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Review

Age-Related Adipokine Dyshomeostasis: From Adipose Tissue to the Central Nervous System

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ABSTRACT: Aging is characterized by the progressive loss of physiological integrity, leading to impaired tissue function and increased vulnerability to chronic diseases. As a pivotal regulator of whole-body energy homeostasis and insulin sensitivity, adipose tissue undergoes considerable remodeling throughout aging, a dimension that has received significant academic attention only in the past decade. Concurrently, profound changes in the adipose secretory profile enable these factors to modulate peripheral metabolism and, via endocrine pathways, drive central nervous system (CNS) aging alongside associated metabolic dysfunctions. In this review, we comprehensively summarize the age-related dynamic alterations of six key factors (adiponectin, leptin, FGF21, GDF15, resistin, and chemerin) in adipose tissue, systemic circulation, and cerebrospinal fluid. We highlight the age-dependent shifts in the central effects of adipokines, influenced by factors such as blood–brain barrier (BBB) permeability and receptor expression, and summarize their multifaceted anti-aging roles in the brain. Finally, we discuss the most promising pro-longevity interventions developed in recent years, highlighting the mechanisms through which they attenuate adipose tissue senescence. By offering a systematic and timely synthesis of the "aging adipose–brain axis", this review emphasizes that the homeostatic dysregulation of adipokines and the attenuation of their central neuroprotective effects are potential contributors to the exacerbation of CNS aging. Ultimately, this review highlights a theoretical foundation for targeting peripheral adipose tissue health, providing a preliminary perspective for future translational research into the early diagnosis and management of age-related neurometabolic disorders.

Keywords: Aging, Adipokines, Adipose-brain axis, Therapeutic strategies

Introduction

By 2050, the global population aged ≥ 60 will reach 2 billion, posing profound healthcare and socioeconomic challenges. Aging is characterized by a gradual decline in cellular function [1], leading to impaired tissue integrity and increased susceptibility to chronic conditions such as Alzheimer's disease (AD), type 2 diabetes (T2D), cardiovascular disorders, and osteoarthritis [2, 3]. Although the aging rate varies across different organs [4, 5], the precise triggers that initiate and propagate senescence across tissues remain poorly understood.

Adipose tissue, a critical organ for energy storage, is reported to experience relatively early age-dependent remodeling [6, 7]. Adipose tissue mass typically peaks during middle age and declines in later life [8, 9]. With age, the depot undergoes extensive tissue remodeling—characterized by fibrosis, hypoxia, chronic inflammation,

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impaired thermogenesis, and insulin resistance [10-13]. Preadipocytes exhibit early transcriptional vulnerability to senescent cues [14, 15]. Notably, metabolic stress such as obesity significantly exacerbates these aging processes, partly because obese adipocytes exhibit heightened susceptibility to DNA damage-induced senescence [16].

Beyond energy storage, adipose tissue serves as a vital endocrine organ that modulates systemic physiology by releasing bioactive factors through classic secretion, vesicle transport, and exosome release. Aging profoundly alters this secretory landscape [17, 18]. Additionally, the senescence-associated secretory phenotype (SASP) refers to specific factors released by senescent cells, including cytokines and growth factors. SASP significantly impacts the adipose microenvironment and is associated with diseases such as obesity and diabetes [19, 20].

Altered secretomes of aging adipose tissue can further impact the aging of other tissues through endocrine signaling. In CNS, adipose-derived factors play a potential role in chronic inflammation, oxidative stress, neuronal proliferation/apoptosis, the expression of senescence-associated markers, and synaptic dysfunction and impairment of BBB integrity in aged mice [21-25]. However, the relationship between serum adipokine concentrations and the CNS during aging, particularly in late-stage senescence, is not characterized by a simple linear correlation as neuronal senescence progressively accumulates with advancing age. Furthermore, the brain's sensitivity to these various adipokines (e.g., leptin, FGF21) tends to diminish [26-28]. Elucidating the regulatory crosstalk between aged adipose-derived adipokines and the CNS holds significant therapeutic potential for targeting adipose tissue to delay brain aging (Fig. 1).

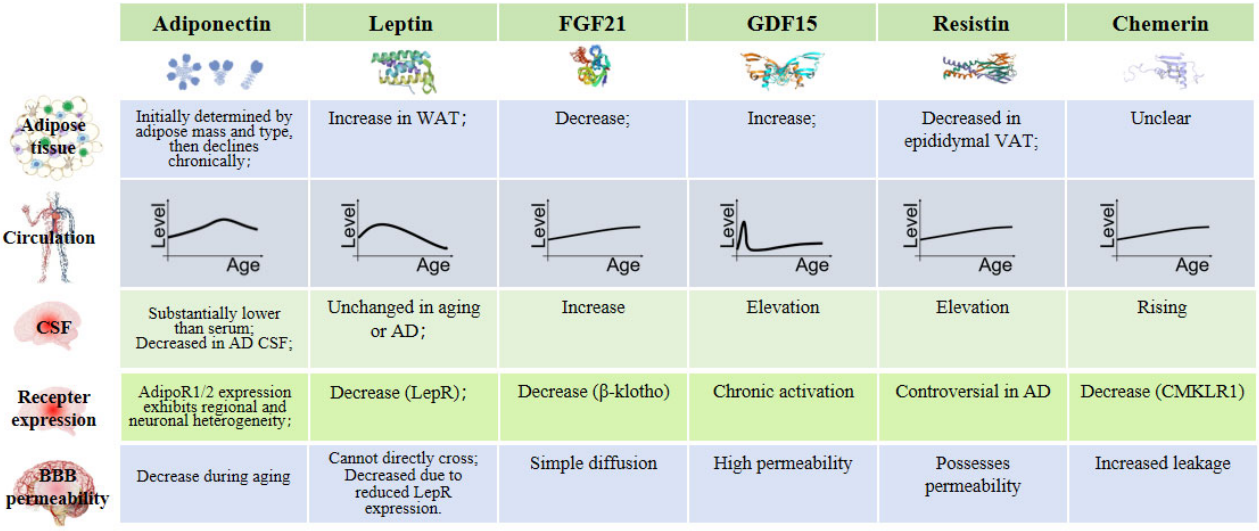


Figure 1. **Age-related homeostatic imbalance of adipokines in adipose tissue, systemic circulation, and the CNS.** During the ageing process, the expression patterns of various adipokines and signaling molecules exhibit complex and dynamic evolutionary profiles in adipose tissue, systemic circulation, and the CNS. (AD: Alzheimer's Disease; CSF: Cerebrospinal Fluid; BBB: Blood-Brain Barrier)

In this article, we systematically summarize: (1) the dynamic alterations of adipokines across adipose tissue, systemic circulation, and cerebrospinal fluid; (2) the dysregulated adipokine signaling underlying the age-dependent shifts in their central effects; and (3) the potential mechanisms through which adipokines exert central anti-aging effects. Finally, we discuss current intervention strategies that achieve anti-aging outcomes by delaying adipose tissue aging, with a focus on their mitigating effects on adipose tissue senescence. This provides a preliminary theoretical foundation for targeting adipose tissue as a potential strategy to mitigate CNS aging and related diseases.

Adiponectin

Adiponectin (APN) is a pivotal anti-inflammatory adipokine whose synthesis and secretion undergo marked temporal deterioration during aging [29]. While age-related redistribution, altered cellular composition, and shifts in tissue responsiveness dynamically modulate APN quality in the short term [30], advanced senescence eventually drives adipose atrophy and secretome dysfunction, precipitating a systemic decline in APN production [31].

Although APN is one of the most abundant plasma proteins, its circulating levels become negatively correlated with age in advanced aging [32, 33],

establishing it as a biomarker of aging. Notably, this trajectory is not universally consistent: some human cohorts report elevated, rather than reduced, circulating APN in advanced old age, a discrepancy often attributed to comorbidities, renal function, and body composition confounders. In addition, whether these circulating APN fluctuations originate predominantly from adipose tissue remains elucidated. AdipoR2 is progressively downregulated across both clinical and murine tissues with advancing age [34-36]. This receptor loss suggests a state of age-related "adiponectin resistance," wherein even preserved or paradoxically altered circulating ligand fails to trigger protective downstream cascades.

Disruption of adiponectin signaling is widely involved in age-related pathologies, but it is essential to separate aging-intrinsic APN changes from disease-specific alterations. In disease cohorts, serum APN levels in middle-aged and elderly individuals correlate with onset and progression of multiple disorders including premature ovarian failure and AD [37, 38]. However, these associations do not establish causality, and APN changes in AD may partly reflect disease-driven metabolic or inflammatory remodeling rather than primary aging.

The BBB exhibits high selectivity for APN, allowing only low-molecular-weight trimers and a subset of hexamers to cross into the CNS [39, 40]. Although APN levels in the cerebral cortex decline significantly during aging [32], local APN expression in the cortex and striatum remains unchanged with age, alongside the inherently low endogenous expression of APN in the CNS [41]. This indicates that the age-related reduction of cortical APN is directly attributable to the decrease in circulating peripheral APN.

APN deficiency accelerates brain aging and associated CNS pathologies [32, 42, 43]. Functioning as an integrated neuroprotective system, APN preserves structural plasticity by elevating BDNF, restoring dendritic complexity, and enhancing LTP via AdipoR1/AMPK signaling [40, 44-46]. This structural support is coupled with immune homeostasis, where APN reprograms microglia via the PPARγ pathway to suppress neuroinflammation [38, 47]. At the pathological level, APN signaling directly targets hallmark protein aggregates—activating AMPK/SIRT1 to promote autophagic Aβ clearance [48], while synergizing with GSK3β to reduce Tau hyperphosphorylation [49].Importantly, these anti-aggregation effects have largely been characterized in disease or injury models; it remains unclear whether endogenous APN signaling modulates physiological Aβ/Tau turnover during uncomplicated aging.

Leptin

Leptin is a protein hormone primarily secreted by adipose tissue, and its circulating levels not only reflect adipose tissue mass but also transmit signals regarding energy storage status to the brain [50, 51]. Crucially, leptin levels decouple from fat mass as early as midlife [52]. With advancing age, leptin expression in white adipose tissue declines significantly [53], leading to a progressive reduction in its circulating levels [54, 55]. Furthermore, this decline exhibits clear sexual dimorphism, being far more pronounced in females [56]. This age-associated trajectory is not uniform across cohorts: some human studies report preserved or even elevated circulating leptin in older adults, likely confounded by adiposity, insulin resistance, and systemic inflammation.

Leptin can cross the BBB through a specific transport system, but the transport mechanism becomes dysfunctional with age [57, 58]. Crucially, cerebrospinal fluid (CSF) leptin deficits are not a general hallmark of aging [59] or AD [60], but emerge selectively in memory impairment [61]. This specificity suggests that transport deficits may directly relate to leptin's physiological role in maintaining central cognition and neural plasticity.

Despite decreased peripheral leptin levels and relatively stable CSF concentrations, central responsiveness to the hormone still diminishes with age. Age undermines leptin-dependent synaptic plasticity, blunting long-term potentiation (LTP) at Schaffer collateral (SC) and temporoammonic (TA) inputs to CA1 [62], while extinguishing adult forms of long-term depression (LTD) [63]. This plastic failure is driven by a multi-tiered cascade of central leptin resistance: chronic neuroinflammation acts as the primary priming event [64], reinforcing the transcriptional downregulation of hypothalamic LepR [65]. Intracellularly, this desensitization is executed through the concurrent hyperactivation of negative-feedback regulators (SOCS3, PTP1B, and TCPTP) and the resultant blunting of neuroprotective STAT3 phosphorylation [66].

Leptin and its receptor (LepR) signaling pathways play a crucial role in central aging and associated diseases, as evidenced by brain volume reduction and cognitive impairments in signal-deficient mice, alongside the neuroprotective effects of exogenous leptin in aging models [67-69]. A key distinction is required here: protective effects against pathological protein aggregates are largely characterized in AD-like disease models, while whether endogenous leptin modulates physiological Aβ and Tau turnover during uncomplicated aging remains undetermined. This neuroprotection is achieved by concurrently counteracting neuropathology and preserving synaptic function: leptin reduces Aβ deposition and Tau accumulation—in part by

downregulating GM1 via the PI3K/Akt/mTOR pathway to inhibit Aβ assembly [70, 71], while also mitigating Aβ-induced impairments in hippocampal LTP/LTD by preventing the removal of GluA1-containing AMPA receptors from synapses [72, 73].

However, leptin resistance is a major roadblock to anti-aging therapies based on leptin supplementation. The temporal sequence of leptin dysregulation is heterogeneous: in midlife, rising adiposity often drives transient hyperleptinemia before subsequent leptin decline, establishing central leptin insensitivity before peripheral levels fall. This means simply giving exogenous leptin late in life may not work. To truly slow brain aging, leptin supplements need to be given early – before midlife onset – or combined with strategies restoring leptin sensitivity. This therapeutic framework remains largely preclinical; whether early leptin intervention or sensitizing agents can improve human age-related cognitive decline has not been validated in randomized controlled trials.

FGF21

Fibroblast growth factor 21 (FGF21) is a pleiotropic metabolic hormone predominantly produced by metabolically active organs including the liver, adipose tissue and pancreas [74-76]. Within adipose depots, diminished FGF21 expression serves as a biomarker of local senescence [77]; conversely, adipose-selective FGF21 overexpression remodels lipid metabolism, suppresses inflammatory signaling and prolongs lifespan in mice [78, 79].

This local reduction in adipose FGF21 stands in stark contrast to the progressive age-dependent elevation of circulating FGF21 [80]. Despite the liver being conventionally viewed as the primary contributor to systemic FGF21, hepatic FGF21 synthesis declines with aging, mirroring the trajectory observed in adipose tissue [81]. This apparent paradox points to noncanonical tissue sources as the major drivers of elevated circulating FGF21 in old age. Skeletal muscle, in particular, exhibits marked compensatory FGF21 upregulation upon age-linked mitochondrial impairment [82], establishing muscle as a critical endocrine source sustaining high systemic FGF21 concentrations.

Sustained high FGF21 exposure correlates with progeroid phenotypes and premature mortality, a phenotype widely attributed to impaired cellular responsiveness to FGF21 [80, 83]. At the molecular level, aging-associated metabolic decline and chronic inflammation downregulate β-Klotho, the obligate co-receptor required for functional FGF21 signaling with documented anti-aging activity [84-86]. The combination of increased ligand availability and reduced β-Klotho abundance gives rise to a state of "FGF21 resistance" [87], which exacerbates age-related metabolic dysfunction.

A comparable signaling paradox exists within the aging CNS. Although cortical FGF21 transcript/protein levels rise during aging [88], β-Klotho expression and downstream FGF signaling activity are substantially suppressed in the aged CNS [87, 89]. This uncoupling between ligand concentration and pathway activation suggests that FGF21 resistance also emerges in the aged brain, blunting the pathway's endogenous neuroprotective and metabolic homeostatic functions.

A large body of mechanistic work documents protective FGF21 actions, but these data are heavily conditioned by experimental setting and cannot be uniformly extrapolated to physiological brain aging. Circulating FGF21 accesses the CNS via carrier-dependent BBB transport; exogenous FGF21 stabilizes barrier integrity via AMPK signaling, restrains NF-κB-dependent neuroinflammation, boosts antioxidant defense, sustains the astrocyte–neuron lactate shuttle, preserves neuronal mitochondrial function, inhibits p53-mediated senescence, and upregulates SIRT1 [88-93]. FGF21 additionally promotes the clearance of Aβ and Tau aggregates via PPARγ- and AMPK-dependent pathways [94, 95]. Nearly all these beneficial phenotypes derive from exogenous FGF21 administration or amyloid/Tau disease models. Evidence that endogenous FGF21 governs physiological brain aging is limited, and whether age-related FGF21 elevation is adaptive or a marker of FGF21 resistance remains unresolved. Variable β-Klotho loss across brain regions, mouse strains, and human cohorts adds uncertainty for cross-species extrapolation.

GDF15

Growth/Differentiation Factor 15 (GDF15) is a stress-inducible cytokine secreted by multiple organs including the liver, kidney, adipose tissue, and skeletal muscle [96-98]. Its expression is markedly upregulated in both white and brown adipose tissue upon senescence, a response closely linked to age-related mitochondrial dysfunction and activation of the integrated stress response [99, 100]. As a well-validated biomarker of biological aging, GDF15 is also classified as a core SASP component. Adipose-sourced GDF15 therefore exerts dual functions: it signals local senescent status and operates as an endocrine messenger capable of propagating systemic metabolic decline. [101]. Under basal conditions, circulating GDF15 is kept at low levels following a transient postnatal peak [102, 103]. Plasma GDF15 concentrations correlate positively with chronological as well as biological age [104, 105], and senescent cell

populations — endothelial cells, adipocyte progenitors, macrophages and myocytes – constitute its primary cellular reservoir [106]. This secretory profile is a defining feature of the SASP, sustaining the chronic low-grade proinflammatory milieu that predisposes to age-associated pathologies [107, 108].

GDF15 gains access to the CNS across the blood–brain barrier through carrier-dependent transport and is increasingly recognized as a critical node within the adipose – brain axis with translational potential [109]. Although serum and CSF GDF15 levels are positively correlated, CSF GDF15 is not solely derived from peripheral circulation. The hippocampus, temporal cortex, and cerebellum exhibit robust age-associated induction of intrinsic GDF15 expression [110]. Elevated CSF GDF15 tracks with advancing age and is strongly associated with cognitive impairment [111], yet causality between these phenomena remains unestablished.

Sustained GDF15 excess drives constitutive activation of the hindbrain-restricted GDF15 – GFRAL signaling module, which transmits robust anorexigenic inputs [112, 113]. This pathway has been proposed to underpin age-related anorexia, unintentional weight loss and sarcopenia in older adults, while conclusive human causal data are still lacking. Beyond metabolic control, neuroinflammation represents a mechanistic link between GDF15 and brain aging, supported by its positive association with IL-6 in aged human cohorts [110]. At the cellular level, persistent GDF15 may fuel central inflammaging by triggering microglial NLRP3–GSDMD inflammasome activation, promoting recruitment of $CXCR2^{+}$ neutrophils [114], and inducing pathological hippocampal microglial activation together with excessive synaptic engulfment [115].

Of note, while circulating GDF15 rises robustly with age, its canonical receptor GFRAL exhibits highly restricted CNS expression, largely confined to hindbrain neurons. Taken together, definitive evidence that endogenous GDF15 functionally governs physiological brain aging remains limited; even so, current data support a model in which GDF15 modulates central neuroinflammatory signaling and anorexia-related phenotypes in the aging organism.

Resistin

Resistin, a cysteine-rich secreted RELM-family protein, is marked by profound interspecies divergence that itself constitutes a major source of inconsistent aging-related observations. Adipose resistin exhibits heterogeneous age-associated trajectories that vary by species, fat depot, and sex; critically, its cellular origin differs sharply between species: human adipose resistin derives primarily from tissue-infiltrating macrophages, whereas murine resistin is predominantly adipocyte-produced [116-118]. This species divergence complicates direct extrapolation from rodent aging data to human aging cohorts. Correlative data link elevated resistin to inflammaging and metabolic dysfunction; subcutaneous adipose resistin negatively associates with leukocyte telomere length, a biomarker of biological aging, and mechanistic work implicates TLR4/NF-κB proinflammatory signaling in this axis [119-121]. However, causal evidence establishing resistin as a driver, rather than merely a bystander, of physiological inflammaging remains absent.

Plasma resistin levels are significantly elevated in older humans and older rodents [122-124]. Even so, it remains unresolved whether the age-dependent increase in serum resistin stems mainly from adipose tissue. Population-based genetic studies show that offspring of individuals with healthy aging phenotypes have lower circulating resistin and a reduced risk of metabolic syndrome (MetS) [125, 126]. This further implies that maintaining low resistin levels may serve as a crucial protective factor for preserving metabolic health and promoting longevity.

Circulating resistin can cross the BBB, and this permeability depends on the extent of barrier impairment [127]. Published findings diverge sharply in disease contexts: elevated plasma and CSF resistin is reported in AD cohorts, where resistin exacerbates amyloid pathology, suppresses neuronal glucose uptake, and amplifies oxidative injury [128-132]. Opposing work, by contrast, reports reduced resistin in age-related neurodegeneration and describes compensatory neuroprotective actions, including mitigation of neuronal oxidative stress and mitochondrial dysfunction [133-135]. An acute elevation in resistin levels likely represents a compensatory response to Aβ accumulation, serving to bolster the organism's resistance to metabolic aberrations [131], whereas prolonged high resistin exposure may eventually induce insulin resistance in both the periphery and CNS. Notably, much of this evidence is derived from AD pathological models rather than unperturbed physiological brain aging.

Chemerin

Chemerin, a predominantly white adipose tissue (WAT)-derived adipokine, signals via three cognate receptors: CMKLR1 (ChemR23), GPR1, and CCRL2 [136, 137]. These receptors are broadly expressed in metabolic organs and central tissues such as the liver, skeletal muscle, and hypothalamus [138]. The chemerin/CMKLR1 axis is associated with inflammation, metabolism, and cancer development [139, 140]. Although adipose expression of chemerin and CMKLR1 declines post-pubertally in

rodents [141], systemic and central chemerin dynamics diverge during late-stage aging. Notably, circulating chemerin levels are markedly elevated in elderly populations [142]. Because chemerin readily crosses the BBB under both physiological and pathological conditions [143], this peripheral increase, together with age-associated BBB impairment, drives age-related chemerin accumulation within the CSF.

In contrast to rising ligand levels, receptor availability in the aged CNS displays a paradoxical pattern. Normal CNS aging is marked by a progressive decline in CMKLR1 expression [28]. Intriguingly, this trend is reversed in AD models, where CMKLR1 is markedly upregulated across neurons and glial cells in late disease stages [144-146]. This shift suggests disease-specific remodeling of chemerin signaling, potentially representing either a compensatory response or a pathological alteration.

Functionally, accumulating evidence supports a neuroprotective role for chemerin and its active nonapeptide fragment against CNS aging and metabolic decay. Current research indicates that chemerin mitigates CNS aging by remodeling the neuroinflammatory milieu—facilitating reparative glial polarization and Aβ42 clearance [147-149]. Concurrently, CMKLR1-dependent signaling suppresses apoptotic and inflammatory cell death via the PI3K/AKT/Nrf2 axis [150, 151]. Consistent with these molecular benefits, recombinant human chemerin (rhChemerin) stabilizes BBB integrity and rescues spatial memory deficits [152]. This demonstrates that chemerin-CMKLR1 signaling can bridge cellular-level neuroprotection to functional cognitive preservation.

Aging induces the remodeling of adipose tissue, which in turn regulates the secretion of adipokines and cytokines. Specific adipokines are capable of entering the circulatory system, traversing and modulating the BBB, thus further influencing CNS aging. Various adipokines affect central aging and the progression of related diseases directly or indirectly by modulating neuroinflammation, neuronal activity and regeneration, synaptic activity, and other related processes (Table 1).

Table 1. Aging-related effects of key adipokines on the CNS in the adipose tissue–brain axis.

Adipokines	Model and the changes during aging		Model and the effects on brain aging	
Adiponectin (APN)	15.5 mo vs 6 mo C57BL/6 mice [32];	Cerebral cortex↓;	Aged C57BL/6 WT; APN-KO mice [32]; 18 mo SD rats with APN treatment [47];	Neuroinflammation↓
	3~6 mo 5×FAD mice [234];	Brain↓;	Aged APN-KO mice; aged 5×FAD mice [46]; Primary cortical neurons with AdipoRon treatment [49];	Synaptic Activity↑
	72.5~77.4-y human with or without AD [235];	CSF-APN no change;	Aged APN-KO mice; aged 5×FAD mice [234];	BBB integrity ↑
			Young / aged C57BL/6 WT mice; APN-KO mice [236];	Neurogenesis/proliferation↑
			283 cognitively normal older adults, 55~90 y [38]; Aged 5×FAD, APP/PS1 mice; 5×FAD+APN-KO mice [48]; 6~7 mo APP/PS1 mice with AdipoRon treatment [237]; P301S transgenic male mice with AdipoRon treatment [238];	Tau pathology/Aβ plaque/NFTs↓
Leptin	74~76-y human with or without AD [60];	CSF: no change;	Young/aged Wistar rats (young: 3~4 mo; aged: 22~24 mo); naturally aged C57BL/6J mice (3~4 mo /12 mo /18~24 mo) [239];	Energy homeostasis ↑
	18 mo C57BL/6 mice [240];	Hypothalamus↑;	Aged C57BL/6J mice; hypothalamus-specific SIRT1 KO/overexpression models [241];	SIRT1 ↑
	3 mo vs 12~13 mo C57BL/6 mice and 5×FAD mice [242];	Cerebral cortex↓;	208 cognitively normal older adults [70]; Primary cerebral cortical neurons, astrocytes and microglia with leptin treatment [71]; Aged APP/PS1 transgenic mice [243];	Aβ deposition↓
			Hippocampal brain slices from young/aged rats; naturally aged C57BL/6J mice [72]; Primary cerebral cortex from CD1 mice, primary hippocampal cells from SD rats with Leptin treatment [73]; SD rats with $A\beta_{1-42}$ / leptin treatment[244];	Synapses function↑
FGF21	20 mo vs 2 mo C57BL/6 mice [88];	Hippocampus and cortex↑;	MPTP-HCL induced PD model, FGF21-treated C57BL/6 mice [93]; 14 mo male C57BL/6 mice and FGF21-treated mice [92];	Neuronal death↓

	2, 12, 15 mo C57BL/6 mice [245];	Brain↓;	D-gal induced aging model with rhFGF21 treatment [89];	Genes associated with ageing↓
	15 mo vs 2 mo female CD1 mice [246];	Cortex↓;	2-, 12, and 15-mo C57BL/6J mice with AAV-sh*FGF21* [245]; D-gal induced aging model with rhFGF21 treatment [89]; 14 mo male C57BL/6 mice and FGF21-treated mice [92];	Oxidative stress↓
			2 mo male Kunming mice with D-gal/FGF 21 treatment [247] 2, 12, 15 mo C57BL/6 mice and treated with AAV-shFGF21 [245];	Neuroinflammation↓
			D-gal induced aging model with rhFGF21 treatment [89]; D-gal induced aging model with FGF21 treatment [247];	Number and M2-polarization of microglia↑
			14 mo male C57BL/6 mice and FGF21-treated mice [92]; C57BL/6 mice and SIRT6$^{flox/flox}$ /SIRT6^{ko} mice [248];	Cerebrovascular function and BBB ↑
			14 mo male C57BL/6 mice and FGF21-treated mice [92]; Aβ_{25-35}+FGF21 treated Wistar rat [249];	AD biomarkers: Aβ and tau protein↑
			20 mo vs 2 mo C57BL/6 mice with rhFGF21 or lactate treatment [88];	Age-related lactate accumulation↓
GDF15	33~104-y human with or without AD [110];	Aging: Frontal cortex↑; AD: CSF/Brain no change;	BLSA cohort [250]; C57BL/6, Nlrp3^{D301NneoR} mice [114]; Human subjects aged 33~104 years with or without AD, si*GDF15* treatment [110];	Neuroinflammation ↑
	20 mo vs 2 mo-aged mice [251];	Cerebral cortices↑;		
Resistin	55~83-y human [252];	CSF↑	4 mo (pre-symptomatic stage) male WT mice, and APP/PSN1 mice with HFD/resistin treatment [131]; Primary neuronal cultures (SD rats) [132];	Glucose uptake↓, oxidative markers↑; Aβ42 levels ↑
			N2a cells with resistin/H_2O_2 treatment [135];	Oxidative stress, mitochondrial dysfunction ↑
Chemerin	APP/PS1 transgenic mice [28];	Brain↑	APPswe/PS1dE9 mice with C9-L treatment [28]; CMKLR1 knockout, APP/PS1 double transgenic mice with rhchemerin treatment [149];	Migration of astrocytes, astrocyte aggregation ↑
	9 mo APP/PS1 mice, age-matched WT controls; APP/PS1-*CMKLR1*$^{-/-}$ mice [253];	Hippocampus and cortex↓	Swiss albino mice with rhChemerin treatment [152];	Neuroinflammation↓
			SD rats with BCCAO + C-9 treatment [151];	Neuronal apoptosis↓

Abbreviations: wk, week(s); mo, month(s); y, year(s); APN, adiponectin; APN-KO, adiponectin knockout; AdipoRon, adiponectin receptor agonist; AD, Alzheimer's disease; Aβ, amyloid-β; NFTs, neurofibrillary tangles; CSF, cerebrospinal fluid; BBB, blood–brain barrier; 5×FAD, transgenic mice carrying five familial Alzheimer's disease mutations; APP/PS1, amyloid precursor protein/presenilin 1 double transgenic mice; SD rat, Sprague–Dawley rat; WT, wild type; FGF21, fibroblast growth factor 21; rhFGF21, recombinant human FGF21; AAV, adeno-associated virus; shFGF21, short hairpin RNA targeting FGF21; MPTP-HCl, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride; PD, Parkinson's disease; D-gal, D-galactose; SIRT1, sirtuin 1; SIRT6, sirtuin 6; GDF15, growth differentiation factor 15; BLSA, Baltimore Longitudinal Study of Aging; Nlrp3, NLR family pyrin domain containing 3; siGDF15, small interfering RNA targeting GDF15; HFD, high-fat diet; N2a, Neuro-2a mouse neuroblastoma cell line; H_2O_2, hydrogen peroxide; C9-L, chemerin-derived peptide C9-L; rhChemerin, recombinant human chemerin; BCCAO, bilateral common carotid artery occlusion. ↑, increase; ↓, decrease; No change, no significant alteration.

Regulatory Effects of Anti-Aging Strategies on Adipose Tissue

The systemic dysregulation of adipokine signaling pathways induced by adipose tissue senescence does not occur in isolation. By targeting the "upstream mechanisms" of aging hallmarks within adipose tissue, it may be feasible to reshape the local and systemic milieu, thereby mitigating age-associated adipokine metabolic dysfunction and potentially delaying age-related systemic pathology. The following sections will delineate several highly promising anti-aging strategies and their specific regulatory roles in modulating adipose tissue senescence from a preclinical and translational perspective (Table 2).

Table 2. Therapeutic interventions targeting adipose tissue aging.

Therapeutic strategies (Adverse Events)		Completed Trials	Pathological effects on aging adipose tissues and Key References	
Lifestyle intervention	**DR** Calorie/protein/amino acid restriction; Prolonged/Intermittent fasting; Time-restricted feeding; Fasting-mimicking diet; (Reducing lean mass; Sensitivity to dietary restriction declines with age)	NCT02673515 Healthy non-obese middle-aged human subjects (35~65 y, BMI 22~30), 4-wk ADF RCT; reduced trunk fat, inflammatory and pro-aging markers.	Inhibits the senescence markers of cells	Female and male C57BL/6 mice and *atg7*$^{flox/flox}$ mice with 60% less-calorie food [156]; 3,9,12 mo C57BL/6 mice with 40% DR for 3 mo [254];
		NCT00427193 Healthy non-obese adults (21~50 y, BMI 22~28), 2 y 25% CR multicenter RCT; measured HOMA-IR, cardiovascular risk, circulating SASP / inflammatory markers, DNAm epigenetic clock; reduced inflammation and SASP, slowed epigenetic aging.	Remodels ageing adipose tissue	75-wk aged mice, 2 d ad libitum feeding followed by 24 h fasting [157]; C57BL/6J mice (2 mo vs 12 mo), methionine restriction (0.172%) for 8 wk [255];
			Enhances its secretory functions	C57BL/6J, C3H/HeJ and *Ocn-Wnt10b* mice, control diet or 30% CR diet [160]; C57BLKS/J Gpt-*Lepr*^{em2Cd}/Gpt (*db/db*) mice, normal diet (0.86% methionine) or methionine-restricted diet (0.17% methionine, cystine-free) for 13 wk [162] ; C57BL/6 mice and *Fgf21*-deficient mice, low-protein diet intervention [256]; 3 mo C57BL/6 mice, CR (70% ad libitum intake) for 6 mo [257];
		NCT02460783 Cognitively intact older adults (55~70 y) with insulin resistance, 8 wk 5:2 IF vs healthy living diet RCT; improved neuronal insulin signaling and reduced brain-age-gap.		
		NCT00099151 Healthy non-obese adults (21~50 y, BMI 22~28), 6~12 mo 20%/25%/30% CR RCT; safe, improved cardiometabolic and oxidative aging markers.	Alleviates insulin resistance	3, 12, 20 mo C57BL/6 mice, 13% fat-calorie diet [258];
	Physical exercise Aerobic training; Resistance training; Multicomponent training; (Mild to moderate musculoskeletal soreness, joint discomfort, or temporary fatigue)	NCT00396686 Community-dwelling older adults (≥65 y), 12-mo aerobic walking vs stretching RCT; aerobic exercise increased hippocampal volume by ~2% and BDNF, reversed 1~2 y of age-related hippocampal decline.	Alleviates insulin resistance	16 obese aged human subjects, 12-wk supervised exercise (5 d/wk, 60 min/d, treadmill/cycle ergometer, 85% HRmax) [259];
		NCT02064296 Early AD patients, 6-mo moderate cycling vs low-intensity stretching RCT; cycling attenuated hippocampal/temporal atrophy progression.	Promotes lipolysis	Aged mice scWAT, 4-wk HIIT; human cohort database (20~69 y) [260]; C57BL/6 T2D mice, 12-wk aerobic training [261];
		NCT02000583 Sedentary older adults (~72.9 y) with elevated cerebral amyloid, 52-wk aerobic exercise vs health education RCT; no significant reduction in amyloid deposition rate but improved cerebral perfusion and executive function.	Suppresses immunosenescence	11 mo and aged mice, resistance training or endurance training [166]; 30 y and 65 y human subjects, 15 consecutive d cycling (7~9 h/d, 63%~65% HRmax) [262];
		NCT01072509 Older adults at risk of mobility disability (70~89 y), 2.6-y structured physical activity vs health education RCT; reduced incidence of mobility disability and improved frailty-related markers.	Improves adipokine secretion	16 obese older human subjects (63±1 y), 12-wk supervised exercise (5 d/wk, 60 min/d, 85% HRmax) [259]; 73 sedentary overweight older human subjects with abdominal obesity (67.6 y), 6-mo exercise RCT [263];
Drug repurposing	**Rapamycin** (Gastrointestinal symptoms)	NCT03103893 Healthy adults (40~100 y), 6~8-mo topical rapamycin lotion vs vehicle self-controlled skin RCT; topical rapamycin increased dermal thickness and reduced cutaneous senescence markers.	Diminishes the adipose tissue expansion-related gene	Male NcZ10 mice (12 wk to 30 wk), control diet or diet supplemented with rapamycin, metformin, or their combination [176];
		NCT04488601 Healthy normative-aging adults, 48-wk weekly low-dose rapamycin vs placebo decentralized double-blind RCT (PEARL); low-dose intermittent rapamycin safe, mild improvement in visceral fat and metabolic markers.	Improves inflammatory responses	HET3 mice, rapamycin, acarbose or 17-α estradiol treatment [175];
		NCT02874924 Healthy community-dwelling older adults (70~95 y), 12-mo 1 mg/d oral sirolimus vs placebo RCT; low-dose rapamycin well tolerated, enhanced T-cell IFN	Improves the clearance of aging	Mouse epididymal white AT ex vivo explant, cultured for 7 d; rapamycin, apilimod or Lalistat-2 treatment [177];

		antiviral responses, no cognitive or physical decline.	adipocytes	
	Metformin (Metallic taste; Soft stools/diarrhea; Flatulence)	NCT02432287 Healthy older adults (65~75 y), 1700 mg/d metformin ~1-y open-label self-controlled trial (MILES); metformin reshaped blood gene expression toward longevity-like profile, well tolerated.	Improves the senescent state	C3H/10T1/2 cells, metformin (20 mM) and nicotinamide (1 mM) treatment [188]; 8 obese adult female subjects (40±2 y, BMI 33~42), scAT SVF B cells, in vitro metformin (1 mM) treatment [264]; *Polη*$^{-/-}$ mice (DNA repair deficiency), metformin treatment [265];
		NCT00620191 Amnestic MCI patients, metformin vs placebo randomized double-blind pilot RCT; in non-diabetic aMCI, metformin group showed worse total recall memory vs placebo, no cognitive benefit.	Lessens oxidative stress and mitochondrial dysfunction	ASCs isolated from 10 healthy female subjects, metformin treatment [189]; C57BL/6 mice, metformin treatment for 2 mo [190];
		NCT02986659 Middle-aged/older adults with prediabetes or metabolic syndrome, randomized open-label genomic outcomes trial (GOMET); metformin mildly reshaped blood epigenetic clock and metabolome, small effect size.	Leptin, FGF21, APN	C57BL/6 mice fed 60 kcal% fat diet, daily oral metformin for 14 wk [183]; SAT and VAT from obese human subjects, metformin treatment [186]; Male Wistar rats fed HFD, oral metformin treatment [266];
	GLP-1R and/or GIPR agonists Semaglutide; Tirzepatide; LY3437943; (Reducing lean mass)	NCT03574597 Overweight/obese adults with CVD (~61 y, n≈ 17604), s.c. semaglutide 2.4 mg qw, phase3 RCT (SELECT): 20% MACE reduction, ~10% weight loss; post-hoc proteomics predicted 26% lower 5-y dementia risk.	Improves lipid metabolism	GIPR overexpressed mice fed HFD for 9 mo [267];
		NCT04777422 Aβ-positive early AD, oral semaglutide 14 mg qd, 104-wk phase 3 RCT (EVOKE): missed primary endpoint; CSF biomarkers improved without clinical benefit.	Suppression of inflammatory processes	C57BL/6, GIPR-KO and GLP1R-KO mice fed HFD for 6 mo, followed by GIPRA, GLP-1RA or dual agonist treatment for 1 mo [268];
		NCT04777409 Amyloid-positive early AD (55~85 y, MCI/mild dementia), oral semaglutide 14 mg qd, 104-wk phase3 RCT (EVOKE Plus): missed primary endpoint, similar CDR-SB progression vs placebo; CSF AD biomarkers improved.		
	Thiazolidinediones (TZDs) Pioglitazone; Rosiglitazone; Chiglitazar;	NCT00315146 Overweight/obese older adults (65~79 y, 40 women + 48 men, non-diabetic), 4-arm RCT: hypocaloric diet ± resistance training ± pioglitazone (OPTIMA pilot); pioglitazone reduced abdominal visceral fat in men during hypocaloric weight loss, resistance training preserved lean mass, combination achieved visceral fat loss with muscle preservation.	Adipose tissue remodeling	LPS-induced senescence model of primary SAT + rosiglitazone treatment [269]; Male C57BL/6J mice (≥14 mo), chow with or without rosiglitazone [270]; R26R-RFP mice, Dox/BrdU labeling, rosiglitazone-supplemented chow [271];
			Elevates circulating AND, PAI-1, and mi-690 levels	Male and female WT or *Ocn-Wnt10b* mice, rosiglitazone treatment [202]; Prediabetic humans (troglitazone 100/200 mg bid, 12 wk); *db/m* & *db/db* mice (TZDs in chow); 3T3-L1 adipocytes (TZDs ± TNF-α) [272];
			Anti-inflammatory 'M2-like' phenotype	6 mo male C57BL/6J HFD mice, rosiglitazone (3 mg/kg/d) treatment in the last 4 wk [206];
Emerging Targeted Therapeutics	**Senolytics and Senomorphics** Dasatinib + Quercetin, Fisetin; Navitoclax (ABT-263); (Risk of myelosuppression; Headaches	NCT04063124 Mild-to-moderate AD patients (mean age 76 y), D 100 mg + Q 1000 mg oral 3-day cycles ×12-wk open-label phase 1 pilot (SToMP-AD I); first demonstration that D + Q crosses the BBB, D detected in CSF, safe and well tolerated, CSF senescence and inflammation markers decreased.	Reduces the number of senescent cells and cytokine secretion	WT INK-ATTAC transgenic mice (natural aging), i.p. AP20187 to selectively ablate *p16*^{Ink4a}-positive senescent cells [208]; Male C57Bl/6 mice and naturally aged *Ercc1*$^{-/\Delta}$ mice, D + Q treatmentt [273]; *Ercc1*$^{-/\Delta}$, p16$^{Luc/+}$; *Ercc1*$^{-/\Delta}$ reporter mice and aged WT mice; fisetin via chow (500 ppm) or gavage (100 mg/kg); *Ercc1*$^{-/-}$ MEF senescence model [274] ;
		NCT04785300 Mild AD patients, D + Q open-label pilot; safety established, senescence/inflammation biomarkers		

	and gastrointestinal events)	decreased in blood and CSF.		Middle-aged cynomolgus macaques (lean to obese, normoglycemic/T2DM), D + Q (D 5 mg/kg + Q 50 mg/kg, gavage, 2 consecutive d/mo); 10% calorie restriction for 6 wk [275];
		NCT04685590 Early AD patients, D + Q randomized double-blind placebo-controlled phase 2 RCT (SToMP-AD II); phase 2 efficacy validation ongoing; AD cognition and brain markers directly assessed.	Improves the secretion of inflammatory factors	21 mo C57BL/6 mice, D + Q senolytic treatment [214]; $APP^{NL-F/NL-F}$ mice, fisetin (100 mg/kg) or D + Q (D 5 mg/kg + Q 50 mg/kg) treatment [215];
		NCT02848131 Diabetic kidney disease patients (68.7±3.1 y, n=9), D 100 mg + Q 1000 mg ×3-day open-label phase 1 pilot; 3-day D+Q significantly reduced adipose tissue senescent cell burden at day 11, macrophages shifted to M2 phenotype.	Prevents whitening of BAT and enhances thermogenic genes	Female C57BL/6NTac fed obesogenic diet, D + Q senolytics (gavage, 3 d/wk) for 16~24 wk [276];
Preclinical investigation	**Adipokine mimetics or inhibitors** AdipoRon; Efruxifermin; LY2405319; MK-3655;	None so far (Aging);	Amelioratin g age-related dysregulation of adipokine secretion	STAM model: neonatal C57BL/6N, s.c. STZ + HFD; ALY688 (0.5/5 mg/kg/d, s.c. or osmotic pump) from 6~9 wk; CDAHF model: C57BL/6N fed CDAHFD for 12 wk; ALY688-SR (3/15 mg/kg/d, s.c.) or OCA (30 mg/kg, gavage) as positive control [277];
			Offsetting age-driven resistance	C57BLKS/J db/db mice and aP2-SREBP-1c mice, osmotic minipump for continuous FGF21 infusion [224];
	Heterochronic parabiosis TPE / Plasma Dilution; Albumin Replacement;	NCT02256306 Mild-moderate AD, 4-wk weekly young (18~30 y) male FFP vs saline, randomized double-blind crossover phase1/2 RCT (PLASMA): safe/tolerable, no 4-wk cognitive benefit.	Reverses age-related dysfunction	Male C57BL/6 mice (4 mo young / 18 mo old), heterochronic parabiosis for 4 wk [233]; C57BL/6JN mice (3 mo young / 18 mo old), heterochronic parabiosis for 5 wk [278];
		NCT03520998 MCI/early AD patients, GRF6019 (Alkahest young plasma fraction), randomized double-blind placebo-controlled phase 2 RCT; mild cognitive benefit trend in partial domains; program later terminated by Alkahest.		
		NCT04241159 Frail (Fried ⩾3) or HFpEF older adults (65~80 y), 8-week open-label trial of weekly PF24 young donor plasma; assessed feasibility.	Reduces levels of pro-inflammatory cytokines	C57BL/6JRj young/aged and transgenic mice, anti-IL-6 treatment; isochronic / heterochronic parabiosis [232];
		NCT03981419 Older elective surgery patients, young plasma protein fraction vs placebo randomized controlled trial; young plasma protein fraction modulated postoperative immune-inflammatory response in older surgical patients.		

Abbreviations: wk, week(s); mo, month(s); y, year(s); DR, dietary restriction; ADF, alternate-day fasting; RCT, randomized controlled trial; BMI, body mas index; HOMA-IR, homeostatic model assessment for insulin resistance; SASP, senescence-associated secretory phenotype; DNAm, DNA methylation; IF, intermittent fasting; HRmax, maximum heart rate; scWAT, subcutaneous white adipose tissue; HIIT, high-intensity interval training; T2D, type 2 diabetes; sirolimus, rapamycin analog; AT, adipose tissue; SVF, stromal vascular fraction; ASC, adipose-derived stromal cell; SAT, subcutaneous adipose tissue; VAT visceral adipose tissue; CVD, cardiovascular disease; GLP-1R, glucagon-like peptide-1 receptor; GIPR, glucose-dependent insulinotropic polypeptide receptor; MACE, major adverse cardiovascular event; CDR-SB, Clinical Dementia Rating-Sum of Boxes; TZDs, thiazolidinediones; PAI-1, plasminogen activator inhibitor-1; TNF-α, tumor necrosis factor-α; D, dasatinib; Q, quercetin; i.p., intraperitoneal; STAM, streptozotocin-induced diabetes and high-fat diet; STZ, streptozotocin; CDAHFD, choline-deficient, L-amino acid-defined, high-fat diet; TPE, therapeutic plasma exchange; HFpEF, heart failure with preserved ejection fraction.

Lifestyle intervention

Dietary restriction

As a central hub for nutrient and energy storage, adipose tissue is a primary target of nutritional interventions. Dietary restriction (DR) has been extensively documented to extend lifespan and counteract age-related decline [153-155].

Aging is characterized by a progressive depletion of the quiescent adipose stem cell pool, precipitating tissue dysfunction. Dietary interventions effectively counteract these senescent phenotypes in subcutaneous adipose-derived progenitor cells. These nutritional regimens

alleviate oxidative stress and cellular senescence [156], preserve stemness and adipogenic competency [157], and promote the clearance of senescent cells, ultimately remodeling adipose architecture to preserve metabolic fitness [158]. In parallel, time-restricted feeding regimens ameliorate age-associated adipose inflammation and tissue degradation [158]. Beyond cellular rejuvenation, these restrictive dietary paradigms systemically recalibrate the aging adipokine secretome—notably by sustaining beneficial levels of APN and FGF21 while dampening hyperleptinemia [159-162]—thereby fortifying metabolic resilience during aging.

By tuning energy intake, these strategies optimize metabolic function to counteract aging. However, their efficacy varies by age and carries risks such as muscle loss [163]. Therefore, tailoring specific DR methods is essential for optimal adipose tissue regulation across populations.

Physical exercise

Regular exercise and improved aerobic capacity play a crucial role in combating age-related systemic and organ-specific decline. A reduction in overall adipose tissue volume characterizes the systemic adaptations to exercise in older cohorts [164]. At the molecular level, exercise attenuates the SASP within subcutaneous adipose tissue, partially by reducing IL-6, thereby mitigating chronic inflammation and accompanying metabolic dysregulation [165-167]. Beyond inflammation, exercise is vital for modulating adipose endocrine function by promoting the release of beneficial factors, such as APN, FGF21, and irisin [168-170]. Crucially, these endocrine adaptations bridge peripheral metabolism and CNS health: exercise-driven elevations in APN, coupled with suppressed leptin, critically mediate improvements in mood, learning, and cognitive performance [171, 172].

Drug Repurposing & Clinical-Stage Therapeutics

Rapamycin

Rapamycin is an mTOR inhibitor and effectively delays the aging process and extends lifespan [173]. Growing evidence indicates that its geroprotective efficacy is deeply intertwined with adipose tissue homeostasis. When combined with adipose-derived mesenchymal stem cells, rapamycin synergistically potentiates therapeutic outcomes in age-related degenerative disorders, predominantly by reinforcing anti-inflammatory cascades and dampening adipose inflammation [174, 175]. Additionally, rapamycin may contribute to the clearance of senescent and metabolically dysregulated adipocytes by regulating the expression of genes associated with adipose tissue expansion (such as *Mest* and *Gpam*) and cellular senescence (such as *Serpine1*) [176]. Concurrently, it facilitates the extracellular degradation of dying adipocytes by driving adipose tissue macrophage engagement and activating lysosomal exocytosis [177].

Despite the success of rapamycin in extending lifespan in mice, high doses and prolonged administration may lead to a disconnection between lifespan and health benefits [178, 179]. Studies have indicated that the combination of rapamycin with metformin can reverse the effects of rapamycin on hepatic insulin resistance markers and normalize systemic insulin sensitivity in this inherently insulin-resistant model [176].

Metformin

Metformin is extensively employed in the management of T2D and age-related conditions, such as cancer, muscle degeneration, and inflammatory aging [180-182]. The drug exerts multifaceted effects on the metabolism of aging adipose tissue, although the precise mechanisms remain partially understood.

Metformin appears to mitigate age-associated metabolic imbalances by reducing fat accumulation [183] and inhibiting the SASP in adipose tissue [184, 185]. It also reduces leptin levels and increases FGF21 expression in adipose tissue [183], while upregulating APN gene expression in human SAT and stimulating its secretion [186]. Additionally, metformin in adipocytes markedly ameliorates the expression of age-related metabolic genes [187], reducing mitochondrial oxidative stress, and attenuating the age-dependent decline in *UCP1* expression [188]. Moreover, metformin significantly improves the function of ASCs. *In vitro*, metformin treatment effectively alleviates oxidative stress, mitochondrial dysfunction, and proliferation in ASCs from older donors [189, 190].

GLP-1R and/or GIPR agonists

Intestinal hormones consist primarily of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), and in the management of T2D and obesity, both single-target agonists of the GLP-1 receptor (GLP-1R) and dual-target agonists have shown considerable efficacy [191, 192]. Converging evidence from preclinical and clinical studies underscores the potential of these agonists to mitigate aging and its associated pathological phenotypes; however, the precise mechanistic underpinnings warrant further elucidation.

Providing the first randomized clinical evidence that GLP-1R agonists decelerate biological aging in humans, 32 weeks of weekly semaglutide administration attenuated DunedinPACE by 9% and mitigated morbidity and mortality risks indexed by PCGrimAge [193].

Additionally, a 24-week semaglutide treatment slowed biological aging in 42% of patients and increased telomere length in 49% of patients [194]. While research on GLP-1R and aging is still in its early stages, preliminary findings indicate that GLP-1R agonists may mitigate age-associated diseases and extend healthspan [195-198]. Recent investigations have revealed that prolonged treatment with GLP-1R agonists can lead to improvements in aging phenotypes in the hypothalamus and display omics characteristics comparable to those induced by rapamycin [199]. These findings underscore the substantial potential of GLP-1R agonists in the field of anti-aging therapies.

Thiazolidinediones (TZDs)

Thiazolidinediones (TZDs), such as rosiglitazone and pioglitazone, are antidiabetic drugs that work primarily by activating PPARγ. By modulating PPARγ activity, TZDs control stemness-associated genes, thereby influencing adipose mesenchymal stem cell phenotypes [200, 201]. TZDs additionally modulate aging-related adipokine secretion. Specifically, they elevate circulating APN levels [200, 202], reversing age-associated adipose dysfunction. Plasminogen activator inhibitor-1 (PAI-1)—a key regulator of adipose aging [203, 204]—mediates age-related metabolic dysfunction, while rosiglitazone increases serum resistin by approximately 66.4% in diabetic db/db mice [205]. Moreover, TZDs promote adipose tissue macrophage polarization toward an anti-inflammatory 'M2-like' phenotype to facilitate tissue repair [206]. However, how TZDs regulate adipose and CNS aging remains incompletely understood. Additionally, adverse effects like weight gain and fluid retention limit their clinical application in anti-aging interventions. Given their effects on adipose stem cell differentiation and stemness, TZD benefits may depend on age-related adipose mass dynamics, making late-life stages—marked by progressive tissue atrophy—the optimal window for intervention.

Senolytics and Senomorphics

Aging adipocytes exhibit elevated senescence markers, reduced proliferation, genomic instability, chronic inflammation, and the SASP [207]. Therapeutic approaches targeting senescent cells fall into two main strategies: senolytics, which selectively eliminate senescent cells, and senomorphics, which attenuate the harmful senescence phenotype without cell removal. Senolytics (e.g., dasatinib, quercetin, navitoclax [ABT-263], and piperlongumine) induce apoptosis via the $p16^{INK4A}$ and p21 pathways, thereby delaying age-related phenotypes [208-210].

In senescent adipocytes, quercetin significantly reduces SA-β-gal-positive cells and the production of ROS and pro-inflammatory cytokines [211], potentially through autophagy-related mechanisms [212]. Dasatinib and quercetin (D + Q) selectively eliminate senescent cells in human adipose tissue [213]. D + Q decreases expression of $p16^{INK4A}$ and $p21^{CIP1}$, along with reducing SA-β-gal-positive cells and replicatively impaired adipocyte precursors [213]. Additionally, D + Q suppresses senescence-associated T cells and macrophages [214, 215], reducing the number of adipose tissue macrophages and crown-like structures recruited, anchored, and activated by senescent cells [215].

Senolytics effectively attenuate SASP expression. In human adipose tissue, D + Q selectively suppress pro-inflammatory cytokine secretion [213] and downregulate SASP-related genes [214, 215]. Similarly, ABT-263 decreases plasma levels of SASP factors (e.g., IFN-γ) while modulating leptin and epidermal growth factor concentrations [216].

Cutting-Edge Targeted & Preclinical Approaches

Adipokine mimetics or inhibitors

As growing evidence confirms the role of adipokines in the aging adipose tissue and various systemic organs, as well as associated metabolic diseases, interest is rising in adipokine-targeted therapeutics—including mimetics, inhibitors, receptor agonists, small-molecule activators, and synthetic peptides.

Pharmacological engagement of AdipoR signaling has demonstrated notable metabolic and longevity benefits. These include orally available small-molecule agonists—principally AdipoRon, which extends lifespan in diabetic mice via AMPK/PPARα activation [217], alongside ALY688, AdipoAI, and ADP-1 [218-221]. Current FGF21-targeted therapies, such as FGF21 analogues [222] and FGF21 receptor agonists [223, 224], have predominantly focused on metabolic diseases, leaving their efficacy in directly mitigating aging-related processes unclear. FGF21 signaling also exerts potent neuroprotective and anti-gerontic effects: the engineered analogue LY2405319 reduces Aβ plaque burden and preserves neuronal integrity in organotypic brain slices [225], while rhFGF21 rescues cognitive decline in D-galactose-induced aging mice by curbing neuroinflammation, oxidative stress, and aging-related gene expression [89].

Therapies targeting adipokine dysregulation induced by adipose tissue aging remain in the early stages. Successful clinical translation requires evaluating age- and sex-dependent hormone dynamics while overcoming age-related drug resistance in *vivo*. Nevertheless,

modulating adipose tissue hormone dysregulation using agonists, antagonists, or analogues holds substantial clinical potential.

Heterochronic parabiosis

Heterochronic parabiosis surgically joins young and aged circulations to assess the impact of circulating factors on aging and tissue homeostasis [226, 227]. The rejuvenating effects of young blood are primarily driven by its non-cellular fractions rather than intact blood cells [228, 229]. Notably, young circulating extracellular vesicles (EVs) restore aged skeletal muscle regeneration, establishing EV-based strategies as a promising anti-aging avenue [230, 231]. Heterochronic parabiosis can reverse age-related dysfunction in WAT by restoring immune homeostasis [232] and reversing cellular senescence [233]. Specifically, treatment with young serum suppresses key senescence drivers, downregulating *p16* and *p21* expression across visceral fat and preadipocytes [233]. Concurrently, it alleviates the adipose inflammatory profile by dampening pro-inflammatory cytokines, including MCP-1 and IL-6 [233]. Heterochronic parabiosis demonstrated that the systemic milieu dynamically regulates aging and stem cell function, challenging strictly cell-autonomous paradigms. Although direct human application is infeasible, exploiting its circulating targets (e.g., GDF11 and B2M) offers immense clinical promise.

Conclusion

Adipose tissue responds early to age-related changes and serves as a crucial endocrine organ for lipid storage and energy metabolism regulation. With aging, the distribution and various metabolic functions of adipose tissue can become disrupted, leading to issues such as insulin resistance, reduced energy metabolism, chronic inflammation, oxidative stress, and hormonal imbalances. Accumulating preclinical and observational studies indicate that various adipokines, including APN, Leptin, FGF21, GDF15, Resistinand Chemerin, alter in response to changes in adipose tissue during age. Moreover, the secretion capacity of adipose tissue and the concentrations of these factors in circulation do not exhibit a simple linear relationship with age; rather, they may fluctuate in phases.

Adipose tissue plays a multifaceted role in centrally related metabolic aging. Sensitivity to adipokines in the CNS changes with age, so merely increasing or decreasing the concentration of a specific adipokine is unlikely to yield therapeutic benefits. For instance, the sensitivity of LepRs and FGF21 receptors to external ligands diminishes with age. Therefore, enhancing the sensitivity of target organs to adipokines may have potential therapeutic value. Additionally, certain adipokines from adipose tissue have been reported to exhibit potential anti-aging effects through various physiological mechanisms, such as neuroprotection, reduction of oxidative stress, alleviation of central chronic inflammation, slowing the accumulation of age-related markers in the CNS, and enhancing synaptic function. The effect of individual adipokines may be limited and influenced by factors such as concentration and sex. Consequently, a holistic approach to delaying or improving the aging of adipose tissue may offer a more promising direction for translational research, though its clinical efficacy remains to be systematically validated.

At present, there are no direct treatments for targeting adipose tissue aging. Given the systemic nature of aging, a holistic anti-aging approach presents a pragmatic focus for current research and lifestyle interventions. Strategies like diet and exercise, which are cost-effective and promote health, remain the primary methods. Other interventions often face limitations related to age, sex, side effects, and delivery systems. Adipose tissue serves as a nutrient-sensing organ, highly sensitive to various stressors such as dietary restrictions, exercise, and temperature changes. Its role in maintaining the balance of adipose weight and metabolic functions is vital in the context of delaying aging.

CRediT authorship contribution statement

The study's conceptualization, original draft preparation, and editorial refinements were spearheaded by F.Z. B.S.H. was responsible for supervisory oversight and the critical appraisal of the paper. Intellectual insights and iterative feedback on the manuscript were contributed by W.C., Z.L., Y.X., Z.Y.L., Y.J.L., and L.D. All authors (F.Z., W.C., Y.X., Z.Y.L., Y.J.L., Z.L., L.D., and B.S.H.) have read and agreed to the published version of the manuscript.

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