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Review article

Unlocking longevity with GLP-1: A key to turn back the clock?

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ABSTRACT

Traditionally known for managing blood sugar, GLP-1, a gut hormone, is emerging as a potential key to both lengthening lifespan and combating age-related ailments. While widely recognized for its role in blood sugar control, GLP-1 is increasingly recognized for its diverse effects on various biological pathways beyond glucose metabolism. Research across organisms and humans suggests that activating GLP-1 receptors significantly impacts cellular processes linked to aging. Its ability to boost mitochondrial function, enhance cellular stress resistance, and quell inflammation hints at its wider influence on aging mechanisms. This intricate interplay between GLP-1 and longevity appears to act through multiple pathways. One key effect is its ability to modulate insulin sensitivity, potentially curbing age-related metabolic issues like type 2 diabetes. Its neuroprotective properties also make it a promising candidate for addressing age-related cognitive decline and neurodegenerative diseases. Furthermore, preclinical studies using GLP-1 analogs or agonists have shown promising results in extending lifespan and improving healthspan in various model organisms. These findings provide a compelling rationale for exploring GLP-1-based interventions in humans to extend healthy aging. However, despite the exciting therapeutic prospects of GLP-1 in promoting longevity, challenges remain. Determining optimal dosages, establishing long-term safety profiles, and investigating potential adverse effects require comprehensive clinical investigations before we can confidently translate these findings to humans. This article emphasises the wide applicability of GLP-1.

1. Introduction

According to WHO, healthy aging is a process that includes maintaining the ability of being wellbeing even in the older ages. The world's population is aging rapidly, posing a significant medical and social challenge. This trend is particularly strong in developed nations like Japan, Finland, and Italy, which currently boast the oldest populations. Within the Organization for Economic Co-operation and Development (OECD), countries like Greece, Korea, Poland, Portugal, Slovenia, and Spain are experiencing the fastest demographic shift towards an older population. Beyond the OECD, nations like Brazil, China, and Saudi Arabia are also facing rapid aging populations [1]. A programmed named Community Aging in Place - Advancing Better Living for Elders (CAPABLE) is enculcated in USA which is an innovative 5-month initiative delivers personalized support right to seniors' doorsteps. A dedicated team of experts - a registered nurse, occupational therapist, and handyman - work collaboratively with each older adult. They analyze physical limitations, daily routines, and home environment to pinpoint areas needing improvement. Working hand-in-hand with the seniors, the team establishes achievable goals towards greater health, independence, and safety. From adapting daily routines to adjusting the home environment, the team creates actionable steps to bridge the gap between goals and reality. They empower seniors with vital information and access to community resources that cater to their specific needs [2]. But there are certain hurdles in the path of achieving the healthy aging. As years pile on, the chances of encountering chronic companions like diabetes, heart disease, and dementia rise. Taming these conditions becomes a complex game, requiring specialized care and ongoing vigilance. Without adequate support, navigating this chronic curveball can be a solo struggle. Mental health needs a seat at the table in any discussion about aging well. Depression, anxiety, and loneliness can cast long shadows on the golden years, and social isolation can amplify these challenges. Embracing social connections and prioritizing mental well-being are vital for preserving overall happiness and health in later life. For many seniors, retirement brings financial constraints, with limited pensions or dwindling savings creating a tightrope walk. Juggling

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healthcare costs with everyday needs can become a constant balancing act, potentially compromising access to crucial services and healthy lifestyle choices. Negative stereotypes and ageism can be invisible, yet potent, roadblocks. These outdated biases can discourage older adults from seeking proper healthcare or actively participating in activities that promote healthy aging. Combating ageism and fostering an inclusive environment where everyone feels empowered to prioritize their well-being is key to closing the health gap [3]. There are other emerging therapies that work on the similar motivation. There are senolytic drugs that targets senescent cells which helps in improving health span and reduce age-related ailments [4]. Scientists are studying compounds such as nicotinamide riboside and nicotinamide mononucleotide, which are precursors of nicotinamide adenine dinucleotide (NAD+), due to their potential to enhance cellular energy production and explore their possible anti-aging properties [5]. While GLP-1 works through the incretin pathway, promoting insulin secretion and glucose control. Its potential anti-aging effects may be related to metabolic regulation and cellular signalling pathways [6].

In regards with the challenges, multiple incretin hormanes are consider for the management of healthy aging. The digestive tract plays a key role in managing blood sugar after meals. It produces hormones called incretins, primarily GLP-1 and GIP, that boost insulin secretion in response to rising glucose levels. This “incretin effect” leads to a more controlled blood sugar response compared to intravenous glucose delivery. This makes GLP-1 a valuable target for diabetes treatment. Medications mimicking its action (GLP-1 receptor agonists) or prolonging its activity (DPP-4 inhibitors) effectively lower blood sugar and improve overall glycemic control. While originally known for their impact on insulin, both GLP-1 and GIP exert further effects on fat cells, bones, and the cardiovascular system [7]. While GLP-1's ability to regulate blood sugar, appetite, and gut movement is well-established, the specific role of nervous system pathways in mediating these effects in humans remains ambiguous. One study involving healthy individuals showed that blocking vagal nerve activity via atropine did not affect GLP-1's insulin-stimulating properties [8]. Conversely, another study in non-diabetic men with surgically severed vagal nerves (truncal vagotomy) revealed that GLP-1, while still managing blood sugar after meals, no longer suppressed hunger or slowed stomach emptying [9]. This article emphasis on the application of GLP-1 in various fields including cellular homeostasis, aging, cognitive function, and various chronic disease.

2. GLP-1 and cellular homeostasis in aging

Glucagon-like peptide-1 (GLP-1) is a gut hormone with significant roles beyond regulating blood sugar. It may play a crucial role in maintaining cellular homeostasis, particularly during aging. Aging and its related disorders may cause severe health problems, finding new and efficient treatments is essential to managing diseases associated with aging and slowing down the aging process. GLP-1 receptor agonist is one of the classes of anti-diabetic drug, recommended to manage aging-related diseases. Here, we explained different approaches to maintain cellular homeostasis and reduce aging [10].

2.1. Impact of GLP-1 on insulin sensitivity and glucose metabolism

GLP-1 a gut hormone produced after meals, plays a starring role in regulating blood sugar. GLP-1 also significantly impacts insulin sensitivity and glucose metabolism, making it significant in the fight against diabetes and metabolic disorders. Many research has been suggested and proved that GLP-1 plays an important role in increasing insulin sensitivity and glucose metabolism [11].

Jiang et al. reported that GLP-1 improved adipocyte insulin sensitivity following induction of endoplasmic reticulum (ER) stress. The study was conducted in mice, after habituated Liraglutide (100 μg/ml) was injected intraperitoneally once- daily and phosphate buffer as a saline for 2 weeks. Then mice were sacrificed and the efficacy of drug was measured by body weight and random blood glucose measuring. A study found that, liraglutide reduced ER stress-related gene expression in fat cells and increased insulin tolerance [12]. Ahren et al. carried a study on the efficacy of GLP-1 on insulin secretion, sensitivity, and glucose effectiveness in mice. For determination of insulin sensitivity, IV glucose (1 g/kg) alone or with GLP-1 given to the mice. GLP-1 given at dose was 10 nmol/kg to 10 animals, 100 nmol/kg to 17 animals. Study resulted that, compare to alone glucose, glucose with GLP-1 lead to more insulin secretion therefore it increase insulin sensitivity and metabolize glucose to the normal value [13].

2.2. GLP-1 and mitochondrial function

Studies have explored the potential of GLP-1 to stimulate mitochondrial biogenesis within pancreatic beta cells, as mitochondrial function is critical for optimal insulin secretion. It increases mitochondrial ATP production by utilizing more glucose and fatty acids. It promotes the growth and division of mitochondria, resulting in a greater number of these energy-generating units within cells. Moreover, it protects mitochondria by reducing reactive oxygen species (ROS), stimulate mitochondrial dynamics and protects against mitochondrial damage [14].

Building off of the research by Kang et al., it was observed that GLP-1 plays a role in enhancing mitochondrial biogenesis and function within INS-1 rat insulinoma cells. The study involved seeding INS-1 cells in 23-well plates and exposing them to varying concentrations of GLP-1 (0.100 nM or 200 nM) for a 48-h period. Subsequently, the cells were washed and incubated in Kreb's Ringer bicarbonate buffer (KRBB) at 37 °C for 1 h before being exposed to either 5 mM or 10 mM glucose for another hour. Mitochondrial mass was then assessed using a combination of ELISA, transmission electron microscopy, and RT-PCR techniques. The findings revealed that GLP-1 treatment led to increased mitochondrial function, evidenced by elevated membrane potential and oxygen consumption [15]. Marco et al. checked the effect of GLP-1 receptor agonist on mitochondrial function. In this trial Type 2 diabetic patients involved, they were divided into two groups with and without GLP-1. Treatment with GLP-1 was shown to benefit immune cells (PMNs) by reducing oxidative stress, boosting energy production, and mitigating inflammation and cell-to-cell interaction. This suggests potential therapeutic benefits for conditions related to inflammation and immune dysfunction [16].

2.3. GLP-1 and cellular senescence

Cellular senescence is a process where cells stop dividing but remain alive, releasing inflammatory signals that can harm surrounding tissues. This accumulation of senescent cells contributes to aging and age-related diseases [17]. β-Cells senescence will affect the function of β-cells, and it directly affect insulin secretion. It promotes β-cell function maturation including increase glucose uptake, mitochondrial oxidation and mitochondrial number. However, few senescence associated with aging-related limitation [18]. Although the p16Ink4a overexpression in approximately 35 % of β cells in the established mouse model closely mimics the symptoms seen in typical aging mice, there are several differences to be noticed. For instance, p16Ink4a overexpression only enhances high glucose induced insulin production, but older animals exhibit a reduced ability to respond to glucose variations. Cellular senescence is therefore a more intricate phenomenon involving numerous components and communication pathways [19]. In a study by Krause et al., the antiproliferative effects of liraglutide, a GLP-1 analog, were investigated in HepG2 hepatocellular carcinoma cells. Concentrations of 10, 15, and 20 μM were tested over 24 and 48 h. Results showed that liraglutide promoted cellular senescence and autophagy through increased TGF-β1 levels, suggesting its potential as a therapeutic agent for liver cancer [20].

2.4. GLP-1 and autophagy

GLP-1 can have both activating and inhibitory effects on autophagy depending on the cell type and context. It stimulates autophagy by AMPK/mTOR pathway, oxidative stress reduction, and by ER stress management. While it inhibits autophagy by glucagon suppression, mitochondrial protection and by producing tissue specific effects [21]. Zhao et al. studied the efficacy of liraglutide on autophagy and apoptosis. Induced by high glucose in renal tubular epithelial cells (HK−2). HK-2 cells were cultured and plated in medium containing either 5.5, 16.7, 25- or 40-mM glucose. Liraglutide was administered at concentration 1, 10 and 100 nM and then incubated for 24 to 48 h. Then cell viability assessed via different assays. The assay resulted that, liraglutide inhibited cell autophagy and other harmful effect caused by higher glucose concentration. Then Wu et al. reported the effect of GLP-1 agonist reduce autophagy to ameliorate pulmonary arterial hypertension (PAH) through Drp1/NOX and Atg-5/Atg-7/Beclin-1/LC3β pathways. Liraglutide (10 nM) inhibits all autophagy-relate proteins [22]. Overall, the interplay between GLP-1 and autophagy presents a complex and emerging field with exciting possibilities for developing novel interventions against various diseases.

2.5. GLP-1 and stem cell function

The interaction between GLP-1 and stem cell function is an area with promising implications for regenerative medicine and age-related diseases. GLP-1 have some positive effect on stem cells that include proliferation and differentiation, migration and homing, mitochondrial function and it improves stem cell survival [23]. Habib et al. reported the effect of exenatide (GLP-1 agonist) on nephropathy induced diabetic rats. Adipose derived mesenchymal stem cells (ADMSCs), function check in diabetic rate by administering exenatide. After four weeks the parameters evaluated, the result shown that exenatide has a renoprotective effect [24]. Navabi et al. measured the effect of liraglutide on MSCs, on an inflammatory mediated diabetic animal model (monkeys). Diabetes induced by streptozotocin at dose 30 mg/kg. Then combination therapy group received human clonal MSCs/kg and S·C injection of liraglutide (1.8 mg/day) for 160 days and control group received phosphate buffer saline. The result reported that, combination therapy exhibited more volume of insulin secreting islets cells and increased β-cell function [25]. Overall, the interaction between GLP-1 and stem cell function offers a captivating avenue for regenerative medicine and holds promise for tackling various age-related and chronic diseases. As research progresses, we can expect further advancements in this field, potentially leading to novel therapeutic strategies for improving human health. Find more details in Fig. 1.

3. GLP-1 and age-related diseases

Glucagon-like peptide-1 (GLP-1) is a naturally occurring hormone with surprising potential in tackling various age-related diseases. Initially known for its role in regulating blood sugar levels in type 2 diabetes, GLP-1 has emerged as a promising player in managing and potentially preventing a range of diseases associated with aging.

3.1. Cardiovascular diseases

Cardiovascular diseases (CVDs) are a major threat to T2DM patients,

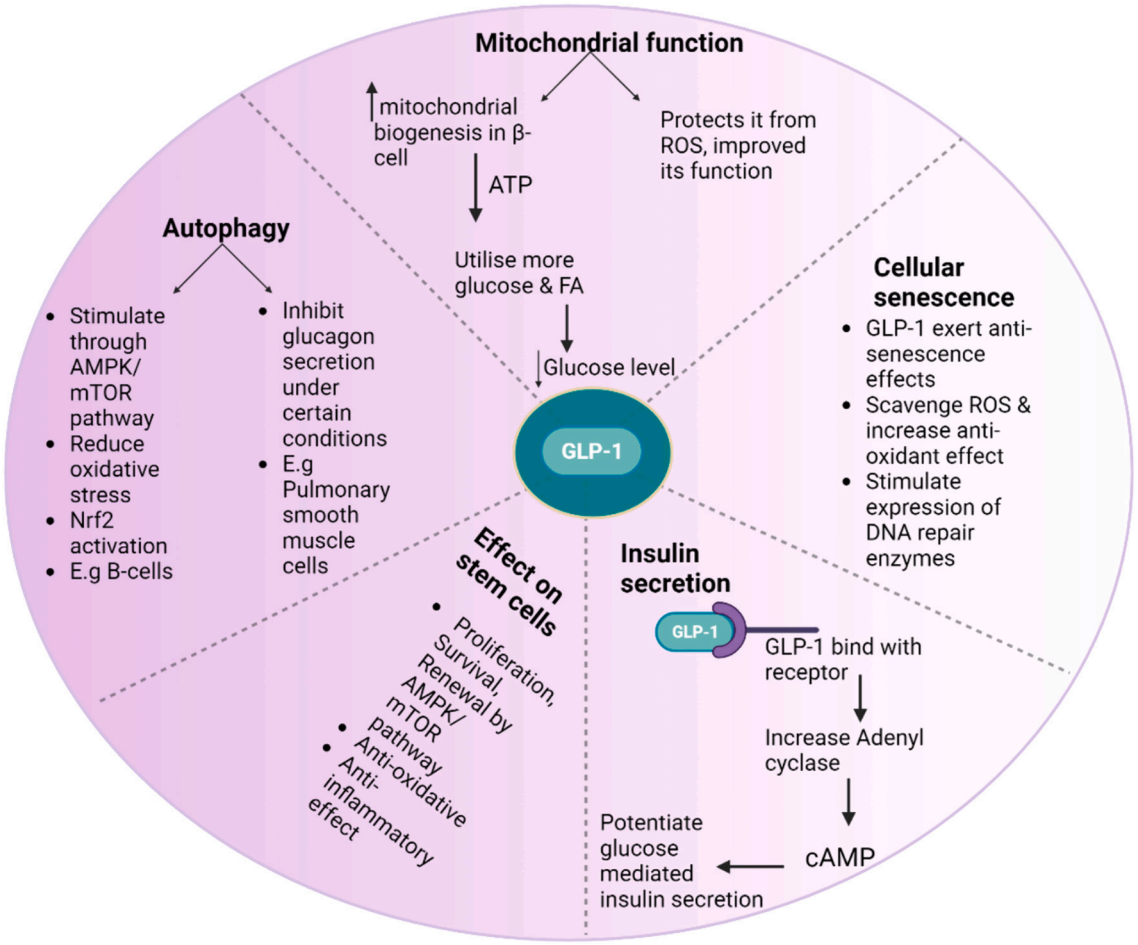

Fig. 1. GLP-1 and cellular homeostasis in aging.

significantly increasing their risk of death. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as promising medications not only for glycemic control, but also for improving established CVD risk factors like dyslipidemia, weight, and hypertension. Research suggests that GLP-1 RAs may have broader benefits beyond these established factors. They could potentially improve endothelial function, enhance blood flow in the heart during stress (coronary ischemia), and even mitigate heart failure. Several recent clinical trials have evaluated the impact of GLP-1 RAs on cardiovascular events in T2DM patients. Among these, liraglutide and semaglutide have demonstrated the most compelling evidence of cardiovascular benefits compared to placebo [26]. Hirata et al. reported anti-hypertensive effect of GLP-1, an incretin peptide. The 4 weeks treatment with GLP-1 in mice at dose 20 mg/kg body weight, inhibit hypertension [27]. While promising, the use of GLP-1 RAs specifically for cardiovascular disease prevention is still evolving. Considering diverse patient profiles and potential side effects, a personalized approach is crucial to determine the suitability of GLP-1 RAs for cardiovascular risk management. More studies are needed to fully understand the long-term effects and mechanisms of action of GLP-1 RAs in preventing and treating specific cardiovascular diseases.

3.2. Neurodegenerative diseases

While chronic hyperglycemia is implicated in numerous diseases, its impact on brain function is particularly complex. Neuroinflammation, mitochondrial damage, altered neurotransmitter activity, and vascular issues all contribute to this phenomenon, culminating in cognitive decline at the neuronal level [28]. Numerous investigations have demonstrated GPL-1's impact on a variety of neural processes, including energy homeostasis, blood pressure regulation, neurogenesis, neurodegeneration, and retinal healing. Moreover, dopamine (DA) levels in Parkinson's disease (PD) and amyloid β peptide aggregation in Alzheimer's disease (AD) can also be impacted by modulating GLP-1 activity. GLP-1 receptor agonists (GLP-1RAs), which primarily function by inhibiting oxidative stress, inflammation, and apoptosis, have demonstrated positive effects on brain ischemia in animal models, including a decrease in the extent of the cerebral infarct and an improvement in neurological impairment. Through modifying synaptic plasticity, they may also have a positive impact on the cognitive impairment brought on by diabetes or obesity, enhancing memory and learning [29]. Mulvaney et al. demonstrate the effect of GLP-1RA on Parkinson's disease (PD). In a one blind study Exenatide and placebo administered to patients for 48 weeks, the primary outcomes resulted that, exenatide improves motor coordination. This study conclude that, exenatide has somewhat diseases modifying effect [30]. Wang et al. studied the role of GLP-1 in Alzheimer's diseases through the Akt/GSK-3β/β catenin pathway. An exedin-4 and GLP-1R agonist has 53 % amino acid sequence homology. After 4 weeks of treatment in mice, there was 50 % improvement in cognitive function [31]. Comparing saline-treated animals in 14-month-old APP/PS1 mouse model, liraglutide (25 nmol/kg, intraperitoneally, for 2 months) enhanced spatial memory. Neuronal progenitor cells in the dentate gyrus increased, while inflammation and plaque load were also decreased. Synapse counts in the cortex and hippocampal regions rose, and long-term potentiation was also significantly improved [32]. While preclinical studies in animal models show promising results, clinical trials in humans are still in their early stages. More research is required to confirm the efficacy and safety of GLP-1RAs for treating neurodegenerative diseases.

3.3. Cancer

The efficacy of GLP-1 in cancer is a complex and evolving one, with potential benefits and risks. GLP-1 have somewhat potential effect against cancer that include tumor growth inhibition, restoring natural killer cells and prevent progression of tumor. While it may increase risk of thyroid cancer and pancreatic cancer [33,34]. Yang et al. concluded in pharmacovigilance study that, combination treatment of GLP-1RA with DPP4 lead to tumor related adverse effects [35]. Zhao et al. attempted to find out whether and how pancreatic cancer cells' chemoresistance and chemosensitivity to gemcitabine are impacted by the GLP-1 receptor agonist liraglutide, both in vitro and in vivo. It was demonstrated that adding liraglutide does not enhance the growth of cancer cells, but rather has the opposite effect. Several pancreatic cancer cell lines had dose-dependent inhibition of growth and an increase in apoptosis during incubation with liraglutide [36]. Wang et al. studied differential risk of cancer associated with GLP-1 receptor agonist, the occurrence of cancer ratio was estimated by using metformin and GLP1Ra. The 619,340 patients received metformin and 64,230 received GLP-1Ra, within 5-year study estimated that, GLP-1Ra associated with lower risk of prostate, lung and colon cancer, while thyroid cancer risk was significantly higher. Moreover longer use of GLP-1 would reduce prostate, colon and lung cancer risk [37]. The research on GLP-1 and cancer is mostly based on observational studies, which means that it cannot definitively prove cause and effect. More research, such as randomized controlled trials, is needed to confirm the findings of these studies.

3.4. Musculoskeletal disorders

The effect of GLP-1 on skeletal muscle is less prevalence, but it exerts somewhat effect on skeletal muscle. Pre-clinical and in-vitro study evaluate the efficacy of GLP-1 on bone disorders [38]. Building on the work of Gurjar et al., researchers investigated the potential of long-acting GLP-1 analogs like liraglutide to combat skeletal muscle atrophy in rodents. Utilizing both in vitro C2C12 cell models and in vivo rat models, the study explored liraglutide's effects on myogenic capacity and muscle function under various atrophy-inducing conditions (freeze injury, denervation). The findings revealed that liraglutide administration significantly improved muscle protection against these stressors, leading to enhanced muscular function [39]. Meurot et al. studied the effect of liraglutide (a GLP-1 agonist) in osteoarthritis. Liraglutide reduce cartilage degradation through anti-catabolic effect at in-vitro, and in-vivo it targets cartilage inflammation, its breakdown and reduce pain. In osteo inflammation induce mouse model, liraglutide given via IA injection at dose 5 μ, 10 μg, and 20 μg, after 2 days it shown that it had similar effects with 20 μg dexamethasone (an anti-inflammatory agent). Compared to vehicle group (saline) liraglutide was more effective than dexamethasone and it improves synovitis severity score [40].

3.5. Age-related macular degeneration (AMD)

GLP-1 exerts potential benefits in AMD, it reduced inflammation, neuroprotective effects, and improved blood flow in retina. Preclinical studies (using animal models or cells) have shown promising results for GLP-1RAs in protecting against AMD and promoting retinal health. Seppa et al. reported that liraglutide has neuroprotective effect on aged rat model with destruction in ophthalmic nerve. Liraglutide given to the rat for 6 months, and then effectiveness was measured. The study conclude that, liraglutide reduce neuroinflammation, decrease AMD symptoms and protected retinal ganglion cells [41]. The details for different disease explained in Table 1.

4. GLP-1 and cognitive function

The 30-amino acid peptide hormone known as GLP-1 is created by intestinal epithelial endocrine L-cells through the digestion of proglucagon [55]. GLP-1 is frequently used to treat type 2 diabetes because it can lower body weight in addition to controlling blood glucose. GLP-1 may also be used in the future to treat obesity and type 1 diabetes mellitus as an adjuvant treatment when used in conjunction with insulin [56]. Naturally occurring GLP-1 has very limited effects because it

Table 1
Role of GLP-1 in different diseases.

Age-related disease	Potential benefits of GLP-1	Mechanism of action	Supporting evidence (remark)	Reference
Atherosclerosis	• Improves cholesterol levels • Reduces plaque buildup in arteries	GLP-1RAs exert beneficial effects on vascular health beyond glucose control. GLP-1RAs promote the production of nitric oxide (NO), a key vasodilator, within endothelial cells. This improves blood flow and reduces vascular stiffness. Excessive smooth muscle cell growth contributes to plaque formation in arteries. GLP-1RAs counteract this process, potentially mitigating atherogenesis.	Koska et al. conducted a randomized trial to check the effect of exenatide on carotid atherosclerosis. Exenatide and placebo given to the patients and plasma glucose, lipids and endothelial functions are measured at 3,9 and 18 months. Study reported that, exenatide slower the progression of plaque.	[42,43]
Type-2 diabetes	• Lowers blood sugar levels • Improves insulin sensitivity • Promotes weight loss	GLP-1 is glucose-dependent, indicating that it only causes pancreatic beta cells to produce insulin in response to elevated blood sugar levels. By doing so, hypoglycaemia is avoided and blood sugar is better regulated.GLP-1 inhibits the release of glucagon, slows down the passage of food from the stomach into the small intestine, and lowers food intake, all of which contribute to weight loss. Macrophages play a crucial role in the inflammatory response associated with atherosclerosis. GLP-1RAs can modulate macrophage activity, leading to reduced inflammation and plaque instability.	GLP-1 have a distinct role in type-2 diabetes mellitus, short acting GLPRA (exenatide and lixisenatide) lowers postprandial blood glucose levels through inhibition of gastric emptying, while long acting GLPRA have strong effect on fasting glucose levels. Treatment with GLP1Ra associated with reduction in A1C reduction with 5 μg exenatide, 20 μg lixisenatide and 30 mg albiglutide once a daily	[44,45],
Alzheimer's disease (AD)	• Protects neurons from damage and death • Improves cognitive function and memory • Reduces inflammation in the brain	GLP-1 has the ability to regulate immune cells in the brain, which lowers neuroinflammation, a major factor in the development of AD. BDNF, a protein essential for neuronal growth and survival, is produced in response to GLP-1 stimulation.	Du et al. reported that, GLP-1RA have a role in prevention of AD. Many clinical and preclinical trial reported that, GLP-1RA reduces neuroinflammation and oxidative stress, it decreases Aβ deposition and neurotropic effects. Parthsarathy et al. reported that, liraglutide reduces microglia load, and pro-inflammatory cytokines levels in mice	[46,47]
Parkinson's disease (PD)	• Protecting dopamine neurons • Reduce Alpha-synuclein aggregation	It stimulates the remaining dopaminergic neurons, lead to increased dopamine production. GLP-1 exhibits anti-inflammatory properties by suppressing microglial activation and reducing pro-inflammatory cytokines.	Hogg et al. reported the effect of lixisenatide in PD. Lixisenatide can able to cross BBB, and has neuroprotective effect in PD. subcutaneous injection of 20 μg lixisenatide has been given for 12 months and 10 μg/day was given for 14 days. The trial resulted that, PD symptoms improved.	[30,48]
Diabetic retinopathy (DR)	• Neuroprotection • Anti-oxidant and anti-inflammatory effects • Blood-retinal barrier protection	Retinal cells are shielded from free radical damage by GLP-1, which stimulates antioxidant mechanisms. GLP-1 suppresses immunological responses that accelerate the development of DR and has anti-inflammatory qualities. Retinal cells can receive vital nutrients and oxygen thanks to enhanced blood flow to the retina caused by GLP-1.	Gaborit et al. studied the effect of GLP-1RA on diabetic retinopathy, in that clinical study in vivo effect of exendin-4 resulted that it did not exert any negative effect on retinal neovascularization, while on in-vitro effect demonstrates that, no effect on survival and proliferation.	[49,50]
Rheumatoid arthritis	• Reduced pain and control inflammation • Cartilage protection	Pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1 can be inhibited by GLP-1, and these cytokines are important in RA-related joint inflammation and degradation. In order to mitigate the detrimental effects of ROS, which are a contributing factor to joint degeneration in RA, GLP-1 has the ability to modulate cellular antioxidant mechanisms. The building blocks of good cartilage, collagen and proteoglycans, can be produced more readily by GLP-1, which may aid in cartilage regeneration and repair.	There is no exact evidence of GLP-1RA for prevention and treatment of RA. But some of the in-vitro and in-vivo data suggested that, it exerts anti-inflammatory, reduce cell proliferation, impairment of joint cells and analgesic effects.	[51,52]
CKD	• Protects kidney function • Slows disease progression • Reduces inflammation in the kidneys	The NHE3 in the proximal tubules is inhibited by GLP-1RAs, which also increase renal blood flow. These mechanisms are responsible for the increased excretion of sodium and water. The two main factors causing kidney damage in chronic kidney disease (CKD) are inflammation and free radicals, which GLP-1RAs can scavenge. Improved blood flow and decreased glomerular hyperfiltration can result from GLP-1RAs' direct effects on the function of glomerular cells, including podocytes and mesangial cells.	The risk of CKD is higher in diabetes patients, around 40 % of people with type 2 diabetes have risk of CKD. Yu et al. checked the effect of GLP-1 on glomeruli of diabetic rats. Rats were treated with rh GLP-1 insulin and saline. Then effect was measured using RT PCR and western blot. The study resulted that, rhGLP-1 increase protein kinase C, which reduce oxidative stress in glomeruli and I proved kidney function.	[53] [54]

BDNF - brain-derived neurotrophic factor; CKD - chronic kidney disease; GLP-1Ras - GLP-1 receptor agonists; GLPRA - glucagon-like peptide-1 receptor agonists; NHE3 - sodium-hydrogen exchanger; ROS - reactive oxygen species.

breaks down in the bloodstream in 2–3 min. Many GLP-1 Ras have been created to produce long-term benefits. The GLP-1 receptor, or GLP-1R, is broadly distributed throughout the brain and is activated by GLP-1 RA [57]. The blood-brain barrier can be crossed by GLP-1 and its agonists, which suggests that NDs may benefit from its therapeutic potential. A growing body of research indicates that GLP-1 receptor agonists (GLP-1 RAs) possess neuroprotective qualities, contributing to improved cognitive and non-cognitive function within the central nervous system (CNS) [58]. A study conducted by Li et al. evaluate the influence of GLP-1R in cognitive function in the patient of T2DM (NCT03707171). 50 patients were recruited for the study for the study of 12 weeks. Twelve weeks into the study, individuals receiving GLP-1 therapy demonstrated

superior performance on all cognitive assessments, particularly in memory and attention ($p = 0.040$) after adjusting for various factors. Compared to the control group, liraglutide treatment significantly enhanced brain activity in the dorsolateral prefrontal cortex and orbitofrontal cortex ($p = 0.0038$). Interestingly, following liraglutide administration, improvements in cognitive performance exhibited a significant correlation with the increased activation of these brain regions ($p < 0.05$). Notably, no association was observed between cognitive changes and alterations in body mass index, blood pressure, or glycemic control [59].

4.1. GLP-1 and neurogenesis

The fascinating phenomenon of neurogenesis, responsible for birthing new brain cells, unfolds through a meticulously orchestrated sequence. Neural stem cells (NSCs) begin by multiplying, then engage in a precise balanced and imbalanced divisions, giving rise to a diverse army of progenitor cells. These precursors embark on a guided trek, migrating towards predetermined brain regions where they grow into mature neurons. As they settle into their designated roles, their inherent plasticity allows for fine-tuning, culminating in the forging of intricate synaptic connections with fellow neurons, establishing a vibrant neural network. Two areas of the brain are the primary sites of adult neurogenesis: the subgranular zone of the dentate gyrus in the hippocampus and the subventricular zone of the lateral ventricle. New neurons continuously integrate into the adult hippocampus, highlighting the importance of adult hippocampal neurogenesis in memory and learning processes. Factors like the insulin/insulin-like growth factor (IGF) pathway contribute to the survival, proliferation, and differentiation of these NSCs [60]. Impaired insulin signalling, as seen in diabetes, may have detrimental effects on the delicate process of neurogenesis within the dentate gyrus. This observation suggests that the reduction in new neuron generation observed in the hippocampus of diabetic individuals could contribute to the cognitive decline often associated with the disease [61]. A potential link between type 2 diabetes and Alzheimer's disease is gaining traction, centered on the impact of pro-inflammatory cytokines on endothelial caveolin-1. These inflammatory molecules are proposed to interfere with this key protein's function within caveolae, potentially leading to vascular issues, hampered neurogenesis, and ultimately contributing to neurodegenerative processes [62]. Neuronal differentiation and cell proliferation are caused by activating the GLP-1R signalling pathway [63,64]. Liraglutide increases hippocampus neurogenesis and has positive effects on metabolic management and synaptic plasticity in mice who are extremely obese and insulin-resistant [65]. It is yet unknown how GLP-1 RA affects neurogenesis by what mechanism. Increased expression of mammalian achaete–scute homologue 1 (Mash1), which is thought to enhance hippocampus neurogenesis and plays a significant role in neuronal development, is one potential method [66]. Liraglutide (used for diabetes) showed potential in protecting brain cells and reducing inflammation. Liraglutide reduced brain inflammation in two different mouse models: Alzheimer's disease and radiation-induced brain damage when exposed to rain at the 6 Gy X-ray. A dose of 25 nmol/kg on the daily bases was administered for 30 days. The drug lowered levels of harmful immune cells (activated microglia and astrocytes) and inflammatory chemicals (cytokines and nitric oxide). These results suggest liraglutide could be beneficial for treating various neurodegenerative conditions with chronic brain inflammation [67]. Inflammation is thought to be the major causes of retinal impairment. Particularly in cases of hyperglycaemia, oxidative stress is a prevalent initiator component in the pathophysiology of several inflammatory retinal disorders. By enhancing the release of proinflammatory mediators, elevated levels of ROS can worsen inflammatory conditions. A vicious pattern may start, which could eventually result in cell malfunction and death of cells. By reducing the generation of ROS, GLP-1R activation can reduce oxidative stress, improves the antioxidant barrier effect as well as enhancing the role of mitochondria in preserving membrane permeability and mitogenesis [68]. In comparison to the control group, high glucose levels elevated the amount of sphingosine-1-phosphate receptor 2 (S1PR2) in human retinal vascular endothelial cells (hRVECs) and decreased the expression of the GLP1R. Exenatide reduced the amount of HG-induced S1PR2. HG-induced hRVECs damage was further reduced by exenatide's inhibitory effects on S1PR2 expression. The findings highlight S1PR2 as a potential new target for the treatment of DR and provide evidence for a potential mechanism of exenatide-mediated reduction of S1PR2 production [69].

4.2. GLP-1 and synaptic plasticity

The strength of connections, or synapses, that may be adjusted between nerve cells is referred to as synaptic plasticity. It is commonly known that diabetes alters the synaptic plasticity of the hippocampus, and that this disruption has an impact on cognition [70]. Recent research by Reisi et al. suggests that diabetes can impair synaptic plasticity through a complex interplay of both postsynaptic and presynaptic factors [71]. Diabetic animal models with cognitive deficits exhibited impaired synaptic plasticity, reflected in compromised long-term potentiation (LTP) and long-term depression (LTD) induction [72]. Exendin-4 administration demonstrably boosts CREB phosphorylation and BDNF levels in the brains of high-fat-diet mice, thereby protecting against LTP impairment [73]. Additionally, exendin-4 raised PSD-95 and the AMPA receptor GluR1 subunit's membrane protein levels [74]. A GLP-1 mimetic called ligarglutide protected against the detrimental effects of a high-fat diet on hippocampal synaptic plasticity in a mouse model of Alzheimer's disease [75]. GLP-1R contributes to the impact of GLP-1 RA on neuronal plasticity. LTP in the hippocampal CA1 region was significantly reduced in a GLP-1R deletion animal model [76]. Interestingly, GLP-1 RA were found to upregulate the expression of both mTOR and neurotrophic tyrosine kinase receptor type 2 (Ntrk2) in the hippocampus of mice fed a high-fat diet. These proteins play crucial roles in regulating LTP and, consequently, synaptic plasticity [77]. GLP-1 RAs could be involved in the fine-tuning of neuronal adaptability, possibly by affecting the way calcium signals are generated in response to glutamate and changes in electrical potential across the neuronal membrane, potentially also through their interaction with AMPA receptors [78].

4.3. GLP-1 and aging

GLP-1 RAs have important functions in the aging process. By stimulating the production of apurinic/apyrimidinic endonuclease 1 (APE1), activation of the GLP-1 receptor would improve DNA repair [79]. GLP-1 reduces cellular senescence and DNA damage brought on by a range of oxidative stressors, mitigates H2O2-induced senescence, and modifies the antioxidant defence system [80]. In neurodegenerative illnesses, GLP-1 also promotes DNA repair and has a neuroprotective impact [81]. Liraglutide also has the ability to improve mitochondrial dysfunction through the cyclic AMP (cAMP)/PKA pathway [82]. Exenatide can restore mitochondrial dynamics, improve mitochondrial morphology, and address the mitochondrial energy crisis [83]. Liraglutide also protects cardiomyocytes against interleukin-1β-mediated mitochondrial dysfunction. Methylglyoxal-induced mitochondrial dysfunctions in H9c2 cardiomyoblasts can be considerably suppressed by activating the GLP-1 receptor [84]. Furthermore, through activating Sirt1, the GLP-1 receptor prevents apoptosis and reduces the generation of ROS and inflammatory response [85]. GLP-1 uses the PI3K/Akt/mTOR signalling pathway to prevent cell death [86]. Beta cells are shielded from apoptosis by ligarglutide via the AMPK/mTOR signalling pathway [87]. Moreover, liraglutide reduces inflammation by activating the mTORC1 signalling pathway [88]. Moreover, GLP-1 can help prevent hepatocyte steatosis by triggering the unfolded protein response [89]. Cellular senescence is modulated by the DPP4-GLP-1 axis via the AMPK/SIRT1/FOXO3a pathway [90]. All together, these results show that GLP-1 RAs

have a variety of anti-aging benefits.

5. Clinical trials

In a rare disease called Wolfram Syndrome (WS), caused by a faulty Wfs1 gene, people face dismal chances with no known cure. However, hope emerges from a new type of drug called a "dual incretin agonist." This study tested this drug in a rat model of WS. The researchers found that, compared to untreated rats, those given the dual agonist showed sustained improvement in blood sugar control. This suggests the drug could protect against diabetes, a key symptom of WS. Importantly, the drug also seemed to help regenerate insulin-producing cells in the pancreas. While hearing loss remained unchanged, the treated rats' vision and nerve cell density in the eye were better preserved. This indicates the drug's potential to slow down vision loss, another major symptom of WS. Overall, this study highlights the promising potential of dual incretin agonists as a potential treatment for WS patients, offering hope for managing the disease and improving their quality of life [91].

A study explored adding the drug ipragliflozin to existing treatment for patients with poorly controlled type 2 diabetes. Over 100 patients who were already taking a GLP-1 receptor agonist or a sulfonylurea (or both) participated. The patients took ipragliflozin for 52 weeks, starting with a lower dose (50 mg/day) and increasing to a higher dose (100 mg/day) if needed. Their blood sugar levels and weight were monitored throughout the study. The results showed that adding ipragliflozin significantly improved blood sugar control and led to an average weight loss of 6 pounds. The higher dose was more effective for those whose blood sugar wasn't well controlled with the lower dose. Side effects were common, with nearly half of the patients experiencing something like increased urination, low blood sugar, constipation, or thirst. However, no serious safety concerns were identified. Overall, the study suggests that ipragliflozin can be a safe and effective add-on therapy for patients with type 2 diabetes who aren't achieving good blood sugar control with their current medication [92]. Another research was carried out by Researchers in Japan have studied a medication called DS-8500a as a potential treatment for type 2 diabetes (NCT02628392) [93]. A potential new drug for type 2 diabetes, codenamed DS-8500a, shows promise in managing blood sugar and cholesterol levels. This experimental medication targets a specific receptor in the body called GPR119, involved in both insulin and glucagon-like peptide-1 (GLP-1) production. This dual action could potentially offer better blood sugar control with just one medication, compared to existing regimens. Researchers conducted a 12-week, randomized, double-blind trial to compare DS-8500a's effectiveness and safety against a placebo and sitagliptin, a common diabetes medication. Patients with moderately elevated blood sugar levels received either varying doses of DS-8500a, sitagliptin, or a

Table 2
Clinical trial studies.

Other IDs	Target	Enrolled	Phase	Remark	NCT number
GlukaStase	T2DM	30	Not applicable (NA)	• Comparison between healthy individual and T2DM. • Infused with saline at the dose of 0.2, 0.4, 0.8 pmol GLP-1/kg/min • Patients with type 2 diabetes exhibited a preserved response to GLP-1 • However, in patients with type 1 diabetes, observed no significant changes in glucagon secretion regardless of whether they received saline or GLP-1 infusions.	NCT01507597 [94]
PB119301	T2DM	273	3	• Pegylated Exenatine Injection (PB-119) was used the dose of 150 μg on one day every week for 28 weeks • The dose was administered by dividing the study population with 1:1	NCT04504370
PB119302	T2DM	620	3	• A dose of 150 μg once every week was administered for 52 weeks • The level of HbA1c was measured and compared with previous readings	NCT04504396
SCW0502-1032	T2DM	623	3	• XW003 (ecnoglutide) versus dulaglutide in patients • The study is active but has not started recruiting yet	NCT05680129
NPRP 5-273-3-079	T2DM	410	NA	• Patients were selected who had HbA1c >58 mmol/mol • On follow up of 12 months, HbA1c dropped from a high of 10 % to a near-normal 6.1 % with the combination, compared to only 7.1 % with insulin. • Importantly, people on the combination therapy gained less weight and experienced far fewer episodes of low blood sugar, both potential drawbacks of insulin.	NCT02887625 [95]
1236	CVD	4197	NA	• SGLT2i and GLP-1 RA medications is used against T2DM and ASCVD • The study is active but is not yet recruiting the patients	NCT04862858
300440	CVD	18	NA	• Semaglutide is used against acute pulmonary embolism • Endothelial biomarkers and plasma proteomics were the primary and secondary outcome measures, respectively.	NCT06118203
300003702	CVD	200	2	• Sacubitril (97–103 mg) and valsartan (160 mg) were used as drug in the study • It is a randomized, parallel assignment with quadruple study • The study is yet at the recruiting stage	NCT04055428
ExPD-ESR-18-13,512	Parkinson's disease	60	2	• Either exenatide (2 mg) or the placebo is administered for 18 months on the weekly basis • The study is active and is not recruiting	NCT04305002
Wolfram Tirzepatide	Wolfram Syndrome	10	2	• Trizepatide would be administered on the weekly basis • It predicts to increase the endogenous insulin production and correcting glycaemic lability of patient with Wolfram syndrome type 1	NCT05659368
GLP-1RAs PCOS	PCOS	68	4	• Dulaglutide effect is compare with calorie restricted diet • The study is completed but the data are not available in the public domain	NCT04876027
2020PS624K	PCOS	60	4	• MET monotherapy versus MET plus LIRA is compared for PCOS patients • It was observed that for overweight patients, both the treatment was effective but when considered the reproductive abnormalities and hyperandrogenaemia, the MET LIRA is more effective than MET	NCT04969627 [96]
D5551R00015	Pancreatic cancer	2400	NA	• Exenatide and non-GLP-1 RA based glucose lowering drugs were compared in an observational study • The study is not yet recruiting	NCT05663515
UMississippi	Osteoporosis	48	2	• GLP-1 agonist is used for bone strengthening purpose in post-menopausal women with T2DM • The study is yet in recruiting stage	NCT04964388

ASCVD - atherosclerotic cardiovascular disease; CVD - cardiovascular disease; GLP1-RA - glucagon-like peptide-1 receptor agonist; HbA1c - glycated hemoglobin; LIRA - liraglutide; MET - metformin; PCOS - polycystic ovary syndrome; SGLT2i - sodium-glucose cotransporter 2 inhibitor.

placebo. DS-8500a demonstrated a dose-dependent decrease in HbA1c, a measure of long-term blood sugar control. The highest dose (75 mg) lowered HbA1c by 0.44 %, while the lowest dose (25 mg) achieved a 0.23 % reduction. Higher DS-8500a doses significantly reduced fasting and post-meal blood sugar levels compared to the placebo. While DS-8500a wasn't superior to sitagliptin in terms of blood sugar control, it showed a significant advantage in cholesterol management. At higher doses, the drug lowered total cholesterol, LDL cholesterol, and triglycerides, while slightly increasing HDL cholesterol. This suggests potential additional benefits for diabetes patients at risk of heart disease. DS-8500a was well tolerated overall, with only two cases of mild hypoglycemia reported in the highest dose group. This study suggests that DS-8500a is a promising new drug for the treatment of type 2 diabetes. It shows good blood sugar control, a favourable effect on cholesterol levels, and appears to be well-tolerated. Further research is needed to confirm these findings and evaluate the long-term safety and efficacy of DS-8500a for the treatment of diabetes [93]. Refer Table 2 for more clinical trials.

When considering participant inclusion (PICOs) in clinical trials, several criteria must be carefully evaluated. The targeted population should primarily consist of older adults above a specified age threshold experiencing cognitive decline or individuals diagnosed with specific neurodegenerative diseases. Additionally, the patient population may include those with diabetes or a combination of both conditions. However, challenges such as patient willingness, accessibility to trial sites, and potential biases in participant selection could arise and pose hurdles during the clinical trial process. To effectively evaluate long-term outcomes, various strategies can be employed. These include implementing longitudinal assessments, utilizing biomarkers, incorporating functional measures, and establishing robust safety monitoring protocols. These strategies are crucial for obtaining comprehensive and meaningful data regarding the efficacy and safety of interventions in addressing age-related cognitive decline and neurodegenerative diseases.

6. Conclusion

The quest for healthy aging has taken a promising turn with the exploration of GLP-1 [97,98]. Research paints a compelling picture of this multifaceted molecule, unveiling its potential to combat age-related challenges and pave the way for a healthier, longer lifespan. Traditionally known for its role in glucose control, GLP-1 reveals a hidden depth in the fight against aging. Its influence extends to the brain, protecting neurons and fostering neurogenesis, a process crucial for memory and cognitive function. This suggests a potential weapon against neurodegenerative diseases like Alzheimer's and Parkinson's. The metabolic battlefield is another domain where GLP-1 shines. Its ability to regulate insulin, suppress glucagon, and reduce appetite offers hope for tackling age-related metabolic syndromes like type 2 diabetes and obesity. Targeting it signalling pathways may unlock a future where therapeutics address not just isolated ailments, but orchestrate an overall symphony of healthy aging. Unraveling the mechanisms behind GLP-1's magic is at the forefront of the research agenda. From deciphering receptor interactions to understanding its influence on multiple organs, the quest for knowledge continues. Sustained-release capsules or targeted methods delivering GLP-1 precisely where needed, enhancing its therapeutic power. Combining GLP-1 with other modalities like stem cell therapy or gene editing could create harmonious melodies, revolutionizing treatment for age-related conditions. CRISPR-Cas9 gene editing holds the potential to fine-tune GLP-1 pathways, composing personalized treatments for individual needs. GLP-1 represents a promising note in attaining of healthy aging. The absence of long-term studies raises doubts about the effectiveness of GLP-1 treatments in healthy individuals. It is crucial to delve into the impact of these treatments on overweight individuals and those seeking anti-aging benefits. Understanding how GLP-1 therapies affect these specific patient groups is essential for comprehensive evaluation and informed decision-making regarding their potential benefits in combating age-related issues and promoting overall well-being. By supporting collaboration, research, and innovation, this invention can be a powerful symphony, guiding us towards a future where age is just a number and health reigns supreme.

Contributors

Vivek P. Chavda plotted the ideation of the article, contributed to the drafting and revision of the manuscript, and guided the critical revision of the article.

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