulate nutrient-sensing pathways and metabolic processes, thereby improving cellular resilience. Preclinical studies indicate neuroprotective, cardioprotective, and hepatoprotective effects, while emerging clinical data support improvements in metabolic and inflammatory profiles in older adults. Taken together, GLP-1 RAs exert pleiotropic effects across all 12 hallmarks of aging. Although long-term safety and efficacy require further evaluation, current evidence positions GLP-1 RAs as promising therapeutic agents in translational geroscience, with the potential to mitigate age-related physiological decline and promote a longer, healthier lifespan.

Introduction

Aging results from the interplay of genetic, environmental, and lifestyle factors operating within complex biological systems.[1–4] It is characterized by an irreversible decline in physiological function, leading to increased susceptibility to chronic diseases and reduced resilience to stress.[5] As this decline progresses, systemic integrity is compromised, manifesting as age-associated pathologies and limiting the body's capacity to maintain cellular homeostasis.[6,7] Recently, aging research has gained significant attention, with notable advances in fields such as cancer biology.[8] In 2000, the hallmarks of cancer were articulated, and by 2013, a similar framework was established for aging, identifying twelve hallmarks that collectively define the aging process across species.[1,4] These hallmarks encompass fundamental biological processes, including genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, and impaired nutrient sensing, among others.[1,4] This framework provides a robust foundation for understanding the molecular underpinnings of aging.

Glucagon-like peptide-1 (GLP-1) is a 30-amino-acid hormone predominantly produced from the proglucagon (PG) gene by intestinal L cells. The PG gene consists of six exons and five introns, and the active form, GLP-1 (7–36 amide or 7–37), functions as a potent incretin.[9,10] GLP-1 is secreted in response to nutrient intake, particularly glucose and fatty acids, in the intestinal lumen. It plays a central role in metabolic regulation by enhancing insulin secretion, suppressing glucagon production, and delaying gastric emptying, thereby controlling postprandial glucose levels.[11,12] The regulation of the PG gene is mediated by a complex network of molecular signals responsive to nutrient availability.[13–15] For example, elevated glucose concentrations activate the transcription factor carbohydrate response element-binding protein, which indirectly promotes GLP-1 secretion through regulation of target genes in intestinal L cells.[16–19] Hypoxia-inducible factor 1 also

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modulates GLP-1 production in response to cellular metabolic demands, linking nutrient status to hormone output.[17,20] Dietary fatty acids further stimulate GLP-1 secretion via activation of receptors that trigger signaling cascades involving transcription factors such as peroxisome proliferator-activated receptor gamma and liver X receptor, which upregulate GLP-1 expression.[21–24] Collectively, these findings underscore the critical role of nutrient-mediated regulation of GLP-1, with implications for chronic lifestyle-associated diseases and overall metabolic health.[25]

GLP-1 additionally exerts anorexigenic effects through the central nervous system, particularly within the hypothalamus and brainstem.[26] It promotes satiety and reduces food intake by activating GLP-1 receptors (GLP-1R) in the arcuate nucleus of the hypothalamus, stimulating neurons that release satiety signals such as proopiomelanocortin.[27,28] GLP-1 receptor agonists (GLP-1 RAs) have been developed for the treatment of metabolic disorders, including obesity and type 2 diabetes (T2D).[29,30] Beyond weight reduction, GLP-1 RAs confer additional benefits, including decreased cardiovascular disease (CVD) risk, improved metabolic parameters, and potential neuroprotective effects.[31–35] Endogenous GLP-1 has a very short half-life due to rapid degradation by dipeptidyl peptidase-4 (DPP-4).[36,37] GLP-1 RAs are designed to resist enzymatic degradation, thereby prolonging their bioactivity.[38–40] These therapeutic advancements illustrate the broad potential of GLP-1–based interventions.

Importantly, GLP-1 signaling represents an emerging yet underexplored pathway in aging biology. Studies in humans and animal models indicate that GLP-1R activation can influence central aging-related processes, including mitochondrial function, stress resilience, and inflammation.[41,42] Initially developed for T2D management, GLP-1 RAs are now recognized for their cardioprotective and neuroprotective effects, suggesting potential roles in modulating metabolic decline associated with aging.[31–35,41,42] They have also demonstrated efficacy in treating non-alcoholic fatty liver disease, a condition linked to chronic inflammation and metabolic dysfunction that can adversely affect healthspan.[43–45] By reducing hepatic steatosis, insulin resistance (IR), and inflammation, GLP-1 RAs may stabilize key metabolic pathways that influence aging trajectories, highlighting their pleiotropic potential to preserve functional health throughout life.[46,47]

Despite promising outcomes, direct evidence for the impact of GLP-1 RAs on aging remains limited, revealing significant knowledge gaps, particularly as these agents gain popularity for weight management.[48,49] Investigating GLP-1 agonism could provide critical insights into restoring metabolic homeostasis in aging tissues and may expand the therapeutic scope of GLP-1 RAs beyond their current indications. Enhancing GLP-1 signaling in older individuals could mitigate chronic inflammation, improve metabolic equilibrium, and support neuroprotection, collectively contributing to extended healthspan and potentially lifespan.[50–58]

This review builds upon prior work by examining the role of GLP-1 agonism in aging, integrating contemporary metabolic and molecular findings. We present hypotheses centered on the mechanisms of GLP-1 RAs, proposing them as potential modulators of aging hallmarks and longevity. We aim to develop a conceptual framework to guide future research, inform experimental studies, and facilitate translational testing in humans.

Hence, this review begins by examining how GLP-1R signaling relates to extending healthspan. Next, we examine how GLP-1 RAs impact each of the twelve proposed hallmarks of aging. Our goal is to clarify their possible role in promoting healthy aging. We then address the limitations and safety concerns associated with GLP-1 agonism. Finally, the review addresses the broader implications of these findings for geroscience and outlines future directions for investigating the potential of GLP-1 RAs in healthspan extension, while also acknowledging the limitations and potential biases inherent in this analytical review.

GLP-1R signaling in healthy aging

Recent studies on GLP-1 have examined its possible influence on the aging process, alongside its established roles in regulating glucose metabolism and appetite. An increasing amount of evidence indicates that GLP-1 plays a role in several important age-associated processes, including inflammation, mitochondrial function, and cellular repair. These processes might be connected to some of the hallmark features of aging.[1–4] For instance, GLP-1 helps protect neurons and positively affects the functioning of various organs and systems related to metabolism, cardiac health, and tissue repair. By managing some of these systems, GLP-1 might also play a role in pathways related to longevity. This makes it an interesting target for promoting healthy aging.[10,11,13,24,26,29,30–32,34] Therefore, this section outlines evidence for a biological mechanism through which GLP-1 can enhance healthspan and reduce the effects of aging.

The GLP-1R is a type of G-protein-coupled receptor predominantly located in the pancreas, brain, gastrointestinal tract, and various other tissues.[15] Upon binding with its ligand, GLP-1, the receptor triggers multiple intracellular signaling pathways. These pathways affect significant processes linked to aging and extend beyond merely regulating glucose metabolism.[59–61] The most prominent GLP-1R signaling pathway stimulates adenylyl cyclase, leading to increased concentrations of cyclic adenosine monophosphate (cAMP) and the subsequent activation of protein kinase A (PKA).[62,63] In the pancreas, this pathway boosts insulin release in response to rising blood glucose, helping to keep glucose levels stable.[64] Investigations involving GLP-1R knockout models highlight its significance in appetite control and glucose homeostasis.[65,66] For example, the absence of GLP-1R leads to increased food intake and interferes with the secretion of insulin and glucagon, which impacts glucose management.[67] Regarding aging, activating GLP-1R enhances insulin sensitivity and addresses age-associated IR, a critical factor in metabolic disorders such as T2D.[68,69]

In addition to activating the cAMP/PKA pathway, activation of GLP-1R has been associated with other intracellular mechanisms such as the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathway, which plays a crucial role in regulating key functions like cell survival, mitochondrial activity, and autophagy, or the breakdown and recycling of damaged cellular components.[67,70] Activation of this pathway via GLP-1R imparts resistance to cells and the maintenance of tissue functions with respect to aging and diseases leading to oxidative stress and inflammation, which undermine cellular integrity.[71] It has generally been assumed that the activation of PI3K/Akt from GLP-1R occurs through cAMP-independent pathways, such as β-arrestin signaling or receptor transactivation; however, newer studies suggest that this process may be more complex than previously thought.[72,73] The increase in intracellular cAMP after GLP-1R activation then activates a guanine nucleotide exchange factor called Epac (Exchange Protein directly Activated by cAMP), which induces PI3K activation followed by Akt phosphorylation.[74] As a result, the cAMP/Epac signaling pathway operates alongside the traditional cAMP-independent pathway, highlighting the variety of GLP-1R signaling.[75] Additionally, it

has been shown that the activation of GLP-1R through the cAMP/Epac/PI3K/Akt pathway facilitates antioxidant and anti-apoptotic effects while enhancing mitochondrial function in H9c2 cardiomyoblast cells.[76]

Thus, since PI3K/Akt is activated by both cAMP-dependent and cAMP-independent pathways, there is likely context-dependent variability in GLP-1R signaling, influenced by cell type, receptor architecture, and duration of stimulation. The presence of multiple intracellular signaling systems suggests potential plasticity in GLP-1 action and supports the hypothesis that selective engagement of GLP-1R could preferentially recruit beneficial signaling pathways. It is plausible, though untested, that targeted modulation of GLP-1R activity could maximize the beneficial effects of GLP-1 while minimizing potential adverse effects, particularly in conditions involving metabolic dysfunction, cardiovascular health, or other age-associated pathologies. Phosphodiesterases (PDEs) are significant regulators of the duration and magnitude of cAMP signaling.[77] Pharmacological inhibition of PDEs could theoretically sustain or elevate cAMP levels, potentially enhancing GLP-1 RA signaling.[78] Augmented cAMP signaling might not only strengthen classical cAMP/PKA pathways but could also modulate cAMP/Epac-dependent pathways, including PI3K/Akt, which have been associated with aspects of cellular survival, mitochondrial bioenergetics, and autophagy in preclinical studies.[79] Because aging is characterized by gradual dysregulation of cellular homeostasis and increased oxidative stress, it is hypothesized that enhanced cAMP signaling could support cellular plasticity and resilience, potentially mitigating certain age-related dysfunctions; however, these observations are primarily based on *in vitro* and rodent models.[80,81]

Additionally, it is theorized that combining PDE inhibitors with GLP-1 RAs may provide additive benefits in metabolic and cardiovascular contexts in aging models, although supporting human data remain limited. This aligns with concepts of compartmentalized and biased receptor signaling, where selective pathway engagement could influence functional outcomes.[82–85] Nevertheless, the optimal targeting of specific PDE isoforms across tissues remains uncertain.

Furthermore, GLP-1R activation may modulate ERK/MAPK pathways, which have demonstrated anti-inflammatory and neuroprotective effects in rodent and *in vitro* studies.[86,87] These pathways are proposed to support brain health during aging by reducing neuroinflammation and promoting synaptic plasticity and neurogenesis.[88,89] Sirtuins, a family of nicotinamide adenine dinucleotide (NAD)+-dependent enzymes, regulate cellular metabolism, mitochondrial function, and stress responses.[90,91] GLP-1R signaling is suggested to intersect with sirtuin-mediated processes to promote mitochondrial biogenesis and mitophagy, thereby supporting cellular energy homeostasis and mitigating oxidative stress in aging tissues, with evidence primarily from cellular and rodent models.[92,93] Additionally, NAD+ precursors, such as nicotinamide riboside and nicotinamide mononucleotide, may hypothetically synergize with GLP-1R signaling to enhance mitochondrial function and cellular resilience, although the extent of these interactions remains untested in humans.[94–101]

Moreover, GLP-1R not only plays a role in metabolic functions but also governs neuroendocrine activities, including the regulation of the hypothalamic-pituitary-adrenal (HPA) axis, which affects the body's reaction to stress.[102,103] In the context of aging, disruptions in the HPA axis are linked to cognitive decline and mental health issues, including depression.[104,105] The activation of GLP-1R may enhance the brain's capability to cope with stress by facilitating the release of neurotransmitters and managing the stress response, potentially mitigating both cognitive and emotional challenges related to aging.[106–108]

Additionally, GLP-1 RAs play a role in neuroendocrine regulation, affecting the HPA axis, which controls the body's reaction to stress. Disruption of the HPA axis with age has been linked to cognitive decline and mood disorders like depression. Activating GLP-1R improves the brain's ability to cope with stress by influencing neurotransmitter release and pathways involved in the stress response, which may help reduce cognitive and emotional issues related to aging.[106–108]

Aside from neuroendocrine actions, GLP-1R signaling contributes to cardiovascular and vascular health. GLP-1R signaling enhances endothelial function, lowers inflammation, and promotes vasodilation, all of which are important for preventing cardiovascular aging.[109–111] At the same time, GLP-1R is present in the cardiovascular system, and activation of GLP-1R can reduce or delay vascular changes that are associated with aging, such as arterial stiffness and hypertension.[112,113] Several clinical studies support the cardiovascular benefits of GLP-1 RAs, as there is evidence from meta-analyses of cardiovascular outcome trials illustrating that GLP-1 RA therapy lowers the risk of major adverse cardiovascular events by ~14% and all-cause mortality by ~12% in patients with T2D.[114–116]

Real-world comparative data provide further context with regard to vascular safety. In a large U.S. Veterans cohort, for instance, sodium-glucose cotransporter 2 (SGLT2) inhibitors were found to be associated with a higher rate of peripheral artery disease-related surgical events than DPP-4 inhibitors (11.2 vs. 10.0 per 1,000 person–years; adjusted HR 1.18).[117,118] Conversely, analyses of Taiwanese and Korean cohorts have found either neutral or protective effects, including decreased limb ischemia, amputation, and cardiovascular death.[119,120] Additionally, post-marketing data indicate that the apparent risk for amputation was again related to sensor change and enhanced monitoring and that there are equal outcomes overall between SGLT2 inhibitors and GLP-1 RAs.[121] Overall, these data accumulate to show that GLP-1 RAs provide not only metabolic and mitochondrial effects but also meaningful clinical impact for vascular and neuroendocrine protection that may ultimately decrease age-related decline in cardiovascular health, musculoskeletal health, and cognitive health.

In summary, GLP-1 plays a role in more areas than just appetite regulation and glucose management; it is essential for maintaining a healthy lifespan. When GLP-1R is stimulated, various downstream signaling pathways become activated, including cAMP/PKA, cAMP/Epac/PI3K/Akt, and ERK/MAPK. These pathways collaborate to promote the health of mitochondria, support autophagy, provide neuroprotection, and facilitate nearly all cellular repair processes. This results in reduced inflammation, improved insulin sensitivity, and enhanced resilience to stress. Furthermore, GLP-1R signaling participates in the regulation of sirtuins and the creation of new mitochondria, particularly with respect to NAD+ precursors like nicotinamide riboside or nicotinamide mononucleotide. Additionally, GLP-1R signaling significantly influences vascular health, HPA axis regulation, and the generation of new neurons, all of which have a notable impact on aging. Given the complexity nature of these processes, they present opportunities for therapies aimed at enhancing healthspan and mitigating aging-related decline. In this context, Figure 1 illustrates how GLP-1 RAs activate the GLP-1R, subsequently initiating key intracellular signaling pathways such as Epac/PI3K/Akt, cAMP/PKA, and ERK/MAPK. These signaling pathways promote mitochondrial

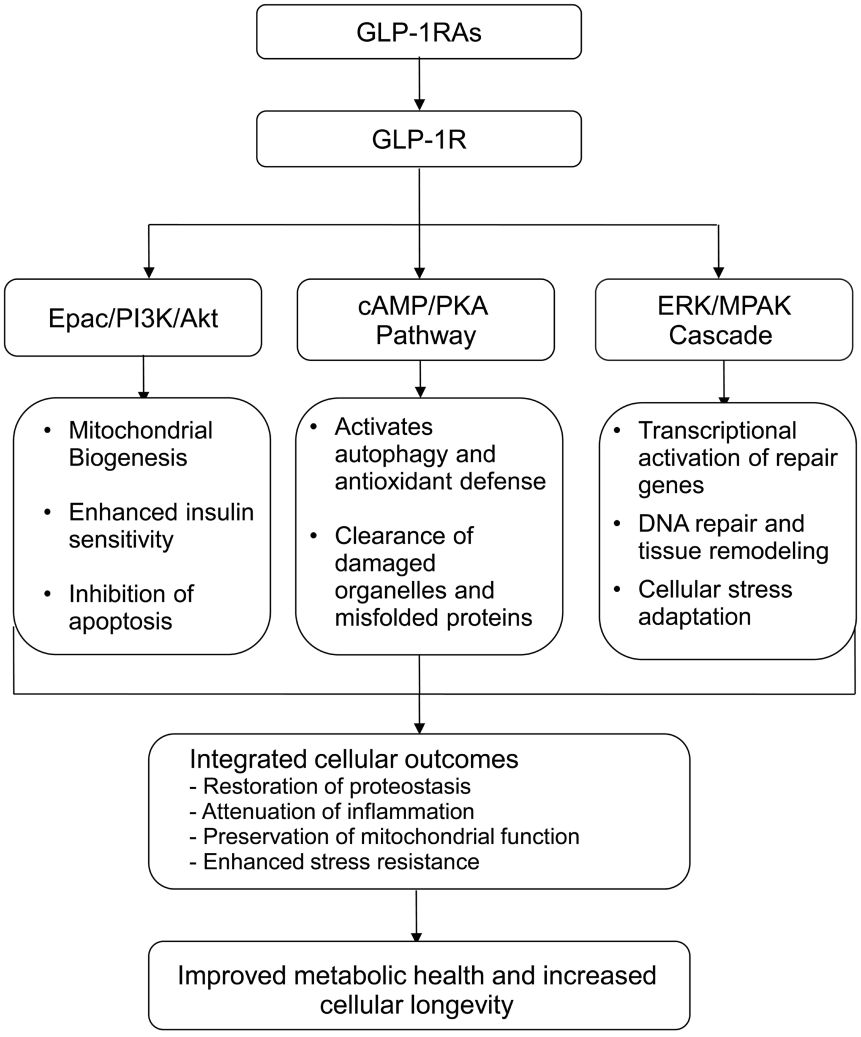

Fig. 1. The mechanistic pathways linking GLP-1 receptor activation to cellular resilience and healthy aging. Engagement of a glucagon-like peptide-1 receptor agonist with the glucagon-like peptide-1 receptor triggers a coordinated cascade of intracellular signaling events that govern metabolic reprogramming and cellular repair. Following ligand binding, activation of the Epac/PI3K/Akt signaling axis promotes mitochondrial biogenesis, enhances insulin sensitivity, and suppresses apoptotic signaling, thereby supporting cellular energy homeostasis. Concurrently, cAMP/PKA signaling induces autophagic flux and upregulates antioxidant defense mechanisms, facilitating the clearance of damaged organelles and misfolded proteins. In parallel, activation of the ERK/MAPK pathway drives transcriptional programs involved in stress adaptation, DNA repair, and tissue remodeling. Collectively, these temporally coordinated and overlapping pathways form a self-reinforcing network that mitigates inflammation, restores proteostasis, and extends cellular lifespan. Through these integrative mechanisms, GLP-1 RAs exert effects beyond metabolic regulation, mechanistically linking receptor activation to systemic rejuvenation and the promotion of healthy aging. Akt, protein kinase B; cAMP, cyclic adenosine monophosphate; Epac, exchange protein directly activated by cyclic adenosine monophosphate; ERK, extracellular signal-regulated kinase; GLP-1R, glucagon-like peptide-1 receptor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A.

biogenesis, autophagy, and cellular repair mechanisms, ultimately fostering overall well-being and aiding in the process of healthy aging.

In the following section, we will explore the impact of activating GLP-1 signaling on various aging hallmarks, with the aim of potentially extending both lifespan and healthspan, as well as gaining insights into how the modulation of GLP-1R signaling may affect aging at both cellular and systemic levels.

GLP-1 RAs and the hallmarks of aging

GLP-1 RAs, which are utilized for T2D and obesity, have shown various benefits beyond managing metabolism and are attracting attention for their potential effects on aging and diseases related to aging. By influencing numerous biological pathways, GLP-1 RAs may affect several important hallmarks of aging. Each of the 12 proposed hallmarks of aging is examined individually in this article to explore how these agents may mitigate various aging processes, either through direct or indirect modulation.

Genomic instability and DNA damage response (DDR)

Genomic instability, which involves damage to DNA and mutations, contributes to the acceleration of aging. If nuclear DNA damage is not resolved, it results in mutations and chromosomal

abnormalities that disrupt transcription and replication. This disruption can result in cellular dysfunction, oncogenic transformation, senescence, aging, and programmed cell death, thereby hastening tissue degeneration and impacting overall health.[122–124] GLP-1 RAs may help mitigate this issue by enhancing the DDR. For example, earlier research in rats demonstrated that menadione, a compound that induces reactive oxygen species (ROS), causes oxidative DNA damage and leads to apoptosis in neurons. Nonetheless, activating the GLP-1R in these rats protects neurons from the oxidative damage induced by menadione by improving the efficiency of DNA repair and preserving genomic integrity.[125] This protective mechanism is likely facilitated through the activation of the adenosine 5′-monophosphate–activated protein kinase (AMPK) pathway, which plays a crucial role in managing cellular stress and the DNA repair process. By improving DDR, GLP-1 RAs may limit the build-up of DNA damage, which in turn diminishes cellular aging and enhances tolerance to cellular stress.[126] These studies suggest that GLP-1R could be a potential target for creating new treatments for cerebral ischemic stroke and human neurodegenerative disorders.[127–129]

Telomere attrition

The gradual reduction of telomeres as we grow older is a significant characteristic of aging, leading to cellular senescence and impairing tissue function.[130–132] When telomeres become severely shortened, the cell detects this as DNA damage, initiating a DDR. This response activates specific signaling pathways, leading to cellular senescence, where the cell ceases to divide but remains metabolically active.[133] GLP-1 RAs might play a significant role in maintaining telomere integrity by boosting the expression of telomerase and ensuring stable telomere length. Preliminary research indicates that the activation of GLP-1R facilitates mechanisms essential for telomere stability, potentially delaying cellular aging and extending cellular lifespan.[134,135] Research has indicated that stimulating GLP-1R may reverse certain changes associated with cellular aging, including the shortening of telomeres and the impairment of DNA repair mechanisms.[136] A recent study involving non-human primates found a strong link between plasma GLP-1 levels from earlier life stages and telomere lengths measured in older individuals, implying a more indirect connection between GLP-1R stimulation and the maintenance of telomeres.[137] These results bolster the notion that GLP-1 RAs could have an impact on cellular aging and potentially diminish age-related cellular aging in humans.

Additionally, GLP-1 RAs might stimulate sirtuin proteins like SIRT1, which play a crucial role in maintaining telomere integrity and preventing cellular senescence.[138,139] By improving insulin sensitivity and reducing metabolic stress, GLP-1 RAs effectively slow the progression of telomere shortening, offering a comprehensive strategy to combat cellular aging. They enhance glucose metabolism, lower oxidative stress, and improve mitochondrial function, all of which safeguard telomeres and decrease the likelihood of health decline associated with aging.[140,141] This synergistic impact on both the metabolic and genetic aspects of aging makes GLP-1 RAs a distinctive approach to postpone cellular aging and encourage longevity.

Cellular senescence

Cellular senescence, an important factor in tissue dysfunction and the aging process, results from cellular stress and is marked by a permanent halt in the cell cycle. The buildup of senescent cells (SCs) plays a role in several conditions associated with aging, including osteoarthritis, CVDs, and neurodegenerative diseases (NDs).[142,143] Research indicates that GLP-1 RAs could play a role in reducing oxidative stress and inflammation, two major factors that contribute to cellular senescence.[144,145] In early investigations, GLP-1 RAs exhibit considerable antioxidant effects by lowering ROS, thereby mitigating oxidative damage in different tissues. In pancreatic β-cells, the stimulation of GLP-1R leads to a reduction in ROS production, safeguarding against apoptosis induced by oxidative stress and promoting insulin secretion.[146–148] GLP-1 RAs enhance the protection of β-cells from apoptosis triggered by endoplasmic reticulum (ER) stress by affecting key proteins involved in the unfolded protein response, reducing ER stress, and fostering cell survival. Given that extended periods of ER stress significantly contribute to β-cell aging, GLP-1 RAs represent a promising approach to slow down or avert β-cell deterioration in diabetes.[149,150]

In addition to its role in the pancreas, stimulating GLP-1R provides further protective benefits in vascular tissues by decreasing ROS-related harm in endothelial cells. This benefit is achieved by boosting antioxidant enzyme levels and enhancing mitochondrial function, potentially contributing to the maintenance of vascular health and postponing age-related CVDs.[151,152] Additionally, GLP-1 RAs lower oxidative stress within the brain, suggesting neuroprotective benefits that could improve neural health and hinder age-related deterioration. Along with their antioxidant properties, GLP-1 RAs also demonstrate considerable anti-inflammatory effects, further diminishing the pro-inflammatory environment that accelerates aging.[153,154] Studies have shown that activating GLP-1R leads to a decrease in pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) in adipose tissue, revealing a systemic anti-inflammatory impact.[155,156] Furthermore, research indicates that GLP-1 RAs decrease neuroinflammation in rodent models of NDs, which may help mitigate the inflammatory processes associated with neuronal aging.[157] Additionally, activation of GLP-1R promotes the AMPK pathway, which plays a vital role in the regulation of autophagy. GLP-1 RAs enhance autophagy in rodent models, facilitating the elimination of damaged mitochondria and increasing cellular resilience to stress.[158,159] Furthermore, activation of GLP-1R in skeletal muscle cells enhances autophagic activity and promotes the generation of new mitochondria, which helps prevent the accumulation of SCs and improves cellular maintenance.[160,161]

Overall, these findings indicate that GLP-1 RAs may lessen the strain that SCs place on the body—not only by reducing oxidative stress but also by inhibiting inflammation and promoting cellular repair mechanisms. Although much of the supporting evidence comes from studies in animals, these results underscore their potential for clinical applications aimed at promoting healthy aging and reducing age-related cellular senescence. While a comprehensive discussion of the literature is outside the scope of this review, the data presented so far certainly demonstrate how quickly our understanding of the potential role of GLP-1 RAs as a strategy for healthy aging is progressing.

Inflammaging

Several age-related pathologies are triggered by inflammaging, which refers to chronic low-grade inflammation.[162,163] GLP-1 RAs decrease inflammation through modulation of the function of immune cells and lowering pro-inflammatory cytokines like TNF-α and IL-6. In preclinical studies, GLP-1 RAs reduced cytokine levels in various tissues, such as adipose and vascular tissues, which significantly contribute to inflammation associated with aging. In rodent models, GLP-1 RAs reduce neuroinflammation, implying

Table 1. Lean-mass effects in GLP-1 RA trials

Trial	Population	Agent & dose	Duration	Fat loss (Kg)	Lean-mass loss (kg)	Reference
STEP 1	Obese Adults	Semaglutide 2.4 mg weekly	68 wks	14.9	2.9	181,182
SURMOUNT-1	Obese adult	Tirzepatide 15 mg weekly	72 wks	24	3.8	183,184
STEP 2	T2D, overweight	Semaglutide 2.4 mg weekly	68 wks	11.2	2.2	185
SURMOUNT-2	Obese adults	Tirzepatide 10 mg weekly	72 wks	18.5	3.1	186,187
SEMALEAN Study	106 adults with obesity (mean BMI: 46.3 kg/m^2; 68.9% female)	Semaglutide 2.4 mg weekly	2 months	~13–15 kg (−18% at M12)	−3 kg (initially, then stabilized)	188

The values represent average changes; reductions in lean mass can vary and may be lessened through resistance training and sufficient protein consumption. BMI, body mass index; GLP-1 RA, glucagon-like peptide-1 receptor agonist; T2D, type 2 diabetes.

that they may provide neuroprotective advantages in aging and NDs such as Alzheimer's.[164,165] Additionally, research involving humans appears to corroborate these results, indicating that GLP-1 RAs reduce inflammatory markers, with clinical trials showing decreases in TNF-α and IL-6 levels among individuals with T2D.[166,167] By reducing inflammation, GLP-1 RAs help mitigate the chronic inflammation associated with aging, promoting healthier aging and lowering the risk of diseases such as CVDs and NDs.

IR

GLP-1 RAs address IR through multiple mechanisms. They stimulate insulin secretion from the pancreas when blood glucose levels are high while inhibiting the secretion of glucagon, which would increase blood glucose further.[168–170] GLP-1 RAs enhance skeletal muscle insulin sensitivity and improve the body's ability to use glucose. Nevertheless, by slowing gastric emptying, GLP-1 RAs decrease the magnitude of high peaks in blood glucose levels following ingestion.[171,172] The anti-inflammatory and antioxidant properties of GLP-1 RAs contribute to maximizing the advantages of a better metabolic condition. GLP-1 RAs enhance the expression of glucose transporters in tissues sensitive to insulin, leading to increased glucose uptake and improved regulation of blood glucose levels.[173,174] Collectively, these mechanisms of action make GLP-1 RAs an important therapeutic agent for the treatment of IR and for improving glycemic control.

Mitochondrial dysfunction

GLP-1 RAs enhance mitochondrial function through multiple interconnected mechanisms.[175] They promote mitochondrial biogenesis via activation of the peroxisome proliferator-activated receptor gamma coactivator 1-alpha signaling axis, increase mitochondrial respiration, membrane potential, and oxygen consumption, and suppress the generation of ROS and oxidative stress.[176,177] These mechanistic effects have been observed in both *in vitro* and *in vivo* studies. mitochondrial dysfunction—characterized by impaired oxidative phosphorylation and elevated oxidative stress—is a well-established hallmark of aging.[178] Consequently, GLP-1 RAs may help restore mitochondrial homeostasis, potentially through AMPK and sirtuin signaling pathways involved in energy sensing, autophagy, and mitochondrial turnover; however, direct human evidence for these mechanisms remains limited.[179,180] In theory, enhancing mitochondrial efficiency while reducing oxidative burden could promote muscle anabolism by redirecting nutrient partitioning toward muscle protein synthesis, thereby countering sarcopenia and functional decline.

Clinical trials have indicated that GLP-1 RA–induced weight loss in older adults can result in measurable reductions in lean mass, with the proportion of lean tissue loss varying depending on the specific GLP-1 RA, dose, treatment duration, and concurrent lifestyle interventions (see Table 1).[181–188] Accordingly, older adults prescribed GLP-1 RAs should undergo routine monitoring of body composition (e.g., via dual-energy X-ray absorptiometry or bioelectrical impedance analysis), ensure adequate protein intake (approximately 1.0–1.2 g/kg body weight/day), and maintain overall nutritional quality and physical function (e.g., resistance training ≥ 2 sessions per week) to minimize loss of muscle mass during weight reduction.[189–191] Additional considerations include appropriate dose titration, renal function monitoring, and review of polypharmacy, as outlined in Table 2.[192–207]

While concerns about potential muscle loss with GLP-1 RAs remain, recent evidence from the SEMALEAN study suggests this risk may be attenuated with semaglutide 2.4 mg.[188,208] Although a modest reduction in lean mass was observed at 12 months, muscle function, assessed via handgrip strength, improved significantly, the prevalence of sarcopenic obesity declined, and resting energy expenditure relative to lean mass increased—indicating enhanced metabolic efficiency. These findings support semaglutide 2.4 mg as an effective therapeutic option for weight and fat mass reduction while preserving, or potentially improving, muscle function and metabolic health. Nonetheless, individualized monitoring remains essential, particularly in older adults and other at-risk populations, to ensure that therapeutic benefits are not offset by declines in muscle mass or physical performance.

In summary, these strategies support the preservation of lean mass, functional capacity, and safety in older adults, while enabling the mitochondrial, metabolic, and broader healthspan-supporting benefits of GLP-1 RAs. The recommendations are informed by preclinical studies, trial-level evidence, and geriatric exercise/nutrition guidelines. Development of a formal clinical guideline, including specific dose-titration protocols, chronic kidney disease (CKD) considerations, and polypharmacy interactions, remains beyond the scope of this review and would require a dedicated systematic investigation.

Epigenetic alterations

Epigenetic changes, such as variations in DNA methylation and

Table 2. Practical monitoring checklist for older adults using GLP-1 receptor agonists

Domain	Recommendation	Reference
Body composition	Baseline and regular DEXA/BIA scans (every 3–6 months)	192,193
Nutrition	Protein consumption should be between 1.0 and 1.2 grams per kilogram of body weight each day; ensure sufficient caloric intake	194,195
Exercise	Resistance training with progressive overload at least twice a week; engaging in aerobic activities as tolerated	196,197
Dose titration	Gradual increase; tailor to the needs of vulnerable older individuals	198,199
Renal function	Periodic eGFR monitoring, especially in CKD or polypharmacy	200,201
Polypharmacy	Assess concurrent medications (diuretics, antihypertensives, glucose-lowering agents)	202,203
Adverse events	Observe for gastrointestinal symptoms, orthostatic changes, tiredness, low blood sugar	204,205
Pausing/Stopping	Briefly suspend or modify dosage due to adverse effects or deterioration in function	206,207

The checklist offers a useful structure to maintain lean mass, functionality, and safety while undergoing GLP-1 RA treatment in older individuals; it is advised to tailor the approach to each person. BIA, bioelectrical impedance analysis; DEXA, dual-energy X-ray absorptiometry; GLP-1 RA, glucagon-like peptide-1 receptor agonist.

histone modifications, significantly influence aging and diseases that are associated with aging.[209–211] One specific locus of interest is the GLP-1R, which plays a crucial role in insulin secretion and the regulation of glucose levels. In individuals with T2D, epigenetic modifications, specifically increased DNA methylation of the GLP-1R gene, reduce receptor expression, impairing the function of GLP-1 and lowering insulin secretion.[212–214] GLP-1 RAs reverse detrimental epigenetic changes by promoting the demethylation of the GLP-1R gene, thereby restoring its expression and improving insulin sensitivity. Additionally, GLP-1 RAs may influence other epigenetic regulators, such as sirtuins and histone deacetylases, which play a role in crucial cellular functions like inflammation and stress response.[215,216] By reinstating proper epigenetic control, GLP-1 RAs could potentially slow down the aging process and mitigate age-related cellular dysfunction, particularly in individuals with diabetes. In essence, GLP-1 RAs might "reconfigure" the epigenetic characteristics of diabetic cells, offering significant therapeutic benefits in addressing IR and reversing harmful epigenetic alterations linked to aging and metabolic disorders. This hypothesis is thought-provoking and deserves thorough investigation.

Dysregulated nutrient sensing

Alterations in nutrient-sensing pathways like insulin/insulin-like growth factor 1 (IGF-1) signaling and mechanistic target of rapamycin (mTOR) play a crucial role in the aging process and the development of age-related illnesses.[217–219] In particular, the insulin/IGF-1 pathway is essential for managing aging and longevity. Increased activity of this pathway is related to enhanced aging and the occurrence of diseases like T2D and CVDs, whereas decreased IGF-1 signaling increases the lifespans of model organisms like worms, flies, and mice.[220] This is further supported by studies in caloric restriction, a type of nutrient restriction that has the effect of lowering both insulin and IGF-1 signaling and increasing longevity.[221,222] Likewise, inhibiting mTOR, particularly with the drug rapamycin, extends lifespan and delays the onset of age-related illnesses in several species.[223,224] Notably, GLP-1 RAs enhance nutrient recognition by increasing insulin sensitivity, regulating mTOR signaling, and promoting autophagy, among other mechanisms, as previously mentioned. These actions improve metabolic adaptability, foster cellular well-being, and could guard against metabolic disorders, aiding in healthier aging.[225]

Altered intercellular communication

GLP-1 RAs enhance communication between cells, a process that typically decreases as we age.[226,227] These medications stimulate the growth and longevity of stem cells, crucial factors for the repair of tissues.[228,229] For instance, GLP-1 RAs facilitate the regeneration of pancreatic β-cells, contributing to tissue restoration.[230,231] GLP-1 RAs have been previously described in this review as improving tissue homeostasis and repair through reducing age-related inflammation (i.e., TNF-α and IL-6).[230,231] GLP-1 RAs also have positive effects on endothelial function, including increasing nitric oxide production, allowing for increased blood flow, decreasing vascular stiffness, and providing nutrients that are delivered to a specific repair area.[232,233] GLP-1 RAs also promote the creation of new mitochondria, which provide metabolic energy for cellular functions, aiding in both communication between cells and the signaling necessary for tissue repair.[234] GLP-1 RAs influence immune system functions and reduce chronic inflammation while facilitating improved wound healing, which collectively promote enhanced tissue regeneration.[235] These combined effects restore communication between cells, improve tissue repair, and may help mitigate the deterioration of tissue homeostasis associated with aging.

Loss of proteostasis

Proteostasis, or the regulation of protein quality and function, declines with age, resulting in the buildup of misfolded proteins and cellular malfunction.[210,211] GLP-1 RAs promote proteostasis by influencing autophagy, a critical cellular process that maintains protein quality and cellular health.[236,237] GLP-1 RAs boost autophagic activity and eliminate misfolded proteins by inhibiting mTOR signaling and activating pathways such as AMPK, among others.[238,239] This function is particularly beneficial in NDs, as the accumulation of toxic proteins can speed up disease progression. By engaging in these and other mechanisms, GLP-1 RAs promote cellular health, reduce neurodegenerative processes, and support healthy aging.[240,241]

Stem cell exhaustion

According to current studies, GLP-1 RAs may have a protective effect against stem cell depletion, which is linked to oxidative stress, inflammation, and cellular aging, factors often associated with aging or chronic conditions like diabetes.[242–244] By potentially mitigating the detrimental effects of oxidative stress, inflammation,

and cellular senescence, GLP-1 RAs can contribute to preserving both the functionality and number of stem cells, thus fostering a healthier cellular environment that supports regenerative processes. Several other studies support that GLP-1 RAs may preserve the function of other stem cell populations (e.g., hematopoietic stem cells, which are crucial for blood cell production).[245–247] Greater detail is warranted regarding the protection of stem cells, which will help us understand the protective processes of GLP-1 RAs. A potential protective mechanism is thought to involve reducing oxidative stress and inflammation, which are two mechanisms through which stem cells deteriorate, as illustrated above. GLP-1 RAs can stimulate antioxidant defenses, influence immune system responses, and encourage angiogenesis (the creation of new blood vessels), all of which contribute to creating an environment that supports the survival and activity of stem cells. These insights hold considerable significance in conditions such as T2D, where ongoing inflammation and weakened vascular integrity adversely affect the functionality of stem cells. In these circumstances, GLP-1 RAs might restore and/or preserve stem cell function, thereby improving the prospects for effective tissue repair and regeneration. As a result, GLP-1 RAs present a beneficial approach to alleviating stem cell exhaustion and optimizing healthspan in aging and disease states.

Dysbiosis

Dysbiosis, which refers to an imbalance in gut microbiota, is linked to systemic inflammation and metabolic dysfunction related to aging.[248,249] It is involved in various chronic diseases. GLP-1 RAs enhance microbial diversity and promote gut health by fostering beneficial bacteria and eliminating harmful ones. Improvements in the gut microbiome lead to better gut barrier function, reduced inflammation, and provide a chance to mitigate the impacts of dysbiosis on the body while enhancing immune function and metabolic stability within a dysbiotic condition.[250,251] Enhancing gut health gives GLP-1 RAs the potential to reverse aging effects and lower the likelihood of age-associated illnesses.

In summary, enhancing the treatment of age-related conditions through the activation of GLP-1R with the application of GLP-1 RAs shows significant potential. By boosting GLP-1 signaling, GLP-1 RAs enhance insulin sensitivity, reduce inflammation, improve mitochondrial function, and promote gut health, all of which may slow the aging process and lower the likelihood of diseases like T2D, CVDs, and NDs. GLP-1 RAs contribute to telomere stability, lessen cellular aging, enhance tissue regeneration, and mitigate the negative impacts of aging. Therefore, by reestablishing cellular and metabolic equilibrium, GLP-1 RAs have the potential to extend lifespan by potentially addressing age-related illnesses. In this regard, Figure 2 depicts how GLP-1 RAs engage the GLP-1 receptor to modulate multiple hallmarks of aging. Through Epac/PI3K/Akt, cAMP/PKA, and AMPK/SIRT1 signaling, they enhance mitochondrial function, autophagy, and metabolic reprogramming, collectively preserving genome integrity, proteostasis, and systemic homeostasis to promote healthy aging.

GLP-1 agonism: Emerging hypotheses and limitations

While GLP-1 RAs hold therapeutic promise for increasing lifespan and reducing the morbidity of age-related illness through action on multiple organ systems, tissue-specific effects of GLP-1R agonism are possible. This highlights the importance of having a targeted treatment approach and exercising caution when using GLP-1 RAs in older populations. A key point is that the activation of GLP-1R can produce specific effects on different organs by addressing age-related diseases in various manners, such as enhancing cognitive function and addressing vascular issues caused by age-related brain changes, while simultaneously raising the likelihood of renal dysfunction in aging organs. Within the brain, agonism of GLP-1 could enhance cognitive function and diminish neuroinflammation and potentially provide a protective effect against diseases that are NDs, including Alzheimer's disease and Parkinson's disease. The UK Biobank study found that different regions of the brain exhibit varying patterns of aging, with certain areas, such as the hippocampus, showing a more rapid decline in volume. This suggests that GLP-1 agonism may produce different effects depending on the specific brain region as well as the unique age-related changes experienced by each individual.[252–254]

Additionally, the aging process of various organs exhibits variability, as demonstrated by the UK Biobank trial, which adds complexity to the impact of GLP-1 RAs and underscores the importance of personalized treatment.[255,256] Since different organs can age at distinct rates, some individuals may experience accelerated aging in certain organs (such as the brain or kidneys), while others may retain better functionality in different organs. This variation illustrates that the effects of GLP-1R stimulation can vary from individual to individual. In simpler terms, GLP-1 RAs might have beneficial effects on the metabolic health of peripheral organs (such as the liver and muscles) by enhancing insulin sensitivity, decreasing fat accumulation, and promoting muscle mass, which can help mitigate sarcopenia, a common age-related condition.[257,258] On the other hand, stimulation of GLP-1R in the kidneys and cardiovascular system may enhance renal function, lower blood pressure, and promote vasodilation. However, certain elements, such as existing CVDs or CKD, could affect how GLP-1 responds.[259–261] As a result, tailored strategies that take into account each patient's specific aging and health issues will be essential for maximizing the benefits of GLP-1 RAs. Importantly, reduced blood flow can diminish the effectiveness of medications for patients with heart disease, and CKD can hinder drug elimination, leading to increased drug levels and a higher risk of adverse effects.[262,263] Considering these obstacles, the predictability and effectiveness of GLP-1 medications may decrease for older individuals with more intricate health problems, making it crucial to customize treatment plans.

An alternative hypothesis suggests that the activation of GLP-1R may influence the gut microbiome in ways that could impact both metabolic and neurological aging. GLP-1R activity might affect the microbiome by altering its composition and functioning through several mechanisms, including the influence on gut motility, modification of nutrient availability in the intestinal lumen, and regulation of immune function within the intestinal lining.[264,265] This could create an environment where beneficial bacterial strains can flourish, potentially enhancing metabolic health. Given that the gut microbiota plays a crucial role in the body's management of inflammation, metabolism, and brain function, the interplay between GLP-1 signaling and the gut microbiome is undoubtedly intricate and complex, warranting further investigation into this relationship.[266,267]

Despite the potential promise of GLP-1 RAs, a number of issues must be addressed if we are to maximize their long-term viability and impact. One major concern is that chronic use of GLP-1 RAs may create a supraphysiological state of GLP-1, leading to gastrointestinal upset, pancreatitis, or excessive stimulation of pancreatic activity.[268] To mitigate the possibility of these problems, healthcare providers should diligently manage dosing and oversee usage

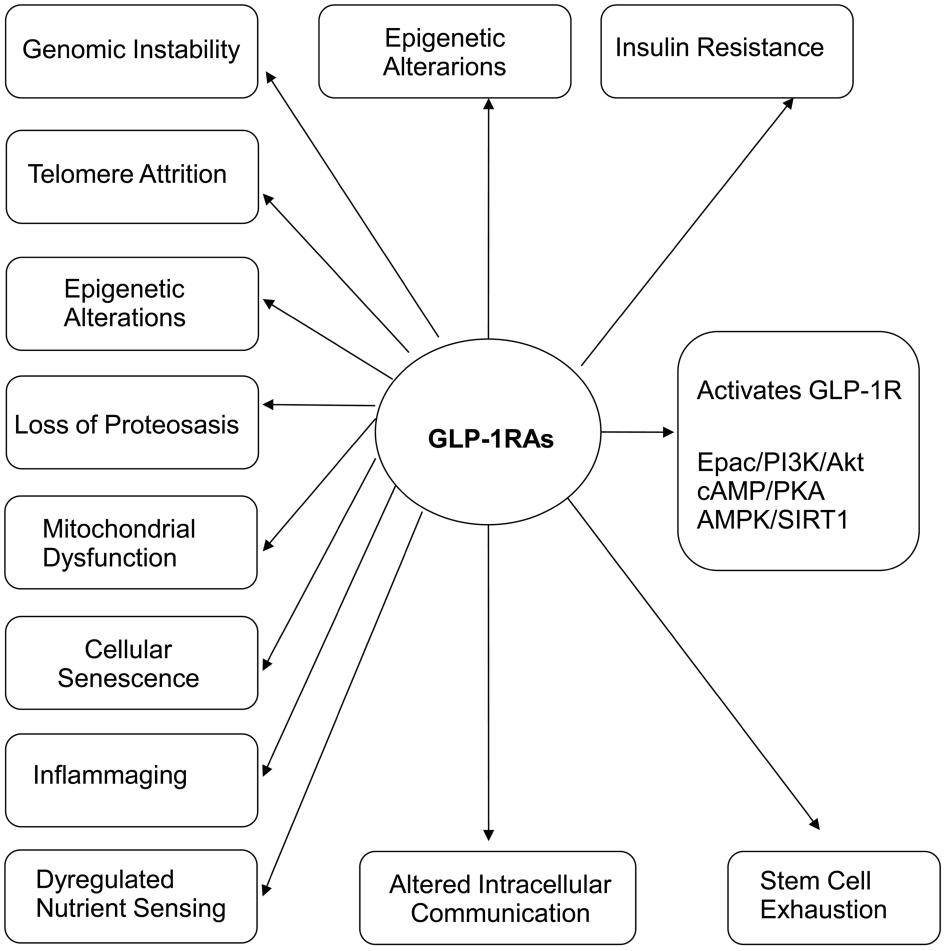

Fig. 2. GLP-1 receptor agonists (GLP-1 RAs) as mediators of aging hallmarks. GLP-1 RAs modulate the twelve hallmarks of aging through an integrated network of signaling pathways. Activation of the glucagon-like peptide-1 receptor (GLP-1R) potentiates the exchange protein directly activated by cyclic adenosine monophosphate/phosphoinositide 3-kinase/protein kinase B (Epac/PI3K/Akt), cyclic adenosine monophosphate/protein kinase A (cAMP/PKA), and adenosine monophosphate-activated protein kinase/sirtuin 1 (AMPK/SIRT1) pathways, which enhance mitochondrial function, autophagy, and metabolic reprogramming. Collectively, these convergent actions maintain genome integrity, preserve proteostasis, suppress inflammation, and attenuate cellular senescence, illustrating how GLP-1 RAs restore systemic homeostasis to promote healthy aging.

over an extended period. A potential issue is that, with extended use of GLP-1 RAs, the body may develop resistance to the drug's effects. This resistance could arise from receptor desensitization or downregulation occurring during prolonged use, hindering sustained benefits.[269,270] The development of resistance biomarkers and reversal of receptor desensitization will be critical in sustaining long-term GLP-1 therapeutic effects. Moreover, to enhance patient adherence, researchers have made extending the half-life of GLP-1 RAs a primary goal. They have accomplished this using advanced techniques such as modifying peptide sequences, lipidating peptides, fusing with albumin, and fusing with Fc. Fc fusion connects the Fc region of an antibody to GLP-1, allowing the medication to resist degradation by attaching to the neonatal Fc receptor. Modifying the peptide sequence enhances GLP-1's resistance to enzymatic degradation, thus extending its effectiveness. Lipidation of peptide molecules enables GLP-1 to attach to albumin, which can ultimately lengthen its duration in circulation.[271,272] To further elaborate, the albumin fusion concept consists of attaching GLP-1 to albumin and, by doing so, benefiting from the longer half-life of albumin to extend the functionality of GLP-1 and enhance its therapeutic potential. The progress made in this field has resulted in GLP-1 medications that require less frequent administration, with certain versions allowing for monthly injections, which enhances adherence, particularly in older individuals. Furthermore, there is ongoing research into oral formulations, providing a non-invasive alternative that may increase patient compliance, especially for those who dislike receiving injections.[273]

Considering the strong preclinical data on GLP-1 RAs in older animals, there is an urgent need for large-scale clinical studies to evaluate their safety and effectiveness in older populations. Older individuals encounter intricate and varied health challenges that can differ greatly from those experienced by younger populations or observed in animal research. Additionally, while animal studies provide valuable insights, translating those findings to humans can be difficult due to differences in physiology, organ aging, and species-specific drug metabolism. Therefore, comprehensive clinical trials must be conducted to determine whether GLP-1 RAs possess genuine therapeutic benefits for age-related conditions and to customize treatment approaches for older adults. Ultimately, examining these factors will be crucial for the safe and effective ap-

plication of GLP-1 therapies in older adults.

Lastly, although many of the beneficial effects attributed to GLP-1 RAs are inferred from established molecular pathways or disease surrogates, it is essential to distinguish between weight-loss–mediated and weight-independent geroscience effects. Current evidence primarily indicates modulation of metabolic and inflammatory pathways; however, direct data linking GLP-1 signaling to improved healthspan—through measures such as physical function, frailty indices, cognition, or time-to-disability—remain limited in humans. Future studies evaluating GLP-1–based interventions should incorporate comprehensive functional and geriatric endpoints to determine whether these therapies confer benefits beyond weight reduction and metabolic improvement.

In summary, while GLP-1 RAs show significant potential for extending lifespan and addressing age-related illnesses, their effects are likely to vary among different organ systems due to the complexities of aging. Research suggesting individual aging trajectories must be taken into account when prescribing GLP-1 therapies. The ramifications of elevated GLP-1 levels, receptor insensitivity, and age-related changes in specific organs highlight the necessity for tailored treatments. Future studies will need to address these issues and improve GLP-1 therapies for older adults.

Clinical uses of GLP-1: Obesity and its link to unhealthy aging

Obesity is a significant modifiable contributor to unhealthy aging, accelerating the onset of CVDs, T2D, neurodegeneration, and certain cancers through chronic inflammation, oxidative stress, mitochondrial dysfunction, and disrupted insulin signaling.[274,275] Consequently, therapeutic strategies that restore metabolic homeostasis and mitigate inflammation are critical for promoting healthspan. GLP-1 RAs, such as semaglutide and tirzepatide, initially developed for T2D management, have recently emerged as highly effective anti-obesity agents.[276] GLP-1 RAs facilitate weight loss by enhancing glucose-dependent insulin secretion, suppressing glucagon release, delaying gastric emptying, and activating hypothalamic satiety centers.[277] Beyond these metabolic effects, GLP-1 RAs exert broad anti-inflammatory actions and modulate pathways implicated in biological aging, including improving lipid metabolism, restoring endothelial function, activating AMPK, and inhibiting mTOR.[278]

Importantly, GLP-1 RAs also exhibit neuroprotective potential. Receptors expressed in the hippocampus and cortex mediate enhanced neuronal survival, synaptic plasticity, and mitochondrial function.[279] In preclinical studies, GLP-1 RAs reduce amyloid-β deposition, attenuate tau phosphorylation, and suppress microglial activation.[280] Correspondingly, human studies demonstrate improvements in executive function, memory, and attention, likely mediated through enhanced cerebrovascular integrity and decreased neuroinflammation.[281] Clinical evidence further indicates organ-specific anti-aging effects: semaglutide treatment in individuals with HIV-associated lipohypertrophy resulted in an approximate 3.1-year reduction in biological age, primarily through improvements in the immune/inflammatory system and the brain.[282,283] Similarly, tirzepatide decreased left ventricular mass and paracardiac adipose tissue in patients with obesity-associated heart failure, corresponding with a reduced risk of heart failure events.[284] Emerging epigenetic data suggest that GLP-1 RAs may decelerate biological aging via DNA methylation modifications at loci associated with inflammatory and metabolic regulation, consistent with observed reductions in biological age.[285,286] Collectively, GLP-1 RAs integrate metabolic, anti-inflammatory, and neuroprotective mechanisms, representing a promising strategy to promote healthier aging, enhance cognitive resilience, and extend healthspan across multiple organ systems. Importantly, Table 3 presents a summary of important GLP-1 trials that focus on aging-related outcomes.[287–299] On the other hand, Figure 3 illustrates GLP-1 RAs as a pivotal element within the geroscience framework. The figure connects the activation of GLP-1R to downstream pathways (cAMP/PKA, Epac/PI3K/Akt, AMPK/SIRT1, ERK/MAPK) that regulate mitochondrial function, autophagy, proteostasis, and stress response, all of which collectively influence the hallmarks of aging to improve both cellular and systemic resilience.

Significance of the review

GLP-1 RAs have shown significant effectiveness so far in a variety of metabolic disorders, and there is increasing interest in their potential effects on CVDs and NDs. Nonetheless, their capacity to influence the biological aging process has not been thoroughly explored. We advocate for a reassessment of GLP-1 RAs—not just as agents that impact metabolism, but as promising candidates for gerotherapeutics that could influence biological aging across different physiological systems. A crucial aspect of this perspective is an in-depth analysis of the existing literature on GLP-1 RAs and the twelve proposed hallmarks of aging. This viewpoint promotes a transition from viewing GLP-1 RAs in a disease-specific manner to a more comprehensive understanding of whether these drugs impact various aging hallmark processes, including mitochondrial dysfunction, impaired proteostasis, and the decline in stem and progenitor cell function—elements that contribute to the diminished functional reserve seen with aging. We highlight several often-neglected additional therapeutic advantages of GLP-1 RAs, such as their ability to decrease neuroinflammation and immune senescence, along with the potential for GLP-1 RAs to help lower vascular stiffness and combat sarcopenia, both of which are major factors affecting mobility, resilience, and overall health in older individuals.

The aging process is marked by significant variability and complexity, as various bodily systems exhibit distinctive rates and patterns of deterioration. This variation demonstrates that the characteristics of aging do not manifest uniformly across different organ systems; certain mechanisms are more prevalent in specific tissues. For instance, the aging of skeletal muscle and the development of sarcopenia are likely driven by muscle degeneration and a decrease in stem cells, whereas factors such as proteostatic failure or ongoing inflammation are probably more influential in NDs. For example, vascular stiffness seems to be closely linked to cellular senescence and alterations in cell communication within the cardiovascular system. Therefore, investigating the unique impact of aging on different tissues can facilitate a precision medicine strategy for aging, allowing for personalized GLP-1 RA treatments aimed at addressing the main pathological mechanisms in each organ system. Consequently, effective tailored therapies can be developed to promote healthy aging and increase healthspan.

By concentrating on the distinct aging patterns of various organs, it is possible to create more focused biomarker panels that aid in both the analysis of biological age and the evaluation of treatment effectiveness. This organ-focused strategy will enhance the accuracy and reliability of aging assessments, enabling interventions that are customized to address the particular vulnerabilities of individual tissues. A deeper insight into how the diverse hallmarks of aging contribute hierarchically in different organs offers a clear foundation for combination therapies aimed at various biological pathways involved in the decline of specific tissues. This aspect of personalized geroscience could improve treatment

Table 3. Ongoing and completed clinical trials on GLP-1 receptor agonists

Trial/Study	Status	Intervention	Population/focus	Key findings/outcomes	Reference
SELECT Trial	Completed	Semaglutide 2.4 mg	Overweight/obese individuals without diabetes	Decreased major adverse cardiovascular events (MACE) by 20% and all-cause mortality by 19% over a 3.3-year period	287
FLOW Trial	Completed	Semaglutide	Patients diagnosed with heart failure with preserved ejection fraction (HFpEF)	Improved physical fitness and overall life satisfaction	288,289
STEP-HFpEF/ STEP-HFpEF-DM	Completed	Semaglutide	HFpEF patients with/ without diabetes	Notable reduction in body weight and improvement in cardiovascular health	290
ACHIEVE-1	Completed	Orforglipron	Type 2 diabetes & obesity	Significant reduction in body weight and improved glycemic control	291,292
Dapiglutid	Ongoing	Dual GLP-1/GLP-2 receptor agonist	Adults with obesity	Phase I clinical study evaluating weight reduction and gastrointestinal health	293
Amycretin	Ongoing	Dual GLP-1/Amylin receptor agonist	Obesity	Early trials demonstrate up to a 22% reduction in body weight, with subsequent phase studies planned	294
NPM-119	Ongoing	Implantable GLP-1 RA	Adults with diabetes	Phase I clinical study evaluating a 6-month efficacy implant	295
MET-097i	Ongoing	Ultra-long-acting GLP-1 RA	Adults with diabetes	Phase 2b study demonstrates favorable outcomes in body weight reduction and glycemic management	296
CagriSema	Ongoing	GLP-1/Amylin receptor agonist combo	Obesity	Late-stage clinical trials evaluating weight reduction	297
Semaglutide in HIV Patients	Completed	Semaglutide	HIV-positive individuals	Significant improvement in epigenetic biomarkers associated with biological aging	298
Barshop Institute Study	Completed	Semaglutide	Older adults with prediabetes or diabetes	Evaluated the effects on physical performance, body composition, and aging-associated biomarkers	299

outcomes, tailoring therapeutic approaches to an individual's distinct organ aging characteristics in addition to their chronological age. Notably, a recent extensive study analyzed biological aging in 11 key organs among 5,676 adults from five different groups by employing machine learning techniques.[300,301] The results showed that around 20% of participants exhibited signs of accelerated aging in at least one organ, while 1.7% showed aging across multiple organs. Additionally, aging in specific organs was linked to a 20%–50% rise in mortality risk and a significant correlation with disease occurrence in the affected organ systems. For instance, people who experience accelerated aging of the heart face a 250% increased risk of developing heart failure. Likewise, the accelerated aging of both the brain and blood vessels emerged as significant independent indicators of progression into Alzheimer's disease, demonstrating predictive power comparable to plasma pTau-181 levels. These results highlight the importance of further exploring the mechanisms underlying organ-specific aging, informed by established hallmarks of aging, which could pave the way for effective interventions aimed at enhancing healthspan and mitigating negative health outcomes related to aging.

Moreover, this review emphasizes critical elements that are lacking in translation to unlock the full potential of GLP-1 RAs in the field of geroscience. Primarily, there is a significant deficit of human studies evaluating functional aging outcomes rather than just common metabolic indicators, which should include assessments of cognitive ability, physical performance, and physiological resilience. Additionally, there is an immediate demand for the creation and application of reliable, standardized biomarkers of aging to assess therapeutic effectiveness not through clinical indicators of metabolic regulation, but through biological aging. By pursuing a comprehensive systems approach, it is possible to initiate a fundamental change in GLP-1 RA research, moving from merely treating diseases to promoting an extended healthspan. This transition is essential to keep in mind when planning trials that concentrate on geroscience, as it will ultimately impact the selection of biomarkers for monitoring and enhance existing therapeutic strategies, specifically addressing the biological processes of aging at the physiological systems level.

In essence, this review presents a unique approach that focuses on tackling biological aging rather than just age-related illnesses. It ultimately suggests a practical strategy for utilizing GLP-1 RAs as therapies to slow down functional decline and enhance healthspan. By referencing well-established aging mechanisms, particularly those linked to metabolic control, this review aims to create a framework for understanding how to support (or prevent negative effects on) older adult health, thus serving as a connection for

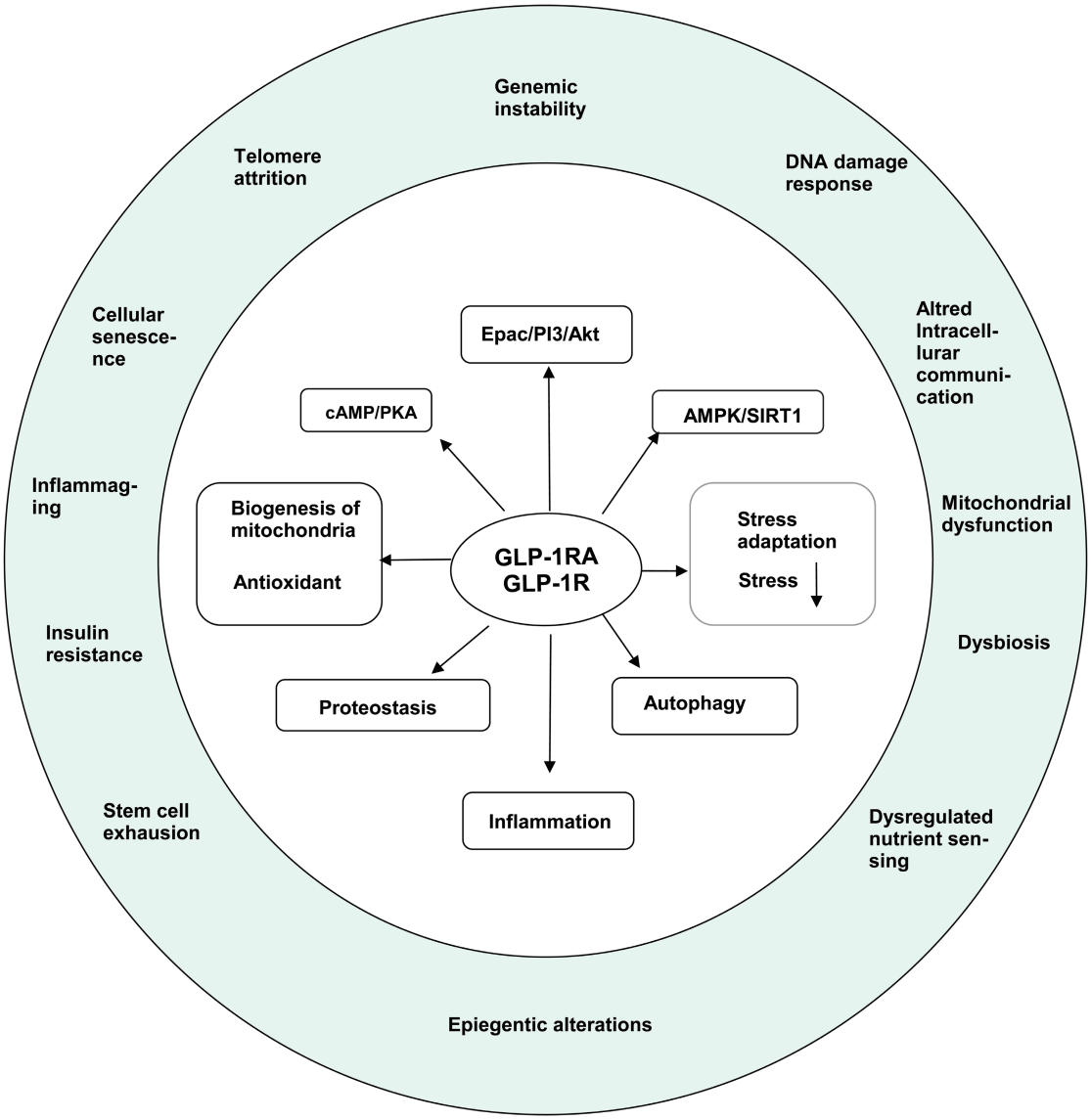

Fig. 3. GLP-1 receptor agonists (GLP-1 RAs) as a central hub in geroscience. The central circle represents activation of the glucagon-like peptide-1 receptor (GLP-1R) by GLP-1 receptor agonists (GLP-1 RAs). The inner ring illustrates key downstream signaling pathways—including cAMP/PKA, Epac/PI3K/Akt, AMPK/SIRT1, and ERK/MAPK—that orchestrate mitochondrial biogenesis, antioxidant defenses, proteostasis, autophagy, stress adaptation, and regulation of inflammation. The outer ring depicts major hallmarks of aging that are positively modulated by GLP-1R signaling, including genomic instability, telomere attrition, epigenetic alterations, cellular senescence, stem cell exhaustion, chronic low-grade inflammation (inflammaging), insulin resistance, mitochondrial dysfunction, altered intercellular communication, dysregulated nutrient sensing, and microbiome dysbiosis. The integrated crosstalk among these pathways enhances cellular repair, energy homeostasis, and resilience, positioning GLP-1 RAs as central modulators of cellular homeostasis and linking molecular repair programs to translational gains in healthspan. Akt, protein kinase B; AMPK, adenosine monophosphate-activated protein kinase; cAMP, cyclic adenosine monophosphate; Epac, exchange protein directly activated by cyclic adenosine monophosphate; ERK, extracellular signal-regulated kinase; GLP-1R, glucagon-like peptide-1 receptor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; SIRT1, sirtuin 1.

conceptualizing the molecular signs of aging and correlating them with clinical practices. Some intriguing extensions of this concept include studying organ-specific aging, implementing biomarker-driven stratification, and advancing precision gerontology to tailor interventions based on individual aging profiles. This comprehensive, systems-oriented viewpoint promotes fundamental shifts towards proactive, mechanism-focused initiatives that enhance and will continue to advance our comprehension of positive, healthy aging, as outlined in Table 4, which highlights critical knowledge gaps and outlines actionable future research directions for GLP-1 RAs in promoting healthy aging.

Limitations and potential biases of the review

Although this review provides a comprehensive synthesis of current evidence on GLP-1 RAs as potential gerotherapeutics, several

Table 4. Essential knowledge deficiencies and upcoming research avenues for GLP-1 receptor agonists in healthy aging

Knowledge gap	Limitation	Actionable research direction
Organ-specific aging	The rates of aging and the effects of GLP-1 RA differ across various organs	Research should concentrate on particular organs utilizing imaging methods, biomarkers, and functional evaluations
Functional outcomes	Emphasis on metabolic outcomes; there is scarce information regarding cognition, mobility, and frailty	Cognitive, physical, and resilience measures should be included in clinical trials
Biomarkers of aging	Absence of standardized and validated markers for aging	Epigenetic, proteomic, and organ-specific aging indices should be integrated
Mechanistic insights	Ambiguous routes connecting GLP-1R to the characteristics of aging	Translational models (organoids, Clustered Regularly Interspaced Short Palindromic Repeats [CRISPR]) should be used to dissect mechanisms
Long-term safety & efficacy	The majority of research is either short-term or concentrated on specific diseases	Multi-year trials should be conducted in older adults, focusing on safety and functional outcomes
Precision medicine	Responses can vary based on factors such as age, genetic makeup, and metabolic condition	Trials should be stratified using genomics, proteomics, and microbiome data, and predictive algorithms should be developed
Preventive use	The ideal timing, length, and target population are not well-defined	Preventive trials should be explored in at-risk but metabolically healthy adults
Access & equity	Restricted supply and elevated cost	Cost-effective formulations and equitable distribution programs should be developed

GLP-1R, glucagon-like peptide-1 receptor; GLP-1 RA, glucagon-like peptide-1 receptor agonist.

limitations warrant consideration. First, a substantial portion of the mechanistic and translational data derives from preclinical studies or small human cohorts, which may not fully capture understudied aspects of aging that vary across populations. Second, publication bias toward positive findings and underreporting of negative or null results may further influence interpretations of GLP-1 RA efficacy. Third, heterogeneity in study designs, primary endpoints, and biomarker assessments limits direct comparability and generalizability. Finally, this review primarily addresses established hallmarks of aging and does not encompass emerging or less-characterized pathways, leaving certain mechanisms open for future exploration. Acknowledging these limitations is essential for contextualizing findings and guiding subsequent research toward rigorous, unbiased evaluation of GLP-1 RAs as gerotherapeutics within geroscience.

Beyond their potential effects on classical hallmarks of aging, GLP-1 RAs may confer healthspan benefits through mechanisms that do not directly modify biological aging markers. These functional benefits include improved metabolic homeostasis, enhanced insulin sensitivity, weight reduction, and cardiovascular performance, along with enhancements in neurocognitive function, physical capacity, and systemic resilience. GLP-1 RAs have also been shown to positively influence gut barrier integrity and immune function, potentially reducing chronic inflammation and supporting overall physiological function without measurable changes in biomarkers such as DNA methylation, telomere length, or cellular senescence. These systemic, functional effects underscore that GLP-1 RAs can enhance healthspan independently of classical biological aging endpoints and reinforce their emerging role as versatile gerotherapeutics.

Future directions

While GLP-1 RAs show therapeutic potential, they are primarily given to those already facing metabolic issues. There is interest in the idea of prescribing them to people with good metabolic health to prevent future complications, but current clinical evidence to support this method is lacking. Interestingly, the degree of weight loss associated with GLP-1 RAs appears to be less noticeable in individuals with T2D. This observation likely reflects interindividual variation in metabolism and drug response. It underscores the necessity for further research into the underlying mechanisms, as well as the diversity in the application of these treatment options. This review does not advocate the indiscriminate use of GLP-1RAs in metabolically healthy individuals. Furthermore, considering the potential for severe malnutrition or weight loss due to appetite reduction, it is essential to tailor the application of these therapies with suitable nutritional guidance and metabolic monitoring.

It is also crucial to recognize that an increasing number of both preclinical and clinical research studies indicate that some therapeutic benefits of GLP-1 RAs, especially their anti-inflammatory and cytoprotective effects, may not be entirely connected to their primary use related to body weight. This insight underlines the rationale for precision medicine approaches that utilize targeted GLP-1 RA therapy for high-risk individuals identified through our understanding of precision medicine (that is, genomic risk and earlier detection via pathways that could involve organ-specific proteome clocks). The mounting evidence that GLP-1 RA effects are not limited to a single organ and have a variety of effects on health across a range of organ systems or organ-specific health conditions is a strong recommendation for their use to assist those who are non-obese but otherwise metabolically healthy to improve overall health. However, it has become important to confirm the clinical relevance and durability of the potential benefits in different population groups who are not necessarily required to lose weight through well-designed and adequately powered trials. Since it is critical to examine the efficacy, safety, and longer-term effects of GLP-1 RAs in a wider population, further investigation remains important. The growing body of evidence suggests that the effects of GLP-1 RAs extend beyond a single organ and can positively

influence health across various organ systems and specific health conditions, indicating their potential use for non-obese but otherwise metabolically healthy individuals to enhance their overall well-being. However, it is essential to validate the clinical significance and sustainability of the possible benefits in diverse population groups who may not necessarily aim for weight loss through carefully designed and sufficiently powered studies. As it is crucial to evaluate the effectiveness, safety, and long-term impacts of GLP-1 RAs in a broader demographic, further research continues to be necessary.

From a public health perspective, there is an increasing body of evidence highlighting a new area of research; however, access to GLP-1 therapies worldwide is still restricted in comparison to the number of individuals who will require them, even among those who can afford the treatment. It is essential to develop public health policies and strategies aimed at enhancing access to these potentially life-altering therapies for populations facing inequities, such as underserved communities and economically disadvantaged groups.

Moreover, when evaluating GLP-1 RAs as a standalone preventive measure, several important factors need to be taken into account. To begin with, it is essential to determine the ideal age to initiate the therapy, the duration of the treatment, and how to categorize patients based on risk. Currently, these elements are not well-defined, and there is a pressing need for well-structured, long-term studies to clarify these issues before we can responsibly broaden the application of GLP-1 RAs in asymptomatic individuals. Second, to safely extend their use beyond existing metabolic contexts, comprehensive clinical research is necessary to evaluate long-term safety, efficacy, and identify appropriate candidates for therapy, particularly among those who are metabolically healthy. Third, although the notion of enhancing healthspan and potentially prolonging lifespan through GLP-1 RA treatment is appealing, its application to asymptomatic individuals in clinical settings is still primarily theoretical and lacks robust empirical support at this time. On a brighter note, recent studies in precision medicine, particularly through AI-boosted proteomic profiling, provide promising approaches for detecting NDs, such as Alzheimer's, before obvious clinical symptoms emerge.[302–304] In this context, a proactive strategy integrating lifestyle interventions with the timely and targeted use of GLP-1 RAs may offer a novel avenue to mitigate aging-related physiological decline, including cognitive deterioration commonly observed in older populations. This conceptual framework posits that such an approach could potentially delay the onset or reduce the risk of progression to clinical dementia. However, it is important to underscore that this hypothesis remains theoretical and requires robust validation through long-term, randomized clinical trials before it can be translated into evidence-based preventive healthcare strategies. Table 4 delineates the critical knowledge gaps and articulates specific, actionable research priorities essential for constructing a strategic roadmap to inform and guide future investigations in this domain.

Conclusions

When considered collectively, GLP-1 RAs demonstrate significant potential for the treatment of age-related conditions and the extension of lifespan. However, their clinical application necessitates a comprehensive assessment of each patient's unique physiological characteristics. By enhancing insulin sensitivity, attenuating systemic inflammation, and supporting mitochondrial function, GLP-1 RAs represent a promising strategy for decelerating the aging process and mitigating prevalent age-associated diseases such as T2D, CVDs, and NDs. Nonetheless, the long-term administration of GLP-1 RAs requires vigilant monitoring to minimize potential adverse effects, including gastrointestinal disturbances and pancreatic overstimulation. Personalized treatment strategies that account for individual aging trajectories and organ-specific responses are essential for optimizing therapeutic efficacy. Future research should prioritize the refinement of GLP-1–based therapies by addressing limitations such as elevated GLP-1 levels and receptor desensitization, while ensuring their safety and efficacy in older populations.

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Conflict of interest

The authors declare no conflict of interest

Author contributions

Conceptualization, formal analysis, original draft preparation (SKC), writing—review and editing (SKC, DC), supervision, project administration, and funding acquisition (SKC). Both authors have approved the final version and publication of the manuscript.

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