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The Research Progress of Vascular Aging Related Diseases

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Abstract

The aging-related factors of population, environment, physical inactivity and unhealthy diet have emerged as significant contributors to the onset of vascular aging, which poses a crucial risk for various diseases including hypertension, coronary heart disease, heart failure and stroke. The structural, phenotypic, and functional changes in vasculature resulting from aging are critical in the pathogenesis of vascular aging-related diseases. Numerous molecular and cellular phenomena, including oxidative stress, mitochondrial dysfunction, vascular inflammation, cellular senescence, and epigenetic alterations, are closely linked to the pathophysiology of vascular aging. Given the escalating hospitalization rates attributed to vascular aging-related illness, the need for efficacious interventions to counteract the decline in vascular function is becoming increasingly pressing. This review provides an overview of recent developments in vascular aging-related disorders, encompassing cardiovascular diseases, neurodegenerative diseases, chronic kidney diseases, and sarcopenia. Furthermore, a comprehensive examination of the pathogenesis of aging is conducted, and the implementation of intervention strategies (including drug and lifestyle interventions) can effectively mitigate the onset and progression of aging-related ailments, thereby facilitating the achievement of healthy aging and longevity.

Keywords: aging, vascular aging, aging-related diseases

1. Introduction

According to the prediction of the China Working Committee on Aging, the populace of China is expected to experience a substantial acceleration in growth rate between 2021 and 2030, leading to a rise in the proportion of elderly individuals to 25% by 2030. The process of aging results in a complex array of structural and functional microcirculatory impairments, which adversely impact tissue oxygenation, nutrient delivery, and waste removal, consequently exerting a negative influence on the functioning of multiple organs (Harvey, A., A.C. Montezano, & R.M. Touyz, 2015). The functional, structural, and phenotypic alterations of the vascular system due to aging are crucial in the development of age-related dysfunction in various organ systems and are significant contributors to the pathogenesis of a wide range of age-related ailments, including but not limited to cardiovascular diseases (Donato, A.J., D.R. Machin, & L.A., 2018), neurodegenerative diseases (Schirò, G. & C.R. Balistreri, 2022), chronic kidney disease (Dai, L., et al., 2019) and sarcopenia (Jeon, Y.K., et al., 2021).

As individuals age, the vascular system experiences a progression of structural and compositional modifications. The pathological changes that occur in the vasculature due to aging are of paramount importance in the morbidity and mortality of older adults. Elderly individuals exhibit varying degrees of intimal and medial changes in their large and medium-sized arteries, which are referred to as vascular aging or age-related intimal degeneration and sclerosis. These changes may be a result of the adaptive mechanism that maintains normal flow, mechanical stress, and/or wall tension conditions. The aged artery is characterized by endothelial disruption, enhanced vascular smooth muscle cell migration and proliferation, extracellular matrix deposition, elastin

fracture, and matrix calcification/amyloidosis/glycation (Wang, J.C. & M. Bennett, 2012). Morphologically, aging vessels showed increased collagen fiber deposition, increased and disordered elastic fibers, disordered arrangement of smooth muscle cells and intimal thickening; In function, it showed increased stiffness, decreased sensitivity to vasodilator factors, increased sensitivity to vasoconstrictor factors and decreased angiogenesis. Aging vessels provide an environment for the occurrence and development of vascular diseases, and vascular diseases accelerate the process of vascular aging (Zieman, S. & D. Kass, 2004). Hallmarks of vascular aging are arterial stiffening and vascular calcification, which are accompanied by aortic root remodeling. Vascular aging and vascular diseases interact. The pathogenesis of vascular aging includes inflammation, mitochondrial dysfunction, oxidative stress, cellular senescence, protein homeostasis imbalance, nutritional sensory disorders, and impaired synthesis and secretion of vasoactive molecules (Khodabakhsh, P., et al., 2021).

Vascular aging manifests earlier than clinical diseases and constitutes a significant factor for vascular aging-related ailments, which exert a substantial burden on socio-economic and public health systems (Guo, J., et al., 2022). Consequently, comprehending the mechanism of vascular aging, detecting and intervening early in vascular aging-related diseases, particularly in the diagnosis, treatment, and prognosis of cardiovascular and cerebrovascular diseases, represents a novel direction. Subsequently, our focus will center on the pathogenesis of aging-related diseases and intervention strategies.

2. Vascular Aging and Cardiovascular Diseases

2.1 Atherosclerosis

Atherosclerosis, a degenerative, chronic inflammatory disease, is a pathological condition characterized by chronic lipid-induced vessel wall inflammation, leading to arterial remodeling and leukocyte infiltration (Carbone, F., et al., 2016). Recent studies have found that aging is directly associated with chronic low-grade inflammation. Macrophages, neutrophils, natural killer cells, and T and B lymphocytes are the central effector cells of immune system-mediated cellular responses. The etiology of a persistent, low-grade inflammatory condition may be attributed to oxidative stress resulting from immune system activity. The generation of reactive oxygen species (ROS) plays a pivotal role in T cell stimulation within the framework of endothelial metabolism. It is imperative to regulate the activation of these T cells to prevent the onset of severe inflammatory dysregulation, which has been noted in numerous cardiovascular pathologies, such as atherosclerosis (Tylutka, A., et al., 2022).

The maintenance of functional integrity in endothelial cells has been shown to have a significant anti-atherosclerosis and anti-thrombosis effect. The initial stage of atherosclerosis is characterized by vascular endothelial dysfunction. The production of endothelin-1 is increased while nitric oxide production is decreased in senescent endothelial cells, resulting in vascular inflammation, impaired vasodilation, and compromised vascular endothelial integrity. These factors contribute to vascular senescence and the development of atherosclerosis. Furthermore, the capacity of aging vessels to supply oxygen decreases with age, leading to the production of excessive oxygen free radicals that cause lipid peroxidation and damage to the endothelium (Jia, G., et al., 2019). The process of aging is associated with a reduction in the oxygen supply capacity of vessels, which leads to the production of excessive oxygen free radicals. This, in turn, results in lipid peroxidation and damage to endothelial cells. The oxidation of the endothelial cell membrane leads to platelet aggregation and ultimately, atherosclerosis. The development of atherosclerosis is further influenced by elevated levels of adhesion molecules, SASP, and ROS, as well as reduced levels of thrombomodulin in senescent vascular endothelial cells. Increased levels of various adhesion molecules, SASP and ROS, and decreased levels of thrombomodulin in senescent vascular endothelial cells contribute to the development of atherosclerosis. NADPH oxidase (NOX) is one of the significant enzymes producing ROS, and NOX1, NOX2, NOX4, and NOX5 isoforms have been found to induce EC dysfunction, inflammation, and apoptosis in atherosclerosis, hypertension, and diabetes, and endothelium-derived microparticles induce premature EC aging through NOX-mediated mitogen-activated protein kinase and phosphoinositide 3-kinase/protein kinase B in patients with acute coronary syndrome (Iring, A., et al., 2019). Aging of the vascular system can lead to and/or accelerate eNOS uncoupling, and NO derived from eNOS can inhibit vascular inflammation, inhibit neointimal damage and thickening, delay atherosclerosis, and contribute to vascular homeostasis (Ghebre, Y.T., et al., 2016). During aging, NO degradation is accelerated due to increased levels of reactive oxygen species (ROS), mediated in part by chronic inflammation, which forms a vicious cycle leading to severe NO depletion. (Delp, M.D., et al., 2008). The imbalance of NOS expression will reduce bioactive NO and increase the production of OONO and ROS driven by iNOS, which is conducive to vascular oxidative and nitrosating stress, eventually leading to endothelial dysfunction and promoting the occurrence and development of atherosclerosis (Yan, G., et al., 2008). A direct relationship between autophagy and arterial stiffness in vascular smooth muscle cells can be demonstrated using Atg7 knockout mice. Atg7-specific deletion in vascular smooth muscle cells induces accumulation of p62 and accelerates the development of stress-induced cellular senescence. Autophagy has been

shown to be required for the development of senescence in VSMC in an in vitro aging model induced by repeated stimulation. Autophagy is essential to maintain homeostasis in endothelial cells, promoting the development of atherosclerosis.

Furthermore, the process of vascular aging is intricately regulated by a diverse array of epigenetic mechanisms that operate at various levels. These mechanisms are pivotal in the pathogenesis of vascular aging and associated disorders. For instance, in pathological states, hypermethylation of the gene encoding endogenous nitric oxide synthase 3 (eNOS3) impedes gene expression and NO production, thereby contributing to the onset of diseases (Chan, Y., et al., 2004). Additionally, SIRT1 exerts a protective effect against vascular senescence by deacetylating protein H4K16, which in turn inhibits replicative senescence of endothelial cells and enhances their function (Ding, Y.N., et al., 2018). Exosomal non-coding RNAs (ncRNAs) and stem cell-derived exosomal microRNAs (SCEV-miRNAs) in vascular aging, especially exosomal microRNAs of mesenchymal stem cells, have important roles in the development of age-related diseases (Ren, H., et al., 2022). Small extracellular vesicles from mesenchymal stem cells (MSCs) attenuate oxidative stress-induced endothelial cell senescence and stimulate angiogenesis via miR-146a/Src.

The senescence of vascular smooth muscle cells has been found to facilitate the advancement of atherosclerosis while hindering plaque restoration, thus rendering vascular aging as the primary risk factor for atherosclerosis. Vascular aging is known to cause a reduction in the quantity of medial VSMCs, an elevation in collagen levels, and a decline in elastin content, resulting in pathological vascular remodeling that reduces arterial compliance and heightens the likelihood of atherosclerosis (Harvey, A., et al., 2016). The risk factors associated with atherosclerosis are linked to the excessive production of oxygen-free radicals in the vascular wall (Leopold, J.A., 2015). Vascular aging is associated with an upregulation of chemokines, adhesion molecules, and innate immune receptors in vascular smooth muscle cells, as well as an increase in the expression of pro-inflammatory molecules and the uptake of plasma lipoproteins (Song, Y., et al., 2012). This leads to the establishment of a pro-inflammatory milieu that facilitates the migration of inflammatory cells and promotes atherosclerosis (Calvert, P.A., et al., 2011). Notably, the investigation revealed a positive correlation between the plasma levels of pro-inflammatory cytokines and aging in humans, which ultimately results in endothelial dysfunction and atherosclerosis (Bruunsgaard, H., et al., 2000). Meanwhile, elevated ROS levels have been found in senescent VSMCs, whereas Nox4 may be one of the critical regulators of phenotypic alterations in VSMC, leading to loss of stability in atherosclerotic plaques (Xu, S., et al., 2014). In addition, the autophagy pathway has recently received attention from researchers. Research showed that VSMCs senescence was accelerated in the arterial wall of autophagic gene-null mice, and defective autophagy in VSMCs could promote neointima formation and atherosclerosis (Chi, C., et al., 2019).

Taken together, vascular aging promotes the formation of atherosclerotic plaques, and atherosclerosis exacerbates the pathological features of vascular aging. Atherosclerosis may also directly accelerate vascular aging, because vascular repair can promote replicative senescence, and proinflammatory states and reactive oxygen species promote stress-induced premature aging (SIPS).

2.2 Hypertension

Hypertension is a systemic disease characterized by elevated arterial pressure, which functional or organic changes in organs such as the heart, blood vessels, brain and kidneys can accompany. On the one hand, with the increase of age, arterial stiffness caused by vascular aging is the main reason for the increase of systolic blood pressure. On the other hand, hypertension leads to arterial wall damage, which leads to arterial stiffness and accelerates vascular aging, thus forming a vicious circle.

The molecular mechanism of endothelial dysfunction is mainly related to increased oxidative stress and impaired nitric oxide (NO) metabolism. NO is the primary endogenous vasodilator produced by endothelial cells. Under physiological conditions, vascular endothelial cells activate soluble guanylate cyclase (sGC) in vascular smooth muscle by continuously releasing NO, increasing cyclic guanosine monophosphP-mediated relaxation of vascular smooth muscle cells, relaxing vascular smooth muscle, and playing a role in blood pressure regulation. NO can inhibit the adhesion between platelets and endothelial cells, inhibit the proliferation of vascular smooth muscle, maintain its normal mitosis, inhibit the infiltration of inflammatory cells, reduce the production of oxygen free radicals, and accelerate the inactivation of oxygen free radicals (Förstermann, U. & W.C. Sessa, 2012). Endothelium-dependent relaxation (EDD) decreases with aging. Studies have shown that the expression of oxidative stress markers during aging is associated with impaired EDD (Gates, P.E., et al., 2007). With aging, the function of endothelial cells in regulating blood flow, anticoagulation, antithrombosis and anti-cell adhesion gradually decreases. Regenerated endothelial cells will partially lose the ability to release NO, and the accumulation of oxygen free radicals in old blood vessels will shorten the half-life of NO, increase the thickness of the vascular intima, prevent the expansion of NO into smooth muscle, and affect the physiological regulation of NO on vascular tone. It is suggested that delaying the senescence of vascular endothelial cells promotes

vascular health and regulates the hypertension. In addition, it is found in the study of hemodynamics that with the continuous aging of the body, the fluid shear stress of the blood is disturbed, and the disturbed fluid shear stress will stimulate pathological vascular endothelial remodeling leading to the occurrence of arteriosclerosis and hypertension; the blood flow disturbance also further aggravates the aging of endothelial cells, so the blood shear stress may be a key factor in regulating vascular aging.

Vascular smooth muscle cells play an essential role in maintaining vascular tone. Smooth muscle cell aging is one of the crucial causes of hypertension (Morgan, R.G., et al., 2014). With aging, the smooth muscle cells gradually change from a static contractile phenotype to a functional synthetic phenotype, increasing the systolic and diastolic blood pressure of the blood vessels. It has been found that H_2O_2 concentrations in VSMCs from hypertensive patients may be elevated due to activation of the phospholipase D pathway compared to normotensive subjects (Touyz, R.M. & E.L. Schiffrin, 2001). Cardiotrophin-1 may regulate arterial stiffness and VSMC aging as it contributes to vascular fibrosis (López-Andrés, N., et al., 2013). Zhou et al reported that Rho-kinase (ROCK) activity was significantly increased in hypertensive rats model, and inhibition of ROCK decreased arterial stiffness and blood pressure. ROCK may act through the serum response factor (SRF)/cardiac myosin pathway, and inhibition of ROCK decreases SRF/cardiac myosin expression and regulate the phenotypic transformation of VSMCs (Zhou, N., et al., 2017). The above studies suggesting that delaying the aging of vascular smooth muscle cells is beneficial to regulate hypertension (Pacinella, G., A.M. Ciaccio, & A. Tuttolomondo, 2022).

2.3 Heart Failure

Heart failure (HF) is a common cardiovascular syndrome in the elderly. With age, the blood vessels age, the arterial stiffness increases, the production of nitric oxide (NO) decreases, the vasodilation is inhibited, and the myocardial compliance decreases. The reduction of NO will further reduce the activity of protein kinase G (PKG) in myocytes, resulting in the impairment of the dependent vasodilation function, the enhancement of the effects of oxidative stress and angiotensin II, and the increase of left ventricular hypertrophy and stiffness (Semba, R.D., et al., 2015), making the elderly more prone to heart failure. Aging leads to arterial stiffness then the premature return of late systolic reflections, resulting in increased central pulse pressure and ventricular load, decreased ejection fraction, increased oxygen demand, and ultimately heart failure, which in turn leads to further vascular damage (Nichols, W.W. & M.F. O'Rourke, 2009). About 50% of patients with signs and symptoms are heart failure with preserved Ejection Fraction (HFpEF), and HFpEF has increased perivascular fibrosis, severely reduced NO bioavailability, earlier endothelial dysfunction, and higher pro-inflammatory cytokine levels than Heart Failure with reduced Ejection Fraction (HFrEF) (Simmonds, S.J., et al., 2020). Matrix metalloproteinases (MMPs) regulate the composition and function of age-related elastin and collagen in the extracellular matrix, and factors dysregulated during vascular aging, such as NO, IL-1, and TNF-α, trigger the synthesis and activation of matrix metalloproteinases, while MMP-2 and MMP-3 are associated with arteriosclerosis and vascular remodeling, and vascular sclerosis is regarded as one of the most general mechanical statements of heart failure (Simões, G., T. Pereira, & A. Caseiro, 2022). Alterations in the extracellular matrix have been observed in rat models of HFpEF, and MMP-2 levels have been found to be positively correlated with left ventricular ejection fraction (EF) in patients with heart failure (Kobusiak-Prokopowicz, M., et al., 2018). Autophagy also plays an essential role in the aging of endothelial cells and vascular smooth muscle and is involved in the development of various cardiovascular diseases, including heart failure (Sanhueza-Olivares, F., et al., 2022).

3. Vascular Aging and Neurodegenerative Diseases

3.1 Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a progressive decline in cognitive function characterized by the accumulation of amyloid plaques and neurofibrillary tangles in the brain (Jia, L., et al., 2020). Both vascular aging and AD are degenerative changes, and there is increasing evidence of a correlation between vascular aging and AD (Arvanitakis, Z., et al., 2016). Amyloid beta-peptide (Aβ) is the core peptide in the pathophysiology of AD. The typical neuropathological features of AD are Aβ plaques and intra-neuronal aggregates of hyperphosphorylated tau (neurofibrillary tangles) (van der Flier, W.M., et al., 2018). The vascular two-hit hypothesis suggests that microvascular damage precedes Aβ deposition in Alzheimer's disease, which may be the origin of the disease. Vascular injury or vascular dysfunction, such as chronic cerebral hypoperfusion, appears early in AD cognitive decline and changes in traditional biomarkers. Neurovascular unit (NVU) injury leads to decreased cerebral blood flow (CBF), which in turn leads to oxygen and nutrient depletion in the brain parenchyma, oxidative stress in brain cells, increased blood-brain barrier permeability, impaired clearance of neurotoxic metabolites (e.g., Aβ), and vascular endothelial cells produce vasoactive mediators under mechanical or chemical stimulation, resulting in unstable blood flow, further affecting cerebral perfusion, and aggravating the disease process; in addition, endothelial cells have an essential nutritional effect on brain cells and help maintain the health of neurons, glial cells, and oligodendrocytes. It has been found that GLUT1, a

transmembrane protein located in brain capillary endothelial cells responsible for glucose transport, has decreased expression in Alzheimer's disease patients and mouse models. In contrast deficiency of GLUT1 is associated with microvascular injury, blood-brain barrier disruption, and pathological deterioration of Aβ (Eisenmenger, L.B., et al., 2023).

3.2 Cerebral Small Vessel Disease

Cerebral small vessel disease (CSVD) is an age-related cerebrovascular disease mainly affecting small arteries, capillaries, arterioles and venules. CSVD is observed in 25% of strokes worldwide and is the most common pathology of cognitive decline and dementia in older adults (Gao, Y., et al., 2022). Vascular aging causes cerebral hypoperfusion and hypoxia. Yarchoanm et al., in a cohort study of 1000 patients, found that only 47% of the average population had Willis atherosclerosis, while 77% of patients with Alzheimer's disease had Willis atherosclerosis. It shows that there is a significant correlation between intracranial atherosclerosis and Alzheimer's disease (Yarchoan, M., et al., 2012). Elevated expression of beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) present on endothelial cells promotes the accumulation of tight junction protein caveolin1 between small cerebral vessels, resulting in increased lysosomal degradation of other tight junction proteins, leading to vascular injury and disrupting the blood-brain barrier; BACE1 promotes the deposition of β-amyloid resulting in decreased eNOS activity, caveolin1 binds to eNOS, both of which directly affect eNOS function, endothelium-derived nitric oxide production is impaired, vascular regulation is impaired, resulting in unstable cerebral blood flow, so the abnormal increase of endothelial fine BACE1 is a new mechanism in the pathogenesis of cerebral small vessel disease (Zhou, H., et al., 2022).

4. Vascular Aging and Chronic Kidney Disease

Chronic kidney disease (CKD) is a chronic kidney disorder and structural abnormality. Accelerated arteriosclerosis and atherosclerosis are major causes of morbidity and mortality in end-stage kidney disease (ESKD) (de Jong, R.W., et al., 2021). Vascular calcification is a pathological change associated with vascular aging. The calcification of the VSMCs layer is a hallmark of vascular aging. Studies have found that vascular calcification is associated with morbidity and mortality in CKD. DNA damage in aging-related mechanisms may promote VSMCs calcification in CKD (Shanahan, C.M., 2013). Replicating senescent vascular smooth muscle cells cultured in vitro can detect significant DNA damage signature markers, such as γH2AX, 53BP1, and p16. DNA damage could drive the SASP in VSMCs. If DNA cannot be repaired, cells undergo senescence. They secrete cytokines and growth factors, including IL-6, bone morphogenetic protein 2 (BMP-2) and osteoprotegerin (OPG) can act to induce osteogenic differentiation of VSMCs as well as of local and circulating stem cells. The presence of senescent VSMC may not only promote osteogenic differentiation and calcification locally. Still, it may also induce calcification of VSMC at distant sites, triggering osteogenic differentiation of local and systemic stem cells. The VSMCs phenotype is critical in regulating calcification, as contractile VSMCs in standard vessel walls are entirely protected from calcium-induced and phosphate-induced calcification, whereas synthetic and damaged VSMCS present in dialyzed vessels with chronic kidney disease exhibit calcification, matrix vesicle release, apoptosis, and osteogenic differentiation (Shroff, R.C., et al., 2010). Klotho is an anti-aging factor mainly produced by renal tubular epithelial cells with pleiotropic functions. Vascular calcification was reduced in SIRT6-transgenic (SIRT6-tg) mice, whereas vascular smooth muscle cell-specific (VSMC-specific) SIRT6-knockout mice developed severe vascular calcification in CKD; SIRT6 inhibited osteogenic transdifferentiation of VSMCs by regulating runt-related transcription factor 2 (Runx2), thereby preventing the development of vascular calcification. It has been shown that SIRT6 expression is lower in CKD patients compared with healthy people; SIRT6 levels are significantly lower in VC patients, indicating that SIRT6 plays a vital role in vascular calcification and is expected to be a new target for CKD treatment (Li, W., et al., 2022).

5. Vascular Aging and Sarcopenia

Sarcopenia is an age-related decrease in skeletal muscle mass and function associated with physiological, metabolic, and functional disorders (Ryall, J.G., J.D. Schertzer, & G.S. Lynch, 2008). After 50 years, muscle mass has been reported to decline at a rate of 1-2% per year, with muscle strength falling by 1.5% per year between the ages of 50 and 60 years and by 3% per year after that (Chen LK., 2023). Vascular calcification impacts skeletal muscle perfusion, negatively impacts nutrient and oxygen delivery to skeletal muscle, and ultimately accelerates muscle loss and functional decline. Additionally, vascular calcification is negatively correlated with grip strength (Rodríguez, A.J., et al., 2018). Endothelial dysfunction leads to muscle reduction by increasing arterial calcification that restricts blood flow and muscle perfusion, attenuating substrate delivery to skeletal muscle and leading to atrophy and loss of function. Endothelial dysfunction caused by vascular calcification leads to decreased NO production (Taniyama, Y. & K.K. Griendling, 2003), which may impair blood flow to the muscle. With aging, inflammation and oxidative stress-induced microcalcification and hormonal dysregulation decrease capillary microcirculation and nutrient and oxygen delivery, which leads to

reduced muscle protein synthesis rates, increased protein breakdown, mitochondrial dysfunction, and apoptosis (Jaiswal, N., et al., 2015). Muscle capillary perfusion and angiogenesis decrease during aging and are limiting factors in adaptive processes that provide nutrients and oxygen to muscles to induce muscle strength and function. Ochi et al hypothesized that age-related decreases in muscle mass and atherosclerosis share standard pathological processes and interact (Ochi, M., et al., 2010).

It has been found that the association between vascular dysfunction and muscle loss (mass and function) may be related to impaired muscle perfusion through reduced peripheral blood flow, depending on anatomical changes and hemodynamic characteristics of aging circulatory physiology. Blood flow restriction in muscle will limit the supply of vital nutrients and hormones to myocytes, affecting muscle structure and function, and is strongly associated with sarcopenia. In addition, this reduction in nutrient supply may be associated with muscle dysfunction and loss through changes in anabolic muscle resistance (Wilkes, E.A., et al., 2009). The link between sarcopenia and vascular dysfunction may be exacerbated by increased cardiovascular risk factors in older adults, compromising blood circulation and muscle supply, constituting additional factors for impaired muscle function and overall function in older populations.

6. Intervention

6.1 Pharmacological Interventions

Rapamycin is an inhibitor of mTOR, a significant regulator of fundamental cellular processes, such as proliferation, differentiation, growth, protein synthesis, and autophagy. Inhibition of mTOR can prevent platelet-derived growth factor (PDGF) -induced phenotypic changes in vascular smooth muscle cells in vitro and can delay cellular senescence by enhancing autophagy in senescent cells (Saxton, R.A. & D.M. Sabatini, 2017).

Spermidine reduces oxidative damage to endothelial cells, reduces plaque formation, and delays the development of atherosclerotic disease. Spermidine attenuates vascular calcification in CKD by up-regulating SIRT1 and inhibiting ER stress (Liu, X., et al., 2021). The natural compound spermidine can reduce oxidative stress, arteriosclerosis, and collagen deposition, and increase the bioavailability of NO in aged mice (LaRocca, T.J., et al., 2013). Spermidine enhances autophagy and mitosis. However, spermidine may mediate its effects through multiple pathways, such as inhibiting inflammatory pathways or reducing oxidative stress (Madeo, F., et al., 2018).

Resveratrol has similar biological activity to spermidine, and resveratrol can reduce vascular calcification and aging by regulating SIRT1. Resveratrol can activate genes encoding cleavage factors in cells, prolong telomeres in senescent cells, restore proliferation, protect and maintain vascular endothelial integrity, enhance endothelial cell resistance to platelet aggregation and leukocyte adhesion, and play a protective role in cardiovascular disease (Kim, E.N., et al., 2018).

Supplementation with NAD^+ is a different approach. Nicotinamide nucleoside, another NAD^+ precursor, increases SIRT-1 activity and activates autophagy, reverses age-related endothelial, mitochondrial dysfunction, and oxidative stress, and can delay age-related vascular complications by improving mitochondrial function (Diguet, N., et al., 2018).

Chloroquine has been shown in animal models to reduce atherosclerosis via a p53-dependent ATM signaling pathway (Razani, B., C. Feng, & C.F. Semenkovich, 2010).

Peroxisome proliferator-activated receptor agonist pioglitazone increases telomerase activity, TRF-2 expression, and Akt phosphorylation, and decreases expression of aging markers p16, cell cycle checkpoint kinase 2, and p53 (Werner, C., et al., 2011).

Antioxidants, statins, and angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers and other drugs may delay premature aging through reactive oxygen species changes and oxidative DNA damage.

6.2 Lifestyle Interventions

Caloric restriction (CR) reduces the caloric intake without malnutrition and is an effective option for delaying vascular aging by improving mitochondrial function (Ungvari, Z., et al., 2008). CR acts as an autophagy promoter and has anti-inflammatory and mitochondrial protective effects.

Exercise can restore NO levels, reduce oxidative stress and inflammation, improve vascular function, and delay vascular aging. Studies have shown that aerobic exercise can reduce arterial stiffness and restore vascular endothelial function in sedentary people over 65; exercise can also reduce risk factors associated with aging and cardiovascular diseases such as hypertension and obesity (Santos-Parker, J.R., T.J. LaRocca, & D.R. Seals, 2014).

7. Conclusion

Our emerging understanding of vascular aging processes enables identifying novel targets for therapeutic

intervention to reverse the deleterious consequences of vascular aging and improve cardiovascular and cerebrovascular health in older adults. Interventions to suppress or delay it may have the potential to facilitate or retard age-associated arterial diseases. Our new understanding of the vascular aging process allows us to identify novel targets for therapeutic intervention to reverse the harmful consequences of vascular aging and improve cardiovascular and cerebrovascular health in older adults. Interventions that inhibit or delay them may potentially facilitate or delay age-related arterial disease.

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Declaration of Competing Interest

There is no conflict of interest concerning this manuscript.

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