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Prevention of Vascular Aging as a Novel Paradigm for GLP-1 Receptor Agonist–Mediated Cardioprotection

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ABSTRACT: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have revolutionized the management of type 2 diabetes and obesity. Due to class-wide reduction in major adverse cardiovascular events in cardiovascular outcome trials and pleiotropic actions in multiple tissues, the use of GLP-1RAs has expanded beyond metabolic diseases. Recent studies have reported GLP-1RA efficacy for the treatment of atherosclerosis, heart failure and peripheral artery disease, alongside evolving potential in chronic kidney disease. The recent discovery that GLP-1RAs can improve vascular regenerative progenitor cell flux during type 2 diabetes has uncovered a novel mechanism implicating 3 classical hallmarks of vascular aging: (1) stem cell exhaustion, (2) altered intercellular communication, and (3) chronic systemic inflammation. In this review we discuss recent evidence demonstrating that imbalances in hematopoiesis during cardiometabolic diseases intersect with the senescence-associated secretory phenotype to elevate chronic inflammation and accelerate vascular aging. With a focus on stem cells as the master regulators of regenerative processes, we integrate the activities of GLP-1RAs that shift the balance from damage accumulation to repair competence in blood vessels prematurely aged by cardiometabolic syndrome.

Key Words: angiogenesis ■ cardiovascular diseases ■ glucagon-like peptide-1 receptor agonists ■ senescence-associated secretory phenotype ■ stem cells

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are an expanding class of medicines originally developed for the management of type 2 diabetes (T2D) and subsequently found to offer clinically meaningful body weight reduction.[1] GLP-1RAs (liraglutide, dulaglutide, and semaglutide among others) are synthetic derivatives of GLP-1 (glucagon-like peptide-1), an incretin hormone secreted by gastric L (enteroglucagon) cells after feeding. GLP-1R (glucagon-like peptide-1 receptor) agonism activates G-protein–mediated adenylate cyclase and ERK/MAPK (extracellular signal–related kinase/mitogen-activated protein kinase) pathways to amplify postprandial insulin release from beta cells. Notably, GLP-1RAs also act in the hypothalamus and gut to increase satiety and slow gastric emptying, providing the mechanistic basis for extended indication as a weight loss agent.[2]

Second-generation incretin-based drugs such as tirzepatide that target GIP (glucose-responsive insulinotropic polypeptide) receptors in addition to GLP-1Rs were designed to accentuate weight loss. The SURPASS-2 (A Study of Tirzepatide (LY3298176) Versus Semaglutide Once Weekly as Add-on Therapy to Metformin in Participants With Type 2 Diabetes) trial confirmed that tirzepatide produced greater reductions in HbA1c (hemoglobin A1c) and body weight compared with 1 mg semaglutide.[3] The most recent addition to the GLP-1RA family is retatrutide, formulated as a triple agonist for GLP-1, GIP, and glucagon receptors. Retatrutide had profound effects on metabolism and unmatched weight loss up to 24.2% within 1 year;[4] it is currently in Phase 3 trials for both obesity and T2D, with additional trials underway for

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Nonstandard Abbreviations and Acronyms

ALDH	aldehyde dehydrogenase
ASCVD	atherosclerotic cardiovascular disease
BH4	tetrahydrobiopterin
CHIP	clonal hematopoiesis of indeterminant potential
cSASP	classical SASP
CVD	cardiovascular disease
CVOT	cardiovascular outcome trial
ECFC	endothelial colony-forming cell
eNOS	endothelial NO synthase
EPC	endothelial precursor cell
ERK/MAPK	extracellular signal–related kinase/mitogen-activated protein kinase
eSASP	emerging SASP
EV	extracellular vesicle
FGF-2	fibroblast growth factor-2
GIP	glucose-responsive insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
GLP-1R	glucagon-like peptide-1 receptor
GLP-1RA	glucagon-like peptide-1 receptor agonist
HbA1c	hemoglobin A1c
HFpEF	heart failure with preserved ejection fraction
HPC	hematopoietic progenitor cell
HSC	hematopoietic stem cell
IFNγ	interferon gamma
MACE	major adverse cardiovascular events
MMP	matrix metalloproteinase
MSC	mesenchymal stem cell
NF-κB	nuclear factor-kappa B
PCSK9	proprotein convertase subtilisin/kexin type 9
ROS	reactive oxygen species
SASP	senescence-associated secretory phenotypes
SOD	superoxide dismutase
T2D	type 2 diabetes
TGF-β	transforming growth factor-beta
TNF	tumor necrosis factor
VEGF	vascular endothelial growth factor
VEGFR2	vascular endothelial growth factor receptor 2
VR	vascular regenerative

cardiovascular diseases as well as liver and kidney disorders, further emphasizing the extensive reach of GLP-1RAs to address chronic diseases.

ACTIONS OF GLP-1RAS ON THE CARDIOVASCULAR SYSTEM

GLP-1RAs and Major Adverse Cardiovascular Events

The landmark cardiovascular outcome trials SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes), PIONEER-6 (Peptide Innovation for Early Diabetes Treatment), LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results), and REWIND (Researching Cardiovascular Events With a Weekly Incretin in Diabetes) demonstrated that GLP-1RAs reduced the 3-point composite of major adverse cardiovascular events (MACE) including cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. A meta-analysis of 8 outcome trials comprising 60 080 participants with T2D revealed that GLP-1RAs reduced 4-point MACE by 14% (hazard ratio, 0.86, [95% CI, 0.80–0.93]; $P<0.0001$).[5] The SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity) trial resolved the debate that the cardiovascular benefits of the GLP-1RA family were independent of glucose-lowering. Remarkably, semaglutide reduced 3-point MACE by 20% compared with placebo in 17 604 people with atherosclerotic cardiovascular disease (ASCVD) but not T2D and a body mass index >27 kg/m^2.[6] Subsequently, an updated meta-analysis by Lee et al[7] found equivalence in MACE benefits between participants with and without T2D ($P_{interaction}=0.345$).

GLP-1RAs and Peripheral Artery Disease

The STRIDE trial (Semaglutide and walking capacity in people with symptomatic peripheral artery disease and type 2 diabetes) enrolled 792 individuals with T2D and symptomatic peripheral artery disease (ankle-brachial index ≤0.90 or toe-brachial index ≤0.70) to receive either semaglutide or placebo. STRIDE reported improved maximum walking distance (treatment ratio, 1.13 [95% CI, 1.06–1.21]; $P=0.0004$) with a median follow-up of 13.2 months among those assigned to semaglutide (Table 1).[11] Remarkably, these benefits were extended for up to 5 weeks after semaglutide discontinuation.

GLP-1RAs and Heart Flow

In a SELECT subanalysis that included 4286 (24.3% of the full cohort) participants who had heart failure at enrollment, the benefit of semaglutide on MACE was independent of heart failure subtype and body mass index (BMI).[13] The STEP-HFpEF DM (Research Study to Look at How Well Semaglutide Works in People Living With Heart Failure, Obesity and Type 2 Diabetes) and STEP-HFpEF (Effect of Semaglutide 2.4 mg Once Weekly on

Table 1. Summary of GLP-1RA Clinical Trials for Alternate Cardiovascular Indications

Study (NCT no.)	Phase	Drug/dosage	Demographic population	Key outcomes/CV benefits
SEMA-VR (URL: https://www.clinicaltrials.gov; Unique identifier: NCT05870462)[8]	Phase 4 (N=46)	Up to 1.0 mg of semaglutide, once weekly; or placebo for 6 mo.	Individuals ≥18 y old with history of ASCVD or ≥2 ASCVD risk factors, documented T2D, and BMI ≥30 or BMI ≥27 with at least 1 weight-related comorbidity	Semaglutide treatment, compared with usual care, was associated with an increase of circulating VR progenitor cells and a decrease of proinflammatory granulocyte precursors and serum cytokines.
SELECT (URL: https://www.clinicaltrials.gov; Unique identifier: NCT03574597)[7]	Phase 3 (N=17 604)	2.4 mg of semaglutide, once weekly; or placebo for up to 240 wk.	Individuals ≥45 y old with CVD and a BMI ≥27 but no history of T2D.	A weekly dose of semaglutide was superior to placebo in reducing the incidence of death from CV causes, nonfatal MI, or nonfatal stroke at mean follow-up.
STEP-HFpEF (URL: https://www.clinicaltrials.gov; Unique identifier: NCT04788511)[9]	Phase 3 (N=529)	2.4 mg of semaglutide, once weekly; or placebo over 52 wk.	Individuals with HFpEF and BMI ≥30.	Patients receiving semaglutide had greater changes in KCCQ-CSS point scores, weight loss, and 6-min walk distance when compared with placebo. Patients receiving semaglutide also had a −43.5% reduction of CRP levels compared with −7.3% in the placebo group.
STEP-HFpEF DM (URL: https://www.clinicaltrials.gov; Unique identifier: NCT04916470)[10]	Phase 3 (N=617)	2.4 mg of semaglutide, once weekly over 52 wk; or placebo.	Individuals with HFpEF, BMI ≥30, and T2D.	Patients receiving semaglutide exhibited greater reductions in heart failure–related symptoms, physical limitations, and greater weight loss than placebo at 1 y.
STRIDE (URL: https://www.clinicaltrials.gov; Unique identifier: NCT04560998)[11]	Phase 3 (N=792)	1.0 mg of semaglutide, once weekly over 52 wk; or placebo.	Individuals ≥18 y old, with T2D, PAD with intermittent claudication, and ABI ≤0.90 or TBI ≤0.70.	Individuals receiving semaglutide exhibited significantly greater walking distances than placebo at week 52.
SUMMIT (URL: https://www.clinicaltrials.gov; Unique identifier: NCT04847557)[12]	Phase 3 (N=731)	Up to 15 mg of tirzepatide once weekly for at least 52 wk, or placebo.	Individuals with HFpEF of at least 50%, and BMI ≥30.	Tirzepatide treatment led to a lower risk of composite of adjudicated death from CV causes or worsening heart failure than placebo after a median follow-up of 104 wk. The tirzepatide treatment also improved health status of patients when compared with placebo.
SURPASS-2 (URL: https://www.clinicaltrials.gov; Unique identifier: NCT03987919)[3]	Phase 3 (N=1879)	Once-weekly dose of 5 mg, 10 mg, or 15 mg tirzepatide, or semaglutide at 1 mg, over 40 wk.	Individuals with T2D, HbA1c level of 7–10.5%, and BMI ≥25.	Tirzepatide proved noninferior and superior to semaglutide, at all doses, with respect to mean change in HbA1c level from baseline to week 40. All doses of tirzepatide also resulted in significant body weight reductions compared with semaglutide.

ABI indicates ankle-brachial index; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CRP, C-reactive protein; CV, cardiovascular; CVD, cardiovascular disease; GLP-1RAs, glucagon-like peptide-1 receptor agonists; HbA1c, hemoglobin A1c; HFpEF, heart failure with preserved ejection fraction; KCCQ-CSS, Kansas City cardiomyopathy questionnaire–clinical summary score; MI, myocardial infarction; PAD, peripheral artery disease; SEMA-VR, Semaglutide and Vascular Regeneration; SELECT, Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity; STEP-HFpEF, Effect of Semaglutide 2.4 mg Once Weekly on Function and Symptoms in Subjects with Obesity-related Heart Failure with Preserved Ejection Fraction; STEP-HFpEF DM, Research Study to Look at How Well Semaglutide Works in People Living With Heart Failure, Obesity and Type 2 Diabetes; STRIDE, Semaglutide and walking capacity in people with symptomatic peripheral artery disease and type 2 diabetes; SUMMIT, A Study of Tirzepatide (LY3298176) in Participants With Heart Failure With Preserved Ejection Fraction (HFpEF) and Obesity; SURPASS-2, A Study of Tirzepatide (LY3298176) Versus Semaglutide Once Weekly as Add-on Therapy to Metformin in Participants With Type 2 Diabetes; T2D, type 2 diabetes; TBI, toe-brachial index; and VR, vascular regenerative.

Function and Symptoms in Subjects with Obesity-related Heart Failure with Preserved Ejection Fraction) trials that enrolled individuals living with both heart failure with preserved ejection fraction (HFpEF) and obesity, and with or without T2D, provided robust data supporting the benefits of semaglutide on participant-reported heart failure–related symptoms and physical limitations.[9,10] A prespecified pooled analysis of these sister trials offered further support for GLP-1R agonism as a safe and efficacious option in people living with HFpEF to afford weight loss, reduce symptomatic limitations, and improve exercise function.[14] In the SUMMIT (A Study of Tirzepatide (LY3298176) in Participants With Heart Failure With Preserved Ejection Fraction (HFpEF) and Obesity) trial that enrolled people with HFpEF and a BMI ≥35 kg/m^2, tirzepatide reduced the risk of worsening heart failure, diminished heart failure symptom severity, and improved exercise tolerance (Table 1).[12]

While the many positive outcome trials with the GLP-1RAs to date reinforce the notion that GLP-1RAs are cardioprotective and have significant therapeutic value, it is plausible that we may just be scratching the surface. Indeed, more insights are expected from ongoing phase 3 trials that include SURMOUNT-MMO (A Study of Tirzepatide (LY3298176) on the Reduction on Morbidity and Mortality in Adults With Obesity),[15] MARITIME-CV (Evaluating the Impact of Maridebart Cafraglutide on Cardiovascular Outcomes in Participants With Atherosclerotic Cardiovascular Disease and Overweight or Obesity), REDEFINE 3 (A Research Study to See the Effects of CagriSema in People Living With Diseases in the Heart and Blood Vessels), SYNCHRONIZE-CVOT (A Study to Test the Effect of Survodutide (BI 456906) on Cardiovascular Safety in People With Overweight or Obesity), TRIUMPH-Outcomes (The Effect of Retatrutide Once Weekly on Cardiovascular Outcomes and

Kidney Outcomes in Adults Living With Obesity), and VANQUISH-2 (VK2735 for Weight Management Type 2 Diabetes Phase 3) (Table 2).

Cardiovascular Benefits: Direct GLP-1RA Signaling Versus Indirect Metabolic Effects

GLP-1RAs lower blood glucose, reduce body weight, combat oxidative stress, and reduce inflammation. However, the mechanisms underlying these systemic effects continue to be debated. Many cardioprotective mechanisms have been proposed for the indirect benefits of reduced oxidative stress and systemic inflammation. Although GLP-1RAs have also demonstrated direct effects in endothelial cells, vascular smooth muscle, and some immune cells in preclinical studies, distinguishing the relative contributions of direct GLP-1R–mediated signaling from indirect systemic metabolic improvements remains challenging.

GLP-1R expression has been consistently detected in vascular smooth muscle cells, whereas expression in endothelial and immune cells remains less clearly established.[16,17] The blood pressure-lowering effects of semaglutide appear to depend on GLP-1R signaling in vascular smooth muscle cells. Deletion of vascular GLP-1Rs abolishes the antihypertensive responses in semaglutide-treated mice.[18] Preclinical data also support direct receptor-mediated effects on endothelial cell survival and vasodilation, including a boost in nitric oxide bioavailability, suppressed nicotinamide adenine dinucleotide phosphate oxidase activity, and reduced intracellular reactive oxygen species (ROS) accumulation.[19] However, clinical cardiovascular benefits, such as MACE reduction and HFpEF symptom relief, are often observed alongside weight loss, improved insulin sensitivity, and attenuation of systemic inflammation, all of which independently contribute to MACE reduction.[20]

This distinction between the direct and indirect actions of GLP-1RAs is not merely academic. Although some cardiovascular effects seem to be independent of weight loss, general improvement in metabolic parameters including glycemic status, lipid profiles, and inflammatory markers is

Table 2. Summary of Ongoing GLP-1RA Clinical Trials and Primary Cardiovascular Outcomes

Study (NCT no.)	Phase	Drug/dosage	Demographic population	Primary outcome measure(s)
SURMOUNT-MMO (URL: https://www.clinicaltrials.gov; Unique identifier: NCT05556512)[15]	Phase 3 (N=15 374)	Escalated doses of tirzepatide or placebo.	Individuals aged ≥40 years with BMI ≥27 kg/m² and established CVD, PAD or multiple CVD risk factors.	Time to first occurrence of any component event of composite (all-cause death, nonfatal MI, nonfatal stroke, coronary revascularization, or HF events) up to 5 years.
MARITIME-CV (URL: https://www.clinicaltrials.gov; Unique identifier: NCT07037433)	Phase 3 (ongoing; estimated N=12 800)	Maridebart cafraglutide or placebo.	Individuals aged ≥45 years with BMI ≥27 kg/m² and a history of ASCVD.	Time to first occurrence of any component event of composite 3-point MACE end point consisting of: CV death, MI, or ischemic stroke up to approximately 35 months.Time to first occurrence of any component event of composite 5-point MACE end point consisting of: all-cause death, MI, ischemic stroke, coronary revascularization, or HF event up to approximately 35 months.
REDEFINE 3 (URL: https://www.clinicaltrials.gov; Unique identifier: NCT05669755)	Phase 3 (N=7101)	Once weekly dose of semaglutide and cagrilintide, or placebo	Adults ≥55 years with BMI ≥25 kg/m², established CVD; individuals with T2D should be diagnosed ≥180 days before screening and have an HbA1c 6.5-10%.	Time to first occurrence of 3-point MACE (CV death, non-fatal MI, non-fatal stroke) up to 242 weeks or more
SYNCHRONIZE-CVOT (URL: https://www.clinicaltrials.gov; Unique identifier: NCT06077864)	Phase 3 (N=5531)	Once weekly dose of 3.6 mg or 6.0 mg survodutide, or placebo	Adults ≥18 years with BMI ≥27 kg/m² and established CVD or ≥2 weight-related complications/risk factors for CVD; or BMI ≥30 with established CVD or CKD or ≥2 weight-related complications/risk factors for CVD.	Time to first occurrence of any of the adjudicated components of the composite end point consisting of: CV death, nonfatal stroke, nonfatal MI, ischemia-related coronary revascularization, or HF event up to 114 weeks
TRIUMPH-Outcomes (URL: https://www.clinicaltrials.gov; Unique identifier: NCT06383390)	Phase 3 (N=10,000)	Once weekly escalated dose of retatrutide, or placebo	Adults ≥45 with BMI ≥27, and established ASCVD or CKD.	Time to first occurrence of composite end point (MI, non-fatal stroke, CV death, or hospitalization or urgent visit due to HF) up to approximately 248 weeks. Time to first occurrence of composite endpoint of end-stage kidney disease; ≥ 40% sustained decline in eGFR, CV death or renal death.
VANQUISH-2 (URL: https://www.clinicaltrials.gov; Unique identifier: NCT07104383)	Phase 3 (N=1100)	Once weekly dose of 7.5, 12.5, or 17.5 mg VK2735, or placebo	Adults ≥18 with BMI ≥27 and T2D (HbA1c 7% to 11%.	Percent change in body weight from baseline to 78 weeks.

ASCVD indicates atherosclerotic cardiovascular disease; BMI, body mass index; CKD, chronic kidney disease; CRP, c-reactive protein; CV, cardiovascular; CVD, cardiovascular disease; GLP-1RAs, glucagon-like peptide-1 receptor agonists; HbA1c, hemoglobin A1c; HF, heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; PAD, peripheral artery disease; and T2D, type 2 diabetes.

associated with sustained weight loss. Therefore, restoration of arterial homeostasis after weight loss could partially reduce cardiovascular risk through these indirect pathways.[21] Furthermore, visceral adipose tissue drives low-grade systemic inflammatory state through the release of inflammatory adipokines, and reduction of adipose-driven inflammatory milieu is associated with improved vascular outcomes.[22] Thus, in the context of vascular homeostasis, both direct actions of GLP-1R signaling and indirect effects are at play. Detailed mechanistic studies are required to fully dissect the cumulative outcomes of GLP-1RA action on human vascular and immune tissues.

Sex Differences in GLP-1RA Efficacy

GLP-1RAs have emerged as cornerstone therapies with widespread use in patients with T2D and obesity, yet drug efficacy is not uniform in women and men. Although men have a higher absolute incidence of MACE, T2D imposes a disproportionately greater CVD burden in women due to complex factors including biological and hormonal differences.[23] Despite the increased risk with age, women have been consistently underrepresented in clinical trials. A systematic review of GLP-1RA randomized controlled trials from 2007 to 2024 found a unique decline in the proportion of females enrolled over time, with females comprising far less than half of the total trial populations.[24] In trials with liraglutide and dulaglutide specifically, female participants reported more moderate gastrointestinal-related side effects than the male individuals in the first few weeks of therapy, though reporting has not been consistent across all agents and trials. Underlying pharmacokinetic differences may partly explain why side effects, such as nausea, seem more frequent in female patients, a pattern attributed in part to slower drug absorption rates in women.[25]

The interplay between sex hormones and GLP-1RA biology introduces additional complexity for outcomes in women. Estrogen and GLP-1R signaling converge on overlapping hypothalamic and brainstem nuclei, and blockade of central estrogen receptors diminishes the appetite-suppressing effects of GLP-1RAs.[25] Postmenopausal women with obesity treated with semaglutide who were also using hormone replacement experienced improved weight loss response compared with those on semaglutide alone,[26] suggesting that estrogen status meaningfully modulates GLP-1RA responsiveness.

For cardiovascular outcomes, meta-analytic evidence suggests broadly consistent benefits across both sexes, though some differences are worth noting. Rivera et al[27] found that GLP-1RAs confer a similar reduction in 3-point MACE in both sexes, despite differences in cardiovascular disease history, body mass index, and kidney function. A 2025 meta-analysis evaluating sex-stratified outcomes across 11 trials and 85 273 patients showed decreased 3-point MACE by 21% in males and 25% in females; however, no sex-based interactions were detected for cardiovascular death, myocardial infarction, or hospitalization for heart failure assessed alone.[23] Taken together, these findings suggest that GLP-1RAs offer broadly comparable cardiovascular protection in both men and women. Although the extent of sex-specific effects remains constrained by the persistent underrepresentation of women in trials and limited availability of sex-disaggregated outcome data, future research should prioritize equitable enrollment and prespecified sex-stratified analyses to inform precision-based therapeutic approaches.

VASCULAR REGENERATIVE CELL EXHAUSTION

Our group,[28–30] and others,[31,32] have established that chronic cardiometabolic diseases (such as T2D, obesity, and ASCVD) are associated with the depletion of circulating vascular regenerative (VR) progenitor cells that coordinate angiogenesis, endothelial repair and vessel homeostasis, a concept termed VR cell exhaustion.[33] We recently completed the SEMA-VR CardioLink-15 trial (URL: https://www.clinicaltrials.gov; Unique identifier: NCT05870462), a translational study that demonstrated 6 months of semaglutide treatment increased multiple circulating VR progenitor cell populations and decreased commitment to inflammatory granulocyte precursors.[8] Although the specific mechanisms driving VR cell recovery during GLP-1RA therapy remain an ongoing area of investigation, VR cell exhaustion encompasses 3 highly studied hallmarks with central relevance to vascular aging: (1) bone marrow–derived stem cell exhaustion, (2) senescence-associated alterations in paracrine intercellular communication, and (3) propagation of chronic systemic inflammation. Herein, we detail translational evidence that the pleiotropic actions of GLP-1RAs converge on these 3 hallmarks of vascular aging accelerated by cardiometabolic syndrome.

VR Processes and Effector Cells

Blood vessel regeneration occurs through 3 complementary and concurrent processes: (1) angiogenesis, the sprouting of new vessels from preexisting vasculature stimulated by angiocrine factor secretion from circulating hematopoietic progenitor cells (HPCs) and monocyte progeny in response to hypoxia; (2) vasculogenesis, the de novo formation of new vessels mediated by circulating endothelial precursor cells (EPCs); and (3) arteriogenesis, the remodeling and recovery of blood flow in preexisting collateral vessels predominantly driven by nonclassical monocyte recruitment and transition to pro-regenerative macrophages.[34]

Bone marrow–derived progenitor cells play a critical role in blood vessel homeostasis. Unlike mature effector

cells, stem and progenitor cells must survive the entire lifespan of the organism and therefore possess the capacity to evade the Hayflick limit, a concept that suggests human somatic cells have a finite replicative lifespan of ≈50 divisions before the onset of senescence.[35,36] Extended replicative potential in highly proliferative progenitor cells is essential not only for hematopoiesis, but is also relevant in the homeostasis of blood vessels, a fundamental process best described as the aggregate balance between vessel damage and repair.

According to the stem cell theory of aging, progressive decline in tissue function is driven by intrinsic and extrinsic alterations in communication between circulating and tissue-resident progenitor cell populations.[37] With advancing age, bone marrow–derived progenitor cells exhibit diminished proliferative capacity and restricted differentiation potential that result in loss of regenerative potency and overproduction of proinflammatory cells.[38–40] This process, referred to as stem cell exhaustion, acts to inhibit vessel repair and intensifies systemic inflammation. To address this deleterious cycle accelerated in people with cardiometabolic diseases necessitates targeted intervention on multiple progenitor cell lineages to restore VR cell functionality.

High Aldehyde Dehydrogenase Activity: A Conserved Marker of VR Stem Cells

There remains a critical need for the identification of biomarkers to associate stem cell depletion with downstream deficits in vessel repair as an undeniable component of vascular aging. Our group has adapted the use of ALDH (aldehyde dehydrogenase) activity as a functionally relevant biomarker of circulating human hematopoietic, endothelial, and mesenchymal stem/progenitor cells with previously established capacity to synergize with blood vessel regeneration after transplantation into immunodeficient mice.[41] Indeed, ALDH^{hi} (high ALDH) activity has been used in clinical trials to purify autologous bone marrow progenitor cells for cellular therapies targeting vascular regeneration to improve walking distance in people with multiple forms of peripheral artery disease.[42–44]

ALDH is a broad superfamily of detoxification enzymes highly expressed in the cytosol of stem and progenitor cells from multiple mesodermal lineages. Paradoxically, ALDH is also the rate-limiting enzyme in the biosynthesis of retinoic acid, a potent morphogen that pushes progenitor cell differentiation.[45] As the highly replicative progenitor cell pool divides and differentiates into more mature effector cells, ALDH activity is gradually reduced up to 100-fold. ALDH family enzymes also play a cytoprotective role through the detoxification of exogenous aldehyde toxins into carboxylic acids more easily eliminated from the body. Essentially, elevated ALDH activity acts to protect long-lived progenitor cells against oxidative stress-mediated damage to lipid membranes, proteins and DNA.[46,47] Thus, use of ALDH^{hi} activity integrated with primitive cell surface marker expression represents a reliable method for efficient and sensitive detection of rare hematopoietic, endothelial and mesenchymal stem/progenitor cells within peripheral blood samples using multiparameter flow cytometry.

Maintenance of high ALDH activity has also been used as a functional tool to select and study bone marrow and umbilical cord blood-derived HPCs, EPCs and mesenchymal stem cells (MSCs) that act as central mediators of VR processes.[33] Conversely, accelerated attrition of cells with ALDH^{hi} activity in circulation can accurately quantify VR progenitor cell depletion induced by T2D, obesity, ASCVD and elevated lipoprotein(a) levels.[29,48–50] Thus, detection of cells with ALDH^{hi} activity in peripheral blood serves as a strong measure of regenerative progenitor cell fluctuations during cardiometabolic disease.

Prevention of VR Cell Exhaustion by Semaglutide

In SEMA-VR CardioLink-15,[8] participants administered semaglutide demonstrated recovery of circulating HPCs with ALDH^{hi} activity as well as ALDH^{hi} EPCs with CD (cluster of differentiation)34^{+}CD133^{+}CD45^{-} phenotype (Figure 1). These findings were the first to establish a potential role for semaglutide to improve VR cell depletion associated with T2D through replenishment of circulating myeloid HPCs and EPCs previously implicated in vessel repair. Changes in VR progenitor cell content occurred alongside a significant reduction in circulating cells restricted to the granulocyte and monocyte lineages. Remarkably, semaglutide treatment decreased ALDH^{hi}SSC^{hi} (high side scatter) granulocyte content >2-fold, particularly in activated neutrophils that coexpressed CD66b and the chemokine receptor CXCL2 (C-X-C motif chemokine ligand 2) involved in homing to areas of inflammation (Figure 1). Using an alternate detection system reliant on cell surface markers alone, Preložnik Navodnik et al[51] demonstrated that individuals with type 1 diabetes demonstrated an increase in CD34^{+}VEGFR2^{+}(vascular endothelial growth factor receptor 2)CD133^{+}CD45^{-} EPCs after 12 weeks of treatment with semaglutide compared with insulin therapy alone. Taken together, the effects on circulating VR progenitor cell content identify GLP-1RAs as a potential therapy to dampen VR cell depletion and reduce inflammation in people with T2D.

GLP-1RAS AND STEM CELL EXHAUSTION

Hematopoietic Progenitor Cells: The Initiators of Angiogenic Repair

Hematopoietic stem cells (HSCs) give rise to mature myeloid and lymphoid cells, erythrocytes and platelets,

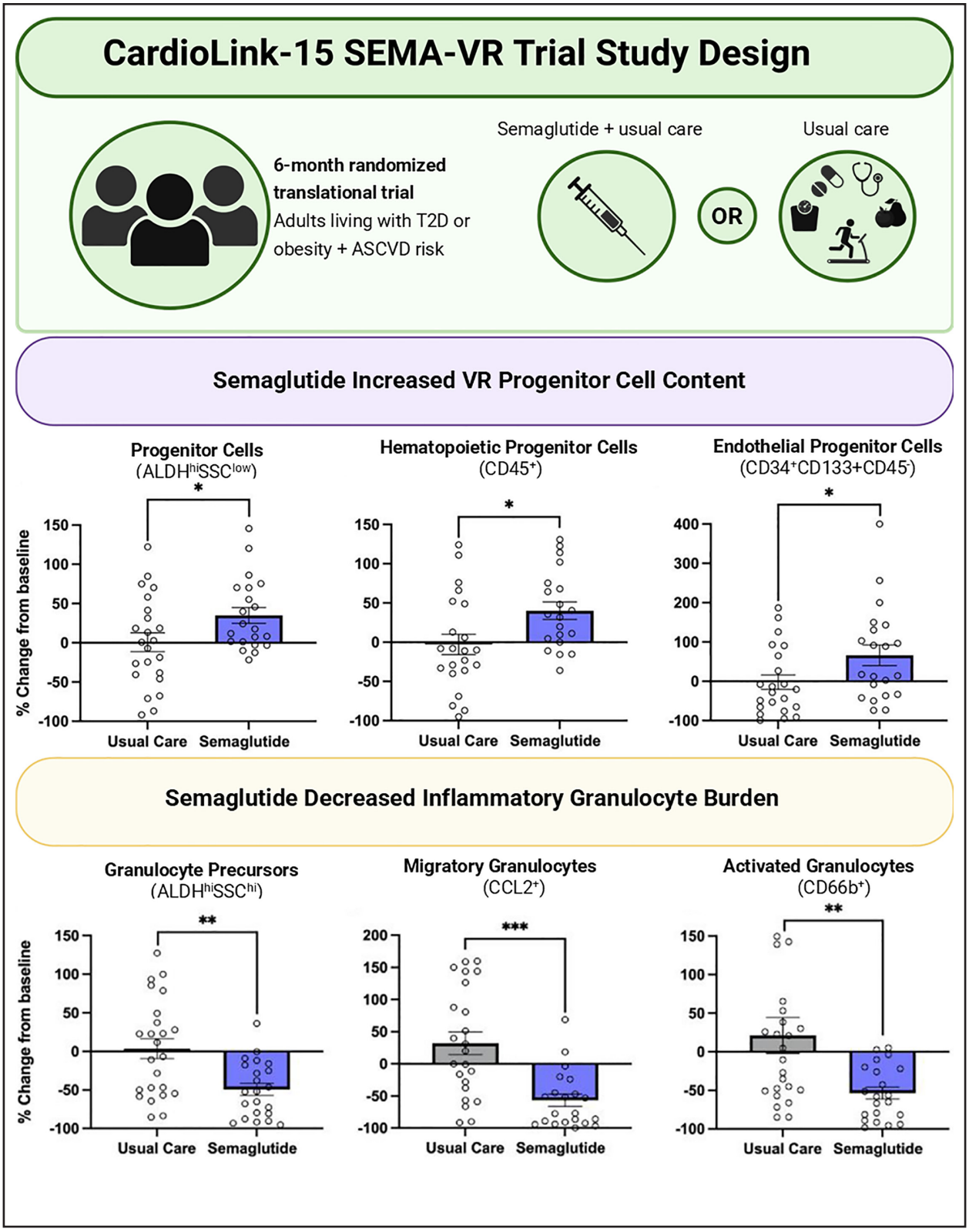

Figure 1. Semaglutide recovered circulating vascular regenerative (VR) progenitor cell content and decreased granulocytes. The SEMA-VR trial compared circulating stem/progenitor cell content in peripheral blood at baseline and 6 months from adults with type 2 diabetes (T2D) or obesity at baseline compared with usual care without semaglutide. Participants treated with semaglutide demonstrated an increase in hematopoietic and endothelial progenitor cell content and a decrease in granulocyte precursors with migratory and activated marker coexpression. ALDH^{hi}, indicates high aldehyde dehydrogenase activity; ASCVD, atherosclerotic cardiovascular disease; CCL, C-C chemokine ligand; CD, cluster of differentiation; SEMA-VR, Semaglutide and Vascular Regeneration; and SSC, side scatter. Created in BioRender. Dennis, Cole. (2026) https://BioRender.com/y3rghwd. Adapted from Park et al.[4]

and serve as the source for hematopoietic replacement throughout life (Figure 2). By definition, HSCs demonstrate multipotency and self-renewal capacity[52,53]; however, true HSCs are rare and usually confined to the bone marrow endosteal niche in a predominantly quiescent state crucial for maintaining a highly proliferative, multipotent HPC pool.[54] Beyond classical roles in hematopoiesis, early myeloid HPCs and monocyte progeny contribute substantially to vessel regeneration through paracrine induction of angiogenesis. Early myeloid HPCs released into the circulation home efficiently to sites of hypoxia or vessel injury, and productively secrete an array of proangiogenic factors to initiate endothelial sprouting and matrix remodeling.[55,56] The early myeloid HPC pool is enriched in the bone marrow within a specialized niche with high vessel density that permits the egress of a continuum of hematopoietic progeny into the circulation.[57] With age, intrinsic alterations within HPCs and extrinsic changes such as elevated oxidative stress imposed on the niche accelerate hematopoietic differentiation and inhibit mobilization of proangiogenic progenitor cells. The bone marrow vascular niche undergoes significant remodeling with the advancement of T2D, obesity, or simply with age, characterized by an increase in adipose stromal cell content,[58–60] reinforced by a feedback loop that promotes adipogenic inflammation.[61] During T2D, marrow-resident adipocytes secrete proinflammatory cytokines and adipokines that skew hematopoiesis towards a proinflammatory myeloid cell bias.[62,63] Further investigation is required to elucidate mechanisms that govern adipogenic content within the bone marrow niche and to clarify how adipocyte accumulation influences vessel regeneration initiated by the paracrine activity of mobilized HPCs.

Aging HPCs are marked by a shift in hematopoiesis favoring myeloid over lymphoid differentiation that impairs adaptive immunity with age. Preferential differentiation of proinflammatory myeloid cells is known as a driver of endothelial dysfunction.[64] In parallel, aged HPCs demonstrate quiescence, reflecting an overall decline in the HPC pool.[65–68] Mouse and human transplantation studies confirm HPCs from aged bone marrow show diminished reconstitution potential after transplantation compared with HPCs from younger donors.[69–71]

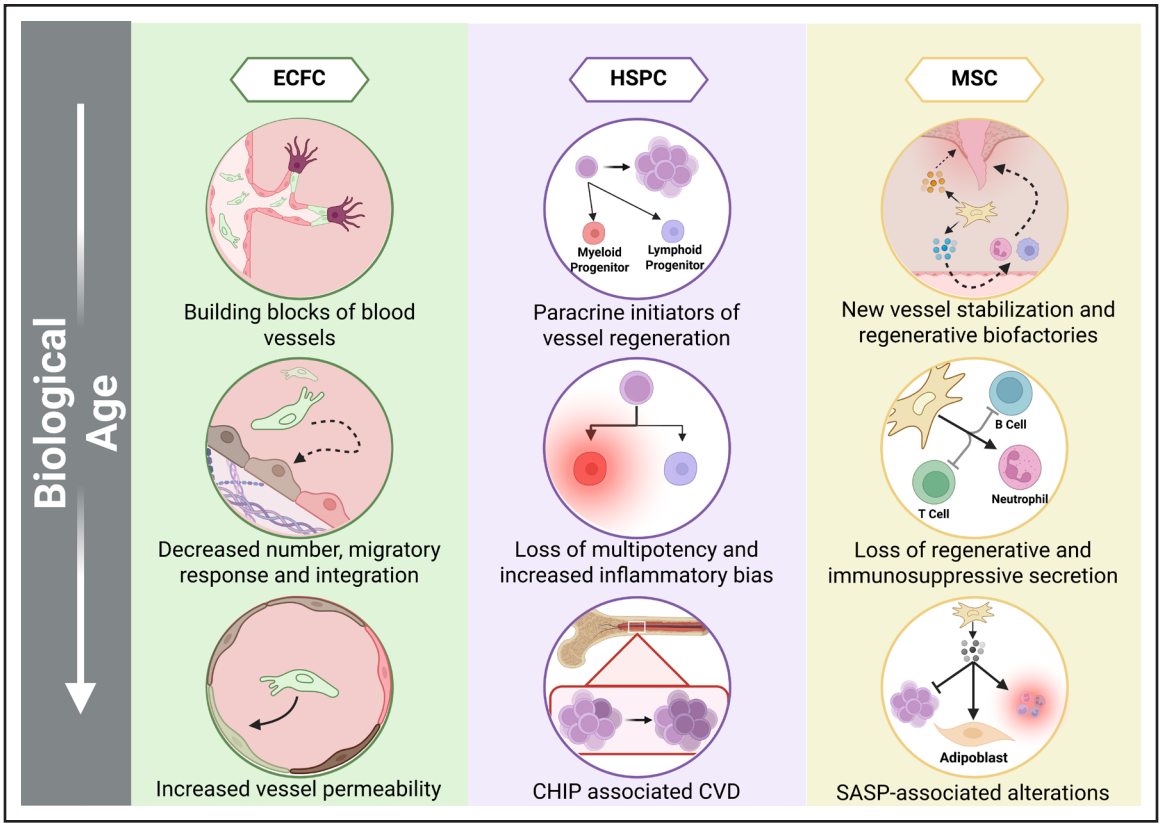

Figure 2. Key functional roles of endothelial colony-forming cell (ECFC), hematopoietic stem/progenitor cells (HSPCs), and mesenchymal stem cells (MSCs) in vascular tissue regeneration.
With increased biological age, ECFCs, HSPCs, and MSCs exhibit progressive functional decline and depletion that collectively contribute to deficits in vascular system repair and cardiovascular disease (CVD) susceptibility. CHIP indicates clonal hematopoiesis of indeterminate potential; HSPC, hematopoietic stem/progenitor cells; and SASP, senescence-associated secretory phenotype. Created in BioRender. Dennis, Cole. (2026) https://BioRender.com/y3rghwd.

GLP-1RA Actions on Hematopoiesis

Although GLP-1RAs exert complex effects on hematopoiesis primarily through indirect actions on anti-inflammatory pathways, GLP-1Rs are expressed on HPCs at low levels.[16] Liraglutide treatment in human CD34+ HPCs corrected high-glucose–induced hyperproliferative dysfunction, rescued CXCR4/SDF-1 (C-X-C motif chemokine receptor 4/stromal cell-derived factor 1) axis migratory activity, and reduced intracellular ROS production.[72] In the aforementioned SEMA-VR CardioLink-15 trial, our group demonstrated that in addition to the recovery of ALDH^{hi} HPC content (Figure 1).[8] Semaglutide decreased granulocyte precursor content and downregulated inflammatory serum cytokine levels in the TNF (tumor necrosis factor) and interleukin families initially over-expressed at baseline. Whether these effects in people with T2D altered HPC differentiation by direct GLP-1RA receptor activation or through indirect effects lowering oxidative stress remain undetermined.

Direct actions of GLP-1RAs on the control of hematopoietic differentiation are plausible but not clearly established. Yan et al[73] reported that exendin-4, a peptide based on the GLP-1R activating peptide in gila monster venom, directly altered HPC proliferation and metabolism. In LDLR$^{-/-}$ (low-density lipoprotein receptor knockout) mice fed a high-fat diet, exendin-4 treatment or GLP-1R knockout in bone marrow suppressed HPC proliferation, deterred myeloid bias, and modified glycolytic metabolism. However, effects of GLP-1RAs on ASCVD progression appeared to be context-dependent. In a study from the Drucker group using mice with GLP-1R knockout in Tie2-expressing hematopoietic and endothelial cells, ASCVD progression induced by viral PCSK9 (proprotein convertase subtilisin/kexin type 9) expression was equivalent after semaglutide treatment in knockout and wild-type mice, suggesting that direct GLP-1R engagement was dispensable for the antiatherogenic actions of GLP-1RAs.[16]

Beyond their effects on myeloid immune cells, GLP-1RAs exert actions on megakaryocytes and platelets. Platelets express functional GLP-1Rs, and exposure to liraglutide in vitro attenuated platelet aggregation through a GLP-1R-dependent mechanism independent of weight loss or glycemic improvement.[74] Suppression of aggregation was mediated via GLP-1R-coupled cAMP/PKA (cyclic adenosine monophosphate/protein kinase A) signaling and eNOS (endothelial NO synthase)–derived NO production, with GLP-1RAs shown to reduce microvascular thrombosis in a manner abrogated in GLP-1R–deficient animals.[75] Clinically, these observations seem to translate into reductions in thrombotic risk, where in a propensity score-matched target trial emulation of over 270 000 patients with T2D, GLP-1RA use was associated with a significantly lower incidence of venous thromboembolism compared with DPP-4 (dipeptidyl peptidase-4) inhibitor use (6.1 versus 7.6 events per 1000 patient-years) with reductions seen for both pulmonary embolism and deep vein thrombosis, and the early separation of event curves suggests mechanisms not modulated by weight loss alone.[76] These studies have resulted in a clinically important counterpoint to emerge. When the combination of GLP-1RAs with aspirin was associated with elevated risks of ischemic heart disease and cardiac arrhythmias compared with monotherapy[77]; particular caution was warranted in older patients where polypharmacy is common.

Endothelial Colony-Forming Cells: The Building Blocks of Blood Vessels

Both circulating and vessel-derived EPCs directly contribute to de novo vessel formation and angiogenic sprouting from preexisting vessels (Figure 2). However, early outgrowth monocyte subsets that demonstrate endothelial cell characteristics such as lectin uptake can contaminate EPC cultures and are often incorrectly labeled as EPCs based on shared cell surface marker identity. To avoid confusion, endothelial colony-forming cells (ECFCs) were named to represent a functionally defined subset of EPCs restricted to the endothelial lineage that exhibit late clonal outgrowth and high proliferative capacity in vitro with the ability to permanently integrate into vessels in vivo.[78] ECFCs are exceedingly rare in the circulation but are enriched in human bone marrow and umbilical cord blood. ECFCs lack the expression of mature hematopoietic lineage markers, such as pan-leukocyte CD45, yet share expression of progenitor cell markers CD34, VEGFR2, and CD133. Vessel-resident ECFCs act as building blocks of newly formed endothelium,[34,79] and perform a unique role in the maintenance of vessel integrity.[80] Mathematical modeling based on rates of endothelial cell proliferation indicates that an alternate reservoir of proliferative ECFCs mobilized from the bone marrow is required to maintain optimal blood vessel homeostasis.[81]

Age-related EPC exhaustion has been observed previously as the deletion and functional decline in circulating ECFC populations. ECFCs from elderly individuals exhibit reduced numbers with decreased replicative capacity and impaired migratory responses compared with ECFCs from younger individuals (Figure 2).[82,83] Most notably, aged ECFCs show attenuated responsiveness to proangiogenic cues such as VEGF (vascular endothelial growth factor) via reduced VEGFR2 expression and impaired signaling.[82] In parallel, a shift in the ECFCs secretome towards augmented production of matricellular proteins links ECFC dysfunction to age-related vascular pathologies.[83,84]

Preclinical studies examining the consequences of aging on ECFCs consistently demonstrate profound deterioration in regenerative potential. Shelley et al[85] demonstrated age-dependent decline in the frequency of circulating ECFCs

alongside drastically diminished vessel formation in nonhuman primates. Complementary evidence in murine models underscored that age-related functional erosion after transplantation of ECFCs from young donors prevented the decline in cardiac angiogenesis in aged mice.[86] Notably, murine ECFCs produced IL (interleukin)-1β in response to stress and implicated chronic inflammation with functional decline.[87] Despite the recognized importance of ECFCs in vessel repair, mechanisms driving the decline in ECFC number and function by chronic cardiometabolic comorbidities remain poorly understood. Herein lies a significant opportunity for future studies to characterize ECFC attrition using well-defined marker panels and omic technologies, allowing for accurate assessment of functional decline with age and CVD status.

GLP-1RA Effects on EPC Function

Endothelial dysfunction plays a central role in the vascular pathogenesis associated with obesity, T2D, and ASCVD. Persistent hyperglycemia and adipokine dysregulation are well known to elevate oxidative stress levels, reduce NO bioavailability, and activate inflammation, thereby accelerating ASCVD development. GLP-1RAs have been shown to enhance EPC number and provascular function. In patients with T2D, treatment with dulaglutide increased circulating EPC numbers (defined as $CD34^+/VEGFR2^+$) and increased proliferative, migratory, and tubulogenic capacity in vitro.[88] High glucose reduced GLP-1R expression and induced apoptosis in EPC, whereas activation of GLP-1R signaling with exendin-4 reversed these effects.[89] In primary human umbilical vein endothelial cells treated with exendin-4, the increase in VEGF production was accompanied by improved tube formation, reflecting restored angiogenic capacity.[90] In preclinical mouse models, semaglutide treatment reduced vulnerable plaque area, monocyte/macrophage accumulation, and extracellular matrix turnover, key contributors to ASCVD.[91]

Mesenchymal Stromal Cells: The Sentinels of Tissue Regeneration

MSCs are plastic adherent, nonhematopoietic, nonendothelial cells with spindle-shaped morphology in vitro that express classical stromal cell markers (CD73, CD90, and CD105) and demonstrate multilineage differentiation into adipocytes, osteocytes, and chondrocytes. MSCs are widely distributed throughout the body during embryogenesis and are maintained in association with the perivascular niche in bone marrow, kidney, liver, pancreas, adipose tissue, umbilical cord blood, and placenta.[92] MSC function is highly studied in the bone marrow, where the primary role of MSCs is to maintain and regulate hematopoiesis.[93] In the periphery, MSCs and progeny wrap and stabilize advancing vessels through the generation of intimal pericytes and smooth muscle cells. MSCs also act as local regulators of tissue healing through the release of regenerative, proangiogenic and immunomodulatory cytokines (Figure 2).[94–96]

MSC content is massively impacted by age. In the bone marrow, MSC frequency consistently decreases with age, and remarkably reaches levels 200-fold lower in aged individuals compared with at birth.[97] Aged MSCs readily undergo senescence and preferentially release proinflammatory factors through an aging phenomenon commonly referred to as senescence-associated secretory phenotype (SASP; Figure 2).[98–100] This age-related shift in secretory signals has negative consequences on hematopoiesis such as the propagation of senescence and impaired clonogenic potential in bone marrow HPCs.[100] Aging also profoundly changes MSC differentiative potential. A defining feature of aged MSCs is bias toward the adipose lineage with concomitant loss of osteogenic potential.[101–103] Thus, functional decline of MSCs within the bone marrow has downstream impact on hematopoiesis that contributes to vascular aging.

MSC Transplantation to Slow Vascular Aging

MSCs have garnered considerable interest as a therapeutic modality to treat cardiometabolic inflammatory diseases due to robust secretion of immunomodulatory and proangiogenic factors.[104] MSC immunosuppressive function is multifactorial and stimulated in inflamed environments in response to increased exposure to IFNγ (interferon gamma).[105,106] In contrast, the proangiogenic composition of the MSC secretome supports MSC transfer in applications where vessel repair or neovascularization are desired outcomes.[34,96,107,108]

MSCs also directly modulate biological aging. Administration of MSCs or MSC-derived extracellular vesicles (EVs) in murine models of aging results in attenuation of senescence and increased lifespan.[109,110] Accumulating preclinical evidence supports the use of MSC-based regenerative therapies as a promising strategy to mitigate age-related vascular decline. Clinical translation of MSC-based therapies is well underway, with >300 MSC-related clinical trials currently registered on ClinicalTrials.gov. Among the subset of trials that address chronic cardiovascular diseases, overall outcomes have been encouraging.[111] One notable randomized controlled trial administered autologous MSCs via intramyocardial injection in individuals with ischemic heart failure.[111] The MSC-treated group exhibited significantly reduced left ventricular end-systolic volume as the primary end point, along with increased stroke volume and left ventricular ejection fraction when compared with placebo.

GLP-1RAs as an Adjunct to MSC Therapy

A recent systematic review has shed light on the pleiotropic effects of GLP-1RAs on MSC function in individuals

with T2D. Weber et al[112] identified 38 studies wherein native GLP-1 or GLP-1RAs stimulated human bone marrow and adipose-derived MSC expansion in a dose-dependent manner and prevented age-related MSC senescence. Increased PI3K/Akt (phosphatidylinositol 3-kinase/protein kinase b) and Wnt (Wingless-related integration site)/β-catenin signaling induced by liraglutide or semaglutide conferred antiapoptotic effects on MSCs and prevented unwanted adipogenic differentiation. Furthermore, GLP-1RAs decreased secretion of IL-6 and TNF-α (tumor necrosis factor-α) and increased secretion of IL-10 by MSCs under high-glucose conditions.[113] Thus, GLP-1RAs modulate key pathways in human MSCs to influence survival, differentiation, and anti-inflammatory functions, promising therapeutic characteristics to prevent pathological MSC attrition in the bone marrow during T2D and obesity.

Genetic engineering approaches have also been used to enhance the therapeutic potential of MSC transfer. Stable overexpression of exendin-4 in MSCs elevated the expression of GLP-1Rs, a positive feedback mechanism that potentiates responsiveness to GLP-1RAs.[114] Transcriptomic analyses of overexpression of exendin-4 in MSCs versus unmodified MSCs grown under high glucose (25 nmol/L) conditions revealed 1323 differentially expressed genes, and enrichment analyses indicated broad regulatory effects on proliferation, apoptosis, and proangiogenic genes.[114] In a similar strategy using MSCs engineered to overexpress and secrete GLP-1 in exosomes, systemic injection of these genetically modified MSCs into hyperglycemic mice reduced nonfasted blood glucose and improved glucose tolerance compared with mice receiving unmodified MSCs.[115]

GLP-1RAS MODULATE INTERCELLULAR COMMUNICATION

Progenitor cell secreted signals act via paracrine mechanisms to elicit rapid responses in neighboring cells. With aging, multisystem intracellular communication deteriorates, leading to impaired vascular homeostatic regulation and shifts the balance between a VR state and systemic inflammation. In the aging vasculature, ROS accumulation, ER stress, mitochondrial dysfunction, and DNA damage can culminate in cell cycle arrest or senescence. When senescent cells are not cleared, damaged cells can reprogram into a highly secretory, proinflammatory state.[116] These SASP alter system-wide intercellular communication patterns and position SASP as a canonical hallmark of aging that connects senescence to broader meta-cellular processes.

Classical, Emerging, and Nonclassical SASP

SASP is classified into classical, emerging, and nonclassical categories. Classical SASP (cSASP) encompasses increased secretion of proinflammatory cytokines (IL-6, IL-8, TNF-α), MMPs (matrix metalloproteinases), and profibrotic factors (Figure 3).[116,117] As cell homeostasis is impacted by age, altered secretory patterns become detrimental to tissue function. cSASP dysregulation is largely driven by NF-κB (nuclear factor-κB) as a central regulator of inflammatory cytokine transcription, with further contributions from p53, p38/MAPK signaling, and the DNA damage response.[118–120] Age-related cSASP has been shown to increase proinflammatory cytokine levels in the bone marrow and vascular niche.[100] As such, vascular aging-associated cSASP is now considered a measurable risk factor for ischemic stroke.[121,122]

The emerging category (emerging SASP) focuses on potent mediators of inflammation packaged in lipid membrane EVs released by all cells to some extent into biological fluids that contain protein, microRNA, and noncoding RNA cargo, as well as nonprotein lipid metabolites and ion reservoirs (Figure 3).[116] EVs are particularly noteworthy when discussing intercellular communication between stem cells and tissue-specific effectors. MSCs abundantly produce EVs carrying anti-inflammatory molecules (eg, prostaglandin E2, TGF-β [transforming growth factor-β]) and immunosuppressive enzymes) and activators of angiogenesis (eg, HGF [hepatocyte growth factor], FGF-2 [fibroblast growth factor-2], VEGF).[123,124] MSC-derived EVs travel distantly via the bloodstream to alleviate oxidative stress-induced senescence in endothelial cells.[125,126] With aging, emerging SASP shifts EV cargo toward a proinflammatory profile and polarizes the endothelium towards a proinflammatory secretory phenotype.[127–129] This age-dependent shift contributes to inflammation in the vascular and bone marrow niche alongside decline and dysfunction in provascular HPC and EPC production.[130]

Nonclassical SASP involves nonsecretory mechanisms, including juxtacrine signaling between adjacent cells (Figure 3). The cell contact-mediated Notch pathway transcriptionally regulates the production of TGF-β family cytokines generally considered as master regulators of nonclassical SASP intercellular communication.[131] Fluctuations in membrane-bound Delta-like and Jagged ligand binding to Notch1 receptors result in activation of TGF-β family–mediated fibrosis and suppression of senescence-associated proinflammatory factors.[132] Therefore, dynamic Notch1-activity dictates the balance between fibrosis and inflammation as a result of a temporospatial regulation of nonclassical SASP composition.[132] As a specific example, nonclassical SASP–related Notch juxtacrine signaling between endothelial cells and HPCs in the bone marrow is essential for hematopoietic repopulation and expansion.[133–135] A recent study by Matteini et al highlighted the importance of Notch signaling in the transition from extrinsic trans-activation to intrinsic cis-inhibition that drives a myeloid bias in hematopoiesis associated with systemic inflammation as age progresses.[136]

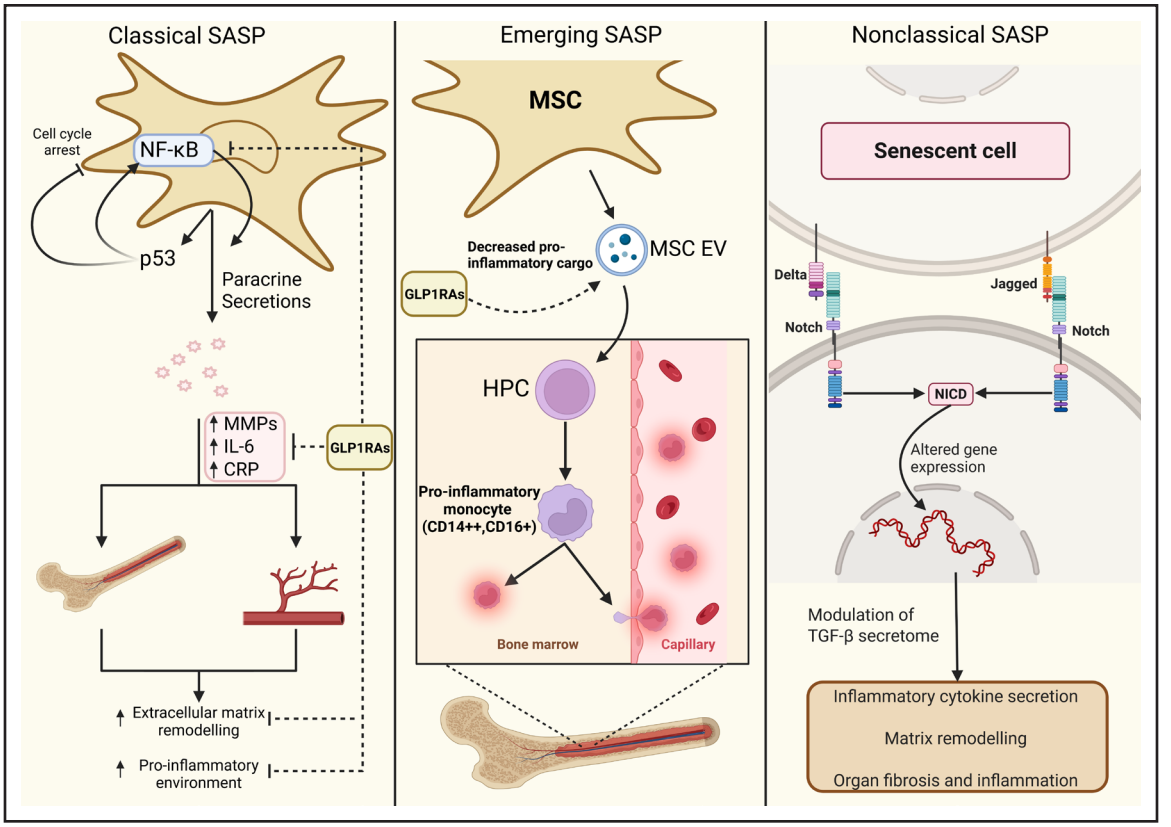

Figure 3. Classical, emerging, and nonclassical senescence-associated secretory phenotype (SASP) compromise vascular health. Classical SASP promotes the secretion of inflammatory cytokines mitigated by glucagon-like peptide-1 receptor agonists (GLP-1RAs) through suppression of NF-κB (nuclear factor-kappa B)–mediated proinflammatory signaling and MMP (matrix metalloproteinase) remodeling. Emerging SASP involves inflammatory cargo packaged within MSC-derived extracellular vesicles (EVs). GLP-1RAs shift EV content back to anti-inflammatory mediators. Nonclassical SASP contributes to vascular dysfunction through dysregulated Jagged/Delta–Notch interactions resulting in secretion of profibrotic TGF-β (transforming growth factor-β) family cytokines. CD indicates cluster of differentiation; CRP, C-reactive protein; HPC, hematopoietic progenitor cell; IL, interleukin; MSC, mesenchymal stem cells; and NICD, notch intracellular domain. Created in BioRender. Dennis, Cole. (2026) https://BioRender.com/y3rghwd.

GLP-1RAs Modulate SASP

SASP is associated with elevated systemic inflammation and fibrotic tissue remodeling. Therefore, it is anticipated that the anti-inflammatory activities of GLP-1RAs may be mediated by abrogation of SASP-mediated vascular aging. Three interrelated mechanisms have emerged in preclinical studies to explain how GLP-1RAs abolish senescence programs and reduce SASP: (1) direct modulation of insulin production; (2) activation of anti-inflammatory and antioxidant pathways; and (3) indirect effects on SASP drivers such as hyperglycemia and weight loss.

Hyperinsulinemia during T2D is associated with senescence-driven metabolic dysfunction in the liver. Chronic hyperinsulinemia activates senescent gene expression patterns in hepatocytes, which in turn amplifies insulin resistance and liver dysfunction through SASP secretion.[137] Exendin-4 has been reported to reverse SASP-related gene expression in pancreas, adipose tissue, liver, and skeletal muscle tissues.[138] For example, exendin-4 treatment of primary hepatocytes exposed to high insulin markedly suppressed transcription of the classical senescence markers p53 and p21, and concurrently decreased the secretion of the SASP inflammatory factors (CXCL8, IL-18, and MMP3), to effectively dampen hepatocyte damage triggered by oxidative stress.[139] GLP-1RAs function in endothelial cells through activation of AMPK (AMP-activated protein kinase) and NRF2 (nuclear factor erythroid 2-related factor 2), 2 key regulators of endothelial cell stress responses that improve mitochondrial function and activate protective oxidant scavenging pathways.[140] Exendin-4 reduced NF-κB accumulation known to drive SASP-mediated gene transcription in immune cells.[141] These general benefits of GLP-1RA use may shift the systemic milieu away from chronic, multiorgan prosenescent conditions.

GLP-1RAS REDUCE CHRONIC VASCULAR INFLAMMATION

Chronic, low-grade inflammation plays a central role in vascular disease progression and overlaps as a central

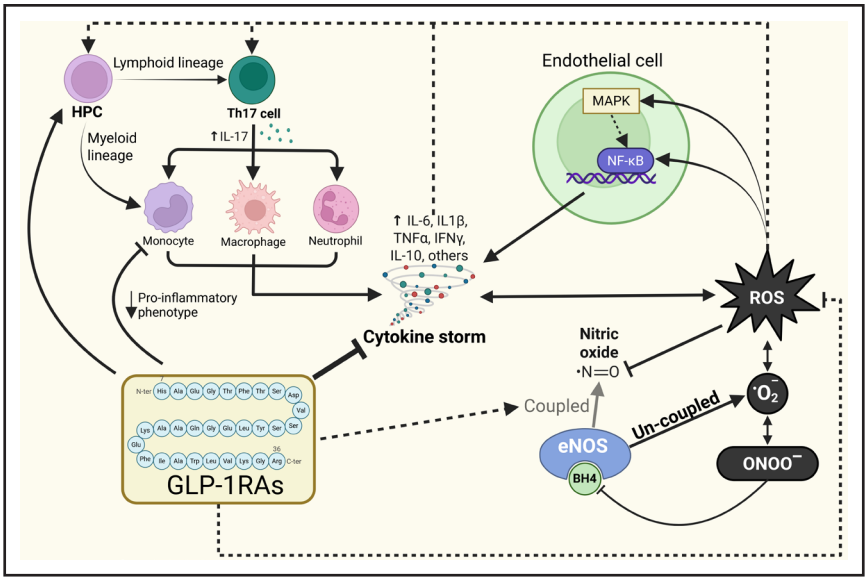

Figure 4. Convergence of oxidative stress and inflammatory pathways that collectively drive a cytokine storm.
IL (interleukin)-17 secretion from T-helper lymphocytes and elevated reactive oxygen species (ROS) and MAPK (mitogen-activated protein kinase)/NF-κB (nuclear factor-κB) signaling, eNOS (endothelial NO synthase) uncoupling in hematopoietic progenitor cells (HPCs) form a self-reinforcing network that sustains chronic inflammation. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) disrupt this cycle by dampening cytokine amplification, reducing myeloid bias, and promoting eNOS coupling. BH4 indicates tetrahydrobiopterin; IFNγ, interferon gamma; O_2^-, superoxide, $ONOO^-$; peroxynitrite; Th17, T-helper 17; and TNF tumor necrosis factor. Created in BioRender. Dennis, Cole. (2026) https://BioRender.com/y3rghwd.

hallmark of vascular aging.[142] The concept of inflammaging is implicated in both macrovascular and microvascular pathologies of atherosclerosis.[143–145] During inflammaging, vessel-derived EPCs are implicated in a progressive proinflammatory shift that promotes endothelial dysfunction. Sustained inflammation within the bone marrow alters HPC fate via promotion of premature myeloid differentiation at the expense of balanced progenitor pool maintenance.[146,147] Finally, adipose-derived MSCs shift to proinflammatory adipokine production as obesity progresses with age.

Age-Related Oxidative Stress Drives NF-κB Activity

Oxidative stress represents a major driver of vascular inflammation during aging.[148] Aging reduces oxidative stress resilience in endothelial cells and renders the vasculature more susceptible to the oxidative pathology of hyperglycemia.[149] Blood vessels exposed to chronic low-grade inflammation trigger extracellular matrix remodeling characteristic of arterial stiffening.[150,151] Oxidative stress also promotes ROS accumulation and subsequent damage to lipid bilayers, proteins, and nucleic acids.[152] NF-κB–regulated genes play a central role in ROS homeostasis under normal physiological conditions; however, excessive ROS accumulation in aged cells promotes NF-κB target gene expression and increased production of IL-6, IL-1β, and TNF-α (Figure 4).[148] NF-κB, in conjunction with MAPK/p38 signaling in HPCs and EPCs, represents a critical synergy governing chronic inflammation that leads to impaired hematopoiesis and vascular dysfunction, whereas pharmacological inhibition of NF-κB can restore HPC and EPC functions.[153,154] Collectively, NF-κB–stimulated proinflammatory signals generate a cytokine storm that confers relentless damage to the endothelium that overwhelms VR cell–mediated vessel repair.

NO Bioavailability and eNOS Uncoupling

NO is a critical signaling molecule that maintains vessel tone, inhibits platelet aggregation, and prevents inflammatory cell adhesion. Adequate NO bioavailability is essential for vascular homeostasis, and age-related NO decline predisposes individuals to CVD development.[155] ROS-mediated NO inactivation combined with a reduction in eNOS expression largely contribute to age-related decline in NO.[156] eNOS dysfunction occurs through eNOS uncoupling, whereby superoxide reacts with NO to form peroxynitrite. The essential eNOS cofactor BH4 (tetrahydrobiopterin) is susceptible to oxidation by peroxynitrite, leading to eNOS uncoupling (Figure 4).[156] Reduced BH4 availability shifts eNOS activity from NO production towards superoxide generation, transforming eNOS from a vasoprotective enzyme into a ROS-generating contributor to oxidative stress.[157] eNOS uncoupling has been extensively documented in individuals with CVD,[156–158] and underscores a key mechanism linking oxidative stress to vessel aging.

The contribution of eNOS dysfunction to stem cell exhaustion remains unclear. However, MSCs play an important role in regulating redox balance through secretion of SOD (superoxide dismutase) 1 and 3, enzymes that convert superoxide into nonradical species.[159,160] Aged MSCs have been shown to downregulate SOD1 and SOD3 production.[161] Using the transfer of MSC-derived EVs from young mice, Khanh et al[161] remarkably demonstrated the rejuvenation of aged MSCs and suppression of ROS production in C57BL/6, db/db leptin-deficient mice models of T2D. Further investigation is warranted to clarify the mechanisms by which reduced SOD production by aged MSCs contributes to increased vascular inflammation.

Age-Related Inflammatory Cytokine Secretion

Although inflammatory mediators including IL-1β, TNF-α, and C-reactive protein are well known to contribute to vascular inflammation as reviewed previously,[162,163] alterations in IL-6 and IL-17A signaling together form a central axis that drives vascular inflammation (Figure 4).[164] IL-6 is produced by a wide range of immune cells and is strongly associated with CVD.[165] Indeed, the IL-6 receptor has been pinpointed as a key target for combating coronary artery disease in Mendelian randomization studies.[166] IL-6 acts on HPCs to promote myeloid lineage bias in the bone marrow,[167] and furthermore, IL-6 serves as a key driver of T-helper 17 lymphocyte differentiation, whereby increased secretion of IL-17A amplifies recruitment of neutrophils and activated macrophages to further generate ROS,[168,169] and reinforce local vascular inflammation.[170] Elevated IL-17A levels also induce endothelial cell senescence through the NF-κB–dependent pathway.[164] Sustained IL-17A signaling and prolonged exposure to IL-6 are known to drive stem cell exhaustion through depletion of early myeloid HPCs and expansion of inflammatory myeloid progeny.[171] The myeloid shift favors persistent IL-17A production, continuing a cycle wherein impaired immune cell regulation fuels chronic vascular inflammation. Collectively, the IL-6/IL-17 axis warrants more investigation as a mechanistic link between immune cell dysregulation, VR stem cell exhaustion, and CVD progression.

GLP-1RA Effects on Vessel Inflammation

GLP-1RAs potently suppress NF-κB activation and reduce downstream proinflammatory gene expression in multiple organs including bone marrow, endothelium, and adipose tissues.[172] GLP-1R signaling induced by exendin-4 and liraglutide in immune cells effectively blocks NF-κB activity, thereby lowering inflammatory cytokine production.[173] In endothelial cells, GLP-1-mediated cAMP/PKA signaling enhances eNOS phosphorylation and increases NO bioavailability to alleviate endothelial dysfunction and suppress vascular inflammation.[174]

Some of the most convincing evidence of widespread effects of GLP-1RAs on circulating inflammatory biomarkers in individuals with T2D comes from a recent meta-analysis of 52 randomized controlled trials showing that GLP-1RA treatment consistently reduced serum C-reactive protein, IL-6, IL-1β, and TNF-α, likely through inhibition of the NF-κB pathway. GLP-1R activation in T lymphocytes reduced T-helper 17 differentiation and decreased proinflammatory IL-17 production.[175] Collectively, preclinical analyses overwhelmingly support the suppression of inflammation via direct GLP-1R activation in monocyte, macrophage, and lymphocyte lineages.

GLP-1RAs and Clonal Hematopoiesis of Indeterminant Potential

With chronic oxidative stress exposure over time, somatic mutations may accumulate in HPCs that permit a selective survival advantage leading to the preferential expansion of clonal populations—a phenomenon known as clonal hematopoiesis of indeterminate potential (CHIP). CHIP is defined by a disproportionate contribution to hematopoiesis by a limited number of HPC clones and is typically detected through the presence of recurrent somatic mutations in leukemia-associated genes in individuals without overt hematologic disease (Figure 2).[66,176,177] CHIP is observed in ≈10% of individuals over 70 and up to 20% of those over 90 years of age. Importantly, CHIP is a primary driver of chronic inflammation and is associated with an elevated incidence of adverse cardiovascular comorbidities, particularly in people with T2D.[178]

CHIP promotes a proinflammatory microenvironment in the bone marrow, and individuals with CHIP demonstrate remarkably elevated (>40%) CVD risk.[179] Leukocytes in mouse models of CHIP overexpress inflammatory genes, particularly IL-1β and IL-6.[180] Obesity in combination with CHIP also exacerbates adipogenic remodeling in the bone marrow.[176,181] Recurrent CHIP-associated mutations can disrupt Toll-like receptor–mediated TRAF6 (tumor necrosis factor receptor-associated factor 6) signaling, which predisposes clones toward myeloproliferative neoplasms,[182] and highlights CHIP-driven inflammation as a shared pathological mechanism that links hematopoietic dysregulation with CVD. Improved understanding of CHIP-associated maladaptive inflammatory pathways may reveal novel therapeutic targets to mitigate age-related vascular disease.

Emerging hypotheses suggest that GLP-1RAs represent plausible inhibitors of accelerated meta-inflammation during cardiometabolic disease.[183] Preliminary work and early clinical efforts are underway

to analyze the effects of GLP-1RAs on clonal blood disorders, and direct inhibition of clonal expansion has been reported with GLP-1R agonism in recent conference proceedings.[184] Currently, there are few studies published that link GLP-1RA use with reduction of CHIP-mediated CVD manifestations. Given the potent anti-inflammatory activities of the new 3G agents, mechanistic preclinical or early clinical trials showing GLP-1RAs may reduce CHIP-associated CVD comorbidity are hopefully forthcoming.

Sex-Based Differences in Hematopoietic System Aging and CHIP

Sex-based differences emerge in our understanding of hematopoietic system aging. Male mice showed an earlier decline in HPC function, demonstrated by altered hematopoietic gene expression, compared with females.[185] Moreover, myeloid-biased proinflammatory differentiation appears earlier in male mice, whereas in females, myeloid bias primarily results at a later age.[186] These findings are influenced by hormonal dimorphisms, as estrogens and related hormones such as follicle-stimulating hormone have been shown to potently regulate hematopoiesis.[185,187] Despite enhanced preservation of the female HSC niche, circulating HPC counts tell a more nuanced story. Women demonstrate ≈23% fewer CD34+ HPCs in circulation compared with men,[188] suggesting higher bone marrow reserve does not translate to greater peripheral mobilization.

Although most CHIP driver mutations (TET2 [tet methylcytosine dioxygenase 2], ASXL1 [additional sex combs-like 1]) and mosaic chromosomal alterations show male predominance, DNMT3A (DNA methyltransferase 3A) mutations and copy-number abnormalities are more prevalent in females among ≈450 000 UK Biobank participants. In murine systems, Dnmt3a-mutant HSCs from females with chronic estrogen exposure favored expansion of Dnmt3a-mutant myeloid cells through cell-intrinsic estrogen receptor alpha activity.[189] Therefore, premature natural menopause, but not surgically induced menopause, was independently associated with 36% increased odds of CHIP, driven primarily by enrichment of DNMT3A driver mutations.[190] These findings imply that the hormonal milieu surrounding estrogen loss, rather than estrogen withdrawal, potentially shapes CHIP clonal dynamics.

Preliminary population-level evidence indicates that GLP-1RA use is associated with a statistically significant reduction in risk for myelodysplastic syndromes and myeloproliferative neoplasms compared with metformin.[191] Whether this benefit differs by sex in the context of DNMT3A-predominant CHIP in women remains primarily speculative; the potential consequences of exogenous hormones, such as oral contraceptive pills, alongside GLP-1RA therapy remain an important and

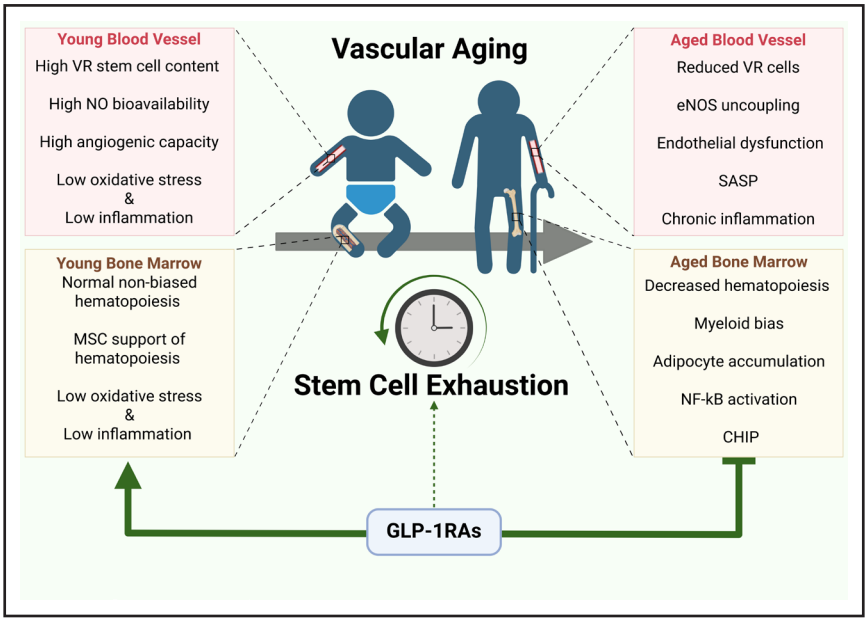

Figure 5. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) help mitigate vascular aging and preserve vascular health. The progression from youthful vasculature to age-associated vascular dysfunction is associated with endothelial damage from oxidative stress-induced eNOS (endothelial NO synthase) uncoupling, senescence-associated secretory phenotype (SASP), and chronic inflammation. Deficits in blood vessel repair result in vascular regenerative (VR) stem cell exhaustion and increased proinflammatory cell production in the inflamed bone marrow driven by myeloid bias, adipocyte accumulation, and clonal hematopoiesis of indeterminant potential (CHIP). GLP-1RAs are proposed to directly and indirectly counteract blood vessel damage and restore the proregenerative vs anti-inflammatory cell production within the bone marrow microenvironment. MSC indicates mesenchymal stem cells; and NF-κB, nuclear factor-κB. Created in BioRender. Dennis, Cole. (2026) https://BioRender.com/y3rghwd.

largely unaddressed question. Nonetheless, convergence of sex-specific HSC aging trajectories, hormonally modulated clonal selection, and estrogen–GLP-1R crosstalk suggests that sex and hormonal status should be explicitly accounted when evaluating GLP-1RA effects on CHIP progression.

CONCLUSIONS

The mechanisms underlying vascular aging are multifactorial and reflect the convergence of metabolic and inflammatory stressors combined with VR cell exhaustion–induced deficits in vessel repair. Defining the relative contribution of opposing damage and repair pathways with the severity of CVD represents a critical step toward rational development of antiaging strategies involving GLP-1RAs. The cumulative impact of vascular aging mechanisms remains incompletely understood and limits the ability to precisely target upstream drivers of CVD. Therefore, therapeutic interventions like GLP-1RAs that demonstrate efficacy in delaying, modulating, or reversing multiple hallmarks of vascular aging remain a practical approach to the mitigation of cardiovascular comorbidities.

Vascular aging is accompanied by an often understudied and progressive decline in vessel regenerative capacity, driven in large part by stem cell exhaustion within VR cell populations. Chronic inflammation and oxidative stress, endothelial dysfunction, and cellular senescence serve as central mechanisms linking VR cell exhaustion to increased CVD risk. Currently, lifestyle modification combined with novel medicines in the GLP-1RA family represent the most scalable approaches to preserve vessel regenerative capacity by restoration of provascular stem cell content (Figure 5). Indeed, GLP-1RAs represent an expanding class of therapeutics that may slow biological vascular aging through complementary mechanisms. Future therapeutic enhancement will likely require an integrated approach that combines GLP-1RA-mediated rejuvenation with targeted regenerative medicine approaches, supported by prior assessment of VR cell depletion using standardized biomarkers, such as high ALDH activity. Collectively, advancement in our understanding of regenerative stem cell depletion and associated overproduction of inflammatory effector cells may offer mechanistic insight into vascular aging and identify actionable targets for the extension of vascular health and longevity.

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