



Review Article

Vascular Aging and Diseases: Molecular Mechanisms and Influences

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ABSTRACT

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Vascular aging plays an important role in the mortality of the elderly, but vascular aging can be dependent on other factors such as diseases. Various diseases such as Alzheimer, diabetes, thalassemia, and other diseases affect the mechanisms of vascular aging. It will harm the recovery process of these patients. There are methods for measuring vascular aging such as instrumental measurements and molecular methods. The best way to measure vascular aging is a combination of methods to determine the mechanism and cause of vascular aging. In this review article, we first summarize the various mechanisms of vascular aging and then discuss the effect of different disease on vascular aging.

Keywords: Vascular; Aging; Disease; Arteries

Introduction

It is believed that the age of the arteries determines the age of the person. This idea originated from an epidemiologic study that shows that vascular diseases are closely related to age (1, 2). In vascular aging, vessels become thicker and firmer, thus the ability to reduce the shape and function of the vessel in changing tissue demand (2). In older healthy people, these changes are spread by lumen dilation, increased arterial stiffness, endothelial dysfunction, and thickening of the intima (3). Of all the chronic diseases, cardiovascular disease remains the leading cause of complications and mortality in the elderly, so understanding the basic mechanism of vascular aging is essential. Although aging changes in vascular function are considered in a set of diseases (4), changes in vascular function can be slow that accelerate this point. Therefore, it is important to understand how aging and other pathophysiological conditions affect the interaction between the different diseases and the arterial network (5). In this review, the study describes the relationship between various diseases and vascular aging are briefly described.

Cellular and molecular mechanism in vascular aging

Developing an accurate understanding of cellular and molecular mechanisms is necessary to develop new treatment methods to prevent vascular aging as well as age-dependent vascular complications that

occur due to old age. The pathophysiological roles of aging depend on cellular and molecular mechanisms such as mitochondrial dysfunction, oxidative stress, molecular stress resistance, genomic instability, mild chronic inflammation, cellular aging, loss of protein homeostasis, epigenetic changes, complications in nutrient sensing system regulation, and stem cell dysfunction (6). The pathogenesis of macro vascular and micro vascular age-related diseases must be investigated through basic studies before expanding the study to vaster dimensions (6, 7). The following has paid an attempt to present a comprehensive and unified study of cellular and molecular mechanisms involved in vascular aging (cellular and molecular mechanism) (3, 4, 6, 7, 4). (Table 1)

How can determine vascular aging?

In recent years, many manufacturers of modern devices that have directly or indirectly estimated vascular stiffness have developed models to calculate vascular age based on stiffness estimation. Standard gold methods such as Complior and SphygmoCor have been expensive to directly assess vascular stiffness, although they are becoming less common over time (8). Other devices have been marketed by various indirect measurement methods (9). Further attention to arterial stiffness and vascular aging, not only among physicians but also among patients has led to the

creation of different methods for calculating the age of arteries based on algorithms that are the underlying factors of age, sex, index (10). Body mass, blood pressure, and smoking are measured by a certain

measure of aortic stiffness or central hemodynamics. Finally, a person's vascular age can be indicated concerning the age of at least one approximation (11, 12).

Table 1. Cellular and molecular mechanism

Mechanism	Factors involved	Mechanism	Treatment
Molecular and cellular mechanisms of vascular aging	NO ROS-MMP	Enhanced vasoconstriction and dysregulation of tissue perfusion the development of cerebral micro hemorrhages	Drugs with effect on preventing large artery stiffening, cerebral micro hemorrhages, and aortic aneurysms
Role of oxidative and nitrate stress	ROS ATP Glutathione	The decline in cellular glutathione content, down-regulation of p66Shc, and/or impaired Nrf2-mediated antioxidant defense responses	Treatment with the mitochondrial antioxidant MitoQ60, resveratrol The potent mitochondria-targeted antioxidative tetrapeptide SS-31 Inhibition of NF-κB
Vascular inflammation in aging	IL-6, IL-1β, TNFα adhesion molecules iNOS	impairs cellular metabolism, increases apoptosis, and contributes to the pathogenesis of vascular diseases	
Maladaptation to molecular stresses	ROS	activation of Nrf2-driven antioxidant defense pathways	Pharmacological activation of Nrf2 anti-aging vasoprotective Pharmacological interventions that stimulate autophagy (e.g. trehalose or
Loss of proteostasis	Chaperones Ubiquitin-proteasome lysosome-	mitochondrial dysfunction and the resulting decline in cellular ATP content likely also impairs the function of ATP-dependent chaperones	
Role of genomic instability	Factors in genomic instability	increased vascular stiffness, increased presence of senescence cells, and hypertension	DNA repair system
Cellular senescence	Endogenous and exogenous stressors	pro-inflammatory secretome changes	Pharmacological treatment with senolytic agents
Increased apoptosis and necroptosis	NO TNFα Mitochondrial oxidative stress	Increased apoptotic cell death likely contributes to aging-induced microvascular rarefaction and the pathogenesis of atherosclerotic vascular diseases and aneurysm formation	Inhibition of necroptosis either genetically, pharmacologically, or by dietary means
Epigenetic alterations	Epigenetic factors	Alterations in DNA methylation patterns, posttranslational modification of histones, microRNAs, long noncoding RNAs, and chromatin remodeling	DNA methyltransferases, histone acetylases and deacetylases, methylases, and demethylases
Deregulated nutrient-sensing pathways	Cellular energy sensing	Growth signals, including mTOR (mechanistic/mammalian target of rapamycin) signaling, adenosine monophosphate protein kinase (AMPK), and sirtuin	mTOR inhibition promoting endothelium-mediated, NO-dependent vasodilation
Renin-angiotensin system	Angiotensin converting enzyme (ACE)	Promotes aging-like changes in the vascular phenotype by vascular smooth muscle cells	ACE inhibitors
ECM remodeling	ECM	ECM components declines alter vascular mechano-transduction	Reconstruction of extracellular matrix
Pro-gerontic and anti-gerontic circulating factors	Vasoprotective endocrine factors	The decline in circulating levels of GH, IGF-1 Regulate multiple aspects of endothelium-dependent vasodilation Autoregulation of blood flow Vascular structural remodeling	Caloric restriction

The connection between disease and vascular aging

High blood pressure and aging have similar mechanisms of vascular function. Structural and functional changes in small blood vessels occur during normal, accelerated aging, possibly due to high blood pressure (13, 14). Mutual discussion may take place between large and small changes in the arteries, interacting with the transmission of pressure and reflection waves, exaggerating heart, brain, and kidney damage, and ultimately leading to cardiovascular and renal complications. Vascular aging, defined as age-related changes in blood vessels, depends on its blood supply for structural and functional integration. As a result, this effect is not limited to one organ and can be involved in wide-ranging tissues and diseases (12).

Vascular aging in diseases associated with high blood pressure

Blood outflow from the aorta results in an onward pressure in arteries (15-17). The pressure wave in each arterial wall cessation moves back toward the heart due to geometric symmetry and vascular elasticity (18). Young people's cardiovascular systems have been designed to maximize the interaction between the aorta and the reflected wave and, subsequently, increase coronary artery perfusion without increasing the systolic load young people's cardiovascular systems (19). Increased reflected waves from the environment and aorta stiffness are the main hemodynamic mechanisms in charge of blood pressure increase in central arteries (20). Artery stiffness disables the vessels to absorb bloodstream energy. High central arterial blood pressure results in the development of left ventricular hypertrophy that, in turn, leads to ventricular relaxation impairment that brings about diastolic heart failure (21). High central arterial blood pressure and arterial stiffness could also result in coronary artery perfusion changes that lead to infarction and myocardial ischemia. High central arterial blood damages the structure of collagen and elastin in artery walls that brings about early artery aging (22). Besides, arterial stiffness and, subsequently, decreased shear stress in vessels due to collagen and elastin disruption lead to lower nitric oxide production and vasoconstrictor limitation that ultimately results in vascular aging. Diseases associated with high blood pressure such as stroke, obesity, and Lupus Erythematosus can leave the same impact on vascular age (23, 24).

Vascular aging in inflammatory diseases

Studies show that chronic, low-grade inflammation is characteristic of the aging process (25). Activation of inflammatory processes plays a major role in a wide range of vascular damage, from vascular dysfunction and organ dysfunction such as Alzheimer's disease (26). Previous studies have shown that there is a proinflammatory change in the gene

expression profile of vascular smooth muscle of vascular endothelial cells (27). Induction of inflammatory cytokines such as interleukin-6, IL-1 β , and TNF- α , adhesion molecules, inducible iNOS synthase and other proinflammatory mediators are involved (28). The proinflammatory environment caused by a number of diseases, such as Alzheimer's disease in the vascular wall, impairs vascular function and disrupts cellular metabolism, thereby increasing apoptosis and contributing to the pathogenesis of vascular disease (29).

Vascular aging in diseases associated with sex hormones

All around the world, cardiovascular diseases are less common among women until they become middle-aged, but the prevalence of such diseases are similar across both genders in their sixth and seventh decade of life (30). The low prevalence of cardiovascular diseases in females before menopause is associated with estradiol a sex hormone that decreases during menopause. The impact of sex hormones on adults' vascular aging might help to explain some reasons for the gender-dependent differences in cardiovascular diseases associated with age (31). Studies have indicated that testosterone and estradiol dysfunction balance endothelial function that is a vascular aging biomarker (32, 35). The vascular endothelium is a layer of cells that acts as a protective layer for maintaining the vessel wall integrity (36). One of the significant features of age-dependent endothelial dysfunction is endothelial-dependent vasodilation decline (37). Gender-related differences have been reported in the extent of endothelial-dependent vasodilation decrease. Endothelial-dependent artery dilatation is maintained until the fourth decade of life in men, while it lasts for one more decade (i.e. the fifth decade of life) in women; but after their fifth life decade, it decreases more rapidly in women compared to men (38). No age-related impairing impact has been observed on the function of vascular smooth muscle cells; however, observations indicated endothelial dysfunction in postmenopausal and premenopausal men and women. Since the age in which women indicate endothelial dysfunction corresponds to the common menopausal age, it has been revealed that estrogen protects endothelial cells in premenopausal women and is later eliminated due to menopause. Endothelial function declines gradually throughout the stages of menopause. Contrary to women whose endogenous estradiol level undergoes abrupt decline due to menopause, a corresponding testosterone decline is not observed in men; still, the level of complete and available testosterone declines with age (39-42). Population-oriented studies focused on men with cardiovascular disease risk factors have indicated that low serum testosterone is associated with reduced endothelial function; however, testosterone deficiency's role in age-related endothelial function decline is less evident in the absence of disease (43, 35).

Hutchinson-Gilford Progeria Syndrome

Hutchinson-Gilford Progeria Syndrome (HGPS) is a very rare scattered genetic disease that includes an inappropriate combination of the LMNA gene (44). Cardiovascular disease is the basis of significant complications and mortality (45). Animal and human studies have supported double ultrasound as a useful tool for diagnosing tissue pathology with a pre-regulated extracellular matrix by increasing echogenicity. Further, in the laboratory, it is studied during the echogenic association with tissue pathology in rats. However, arterial intima-media density is associated with cardiovascular risk and echogenicity of carotid plaque in older adults, and a significant amount of adventitial abnormalities have been observed. HGPS provides a unique opportunity to isolate a subset of factors affecting cardiovascular disease in the elderly population (46). Molecular mechanisms that lead to vascular dysfunction in HGPS may also play a role in vascular aging. The phenotypic and vascular changes observed in HGPS are dramatically similar to those seen with aging, including increased aging, increased altered mechanical transmission, and stem cell burnout (47).

Diabetes

Diabetes and the aging process increase the risk of cardiovascular disease (CVD). Diabetes is a major risk factor for CVD (48). Like aging, diabetes affects vascular function. Vascular endothelial vascular dysfunction is a recurrent finding in the arteries of diabetic animals and patients in both intracranial and extracorporeal conditions (49). Besides, endothelial dysfunction predicts CVD in diabetic patients. Even in young diabetic patients, a decrease in urothelial, flow-dependent, and dilatation leads to early atherosclerotic changes. Endothelial dysfunction appears to be the early stage in the development of vascular complications in patients with type 1 or type 2 diabetes (50). Significantly, some comparative studies have shown more endothelial dysfunction in people with type 2 diabetes. This finding could be related to the destructive effects of insulin resistance on endothelial function. Hyperglycemia and insulin resistance can simultaneously jeopardize endothelial function in type 2 diabetic patients (51-54). Insulin resistance, which is estimated by evaluating the homeostasis model, is independently associated with the next symptomatic vascular disease in the general option. Although endothelial vasodilation is a feature of diabetic vascular function, Arterial stiffness is more common in diabetics, especially in the elderly. Besides, pulse wave velocity has been increased in type 2 diabetic patients. This fact due to arterial stiffness is associated with diabetes as another symptom of vascular function. The pulse rate in diabetic patients increases with vascular aging (55).

Systemic Lupus Erythematosus

The potent predictor of cardiovascular events is the same as that seen in patients with Systemic Lupus Erythematosus (SLE). SLE has a detrimental effect on vascular aging due to high blood pressure. This effect of SLE is most often associated with chronic inflammation. Numerous studies have evaluated arterial stiffness in patients with SLE (56). Aortic stiffness is one of the important indicators of early vascular aging (EVA). EVA and subclinical atherosclerosis are measured by measuring aortic pulse wave velocity and intima-media thickness of carotid. Patients with SLE often have atherosclerotic complications. The role of LDL composition in strengthening premature vascular aging in SLE patients, increasing plasma L5 levels, not the overall concentration of LDL, it may exacerbate premature vascular aging in SLE patients and lead to premature atherosclerosis (57-59).

Chronic kidney disease

Chronic Kidney Disease (CKD) is a clinical model of premature aging associated with cardiovascular disease, persistent uremic inflammation, loss of osteoporosis, and weakness. EVA accelerated by vascular calcification is a characteristic of aging as well as a strong predictor of the complications and mortality of artery vascular in patients with chronic kidney disease (60). Damage-induced cellular aging may be largely related to such pathological conditions of premature aging. Evidence now suggests that signaling related to nuclear factor 2 and red blood cells 2 (NRF2) and vitamin K plays an important role in counteracting oxidative stress, DNA damage, aging, and inflammation, thus activating NRF2 and Vitamin K supplementation may provide a new therapeutic goal to prevent premature vascular aging in patients with chronic renal inflammation (61, 62).

Thalassemia major

Patients with thalassemia major show an increase in the prevalence of vascular complications. The symptoms of this disease are caused by inflammatory reactions that cause vascular damage and atherogenesis. Low-level inflammation and a prothrombotic condition may neutralize atrophic protective mechanisms, accelerate vascular aging, and prove the relatively high prevalence of vascular complications in these patients (63, 64).

Alzheimer's disease

Vascular aging may be exacerbated by Alzheimer's pathology, thus contributed to vascular dysfunction in Alzheimer. These vascular changes include functional and structural changes throughout the brain system, from the hardening of the great arteries to small vascular disease (65, 66). These changes, along with the damaging effects of the amyloid-beta, reduce brain perfusion and impair the ability of cerebral circulation. Also, there is evidence that vascular changes outside the brain may be involved in Alzheimer (67). Systemic hypertension and

atherosclerosis, along with the hardening of the large arteries and prognosis in Alzheimer, may cause damage to cerebral arteries. Plasma amyloid beta levels increase during clinical Alzheimer and decrease as the disease progresses. Elevated plasma A β levels in the early stages of Alzheimer may affect the cardiovascular system on a large scale and potentially affect the course of the disease and its clinical manifestations (68).

Stroke

Survivors of ischemic stroke, even at a young age, have a risk for cardiovascular disease and mortality, indicating that premature arterial aging is common in these patients after a stroke (69). Eighteen percent of patients recovering from a stroke have shown vascular disorders in a prospective study. These symptoms are especially related to high blood pressure. Adjustable cardiovascular risk factors in patients with young and middle-aged stroke emphasize that by implementing effective secondary prevention, there is ample potential to improve prognosis in these patients (70).

Obese

In obese patients with different reasons such as gene-dependent or reduction in circulating growth hormone and IGF-1 insulin growth level, it is significantly effective in vascular dysfunction and vascular aging associated with impaired cellular oxidative stress resistance pathways (71). Obesity in the elderly is accompanied by an alarming rate, and there is evidence that older people are more vulnerable to the devastating cardiovascular effects of obesity than young people. A high-fat diet led to an increase in similar relative weight and increased body fat in mice. Mice fed with a high-fat showed a relative increase in blood glucose levels, low insulin, and glucose tolerance compared with control mice (41). Analysis of serum cytokine levels showed that chronic IGF-1 deficiency exacerbates inflammation. GH / IGF-1 deficiency also impairs endothelial function due to a high-fat diet, oxidative stress, and inflammatory markers (tumor necrosis factor- α , ICAM-1) in aortic mice that can lead to aging in arteries. The results in the past studies, based on available clinical and empirical evidence, show that GH / IGF-1 deficiency makes the cardiovascular system more vulnerable to the harmful effects of obesity and can accelerate vascular aging (72).

Conclusion

Vascular aging is a process that can occur at any age and under different physiological conditions. One of the most important of these conditions is the occurrence of various diseases in the occurrence of vascular aging. Vascular aging can improve the condition and even death of various diseases. In particular, it can affect cardiovascular disease. The effects of the disease can be greatly reduced, by examining the predisposing factors for vascular aging in these patients.

Conflict of interest

None

References

1. Rizzoni D, Rizzoni M, Nardin M, Chiarini G, Agabiti-Rosei C, Aggiusti C, et al. Vascular aging and disease of the small vessels. *High Blood Pressure & Cardiovascular Prevention* 2019; 1-7.
2. Ungvari Z, Tarantini S, Donato AJ, Galvan V, Csizsar A. Mechanisms of vascular aging. *Circulation Research*. 2018; 123: 849-67.
3. Mistriotis P, Andreadis ST. Vascular aging: molecular mechanisms and potential treatments for vascular rejuvenation. *Ageing Research Reviews*. 2017; 37: 94-116.
4. Buford L, Kaiser R, Petronic-Rosic V. Vascular diseases in the mature patient. *Clinics in Dermatology*. 2018; 36(2): 239-48.
5. Guzik TJ, Touyz RM. Oxidative stress, inflammation, and vascular aging in hypertension. *Hypertension*. 2017; 70: 660-7.
6. Ghebre YT, Yakubov E, Wong WT, Krishnamurthy P, Sayed N, Sikora AG, et al. Vascular aging: implications for cardiovascular disease and therapy. *Translational Medicine (Sunnyvale, Calif)*. 2016; 6(4): 1-20.
7. Alfonso MR, Armentano RL, Cymberknop LJ, Ghigo AR, Pessana FM, Legnani WE. A novel interpretation for arterial pulse pressure amplification in health and disease. *Journal of Healthcare Engineering*. 2018; 2018: 1-10.
8. Davies JM, Bailey MA, Griffin KJ, Scott DJ. Pulse wave velocity and the non-invasive methods used to assess it: Complior, SphygmoCor, Arteriograph and Vicorder. *Vascular*. 2012; 20(6): 342-9.
9. Wernick MB, Höpfner RM, Francey T, Howard J. Comparison of arterial blood pressure measurements and hypertension scores obtained by use of three indirect measurement devices in hospitalized dogs. *Journal of the American Veterinary Medical Association*. 2012; 240(8): 962-8.
10. Asmar R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac AM, et al. Assessment of arterial distensibility by automatic pulse wave velocity measurement: validation and clinical application studies. *Hypertension*. 1995; 26(3): 485-90.
11. Nowak KL, Rossman MJ, Chonchol M, Seals DR. Strategies for achieving healthy vascular aging. *Hypertension*. 2018; 71(3): 389-402.
12. Laurent S. How to assess vascular aging. *Journal of Hypertension Research*. 2018; 4: 39-52.
13. Bruno RM, Duranti E, Ippolito C, Segnani C, Bernardini N, Candio GD, et al. Different impact of essential hypertension on structural and functional age-related vascular changes. *Hypertension*. 2016; 69(1): 1-9.
14. Moriya J, Minamino T. Angiogenesis, cancer, and vascular aging. *Frontiers in Cardiovascular Medicine*. 2017; 4: 1-7.

15. Gordon LB, Brown WT, Collins FS. Hutchinson-gilford progeria syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 2019.
16. Hamczyk MR, Del Campo L, Andrés V. Aging in the cardiovascular system: lessons from hutchinson-gilford progeria syndrome. *Annual Review of Physiology*. 2018; 80: 27-48.
17. Mahmud A, Feely J. Effects of passive smoking on blood pressure and aortic pressure waveform in healthy young adults—influence of gender. *British Journal of Clinical Pharmacology*. 2004; 57(1): 37-43.
18. Safar ME, Boudier HS. Vascular development, pulse pressure, and the mechanisms of hypertension. *Hypertension*. 2005; 46(1): 205-9.
19. Eikendal AL, den Ruijter HM, Haaring C, Saam T, Geest R, Westenberg JM, et al. Sex, body mass index, and blood pressure are related to aortic characteristics in healthy, young adults using magnetic resonance vessel wall imaging: the AMBITION study. *Magnetic Resonance Materials in Physics, Biology and Medicine*. 2018; 31(1): 173-182.
20. Furst B. Arterial Pulse. In: *The Heart and Circulation*. Springer: Cham; 2020. p.263-86.
21. Kotsis V, Stabouli S, Karafillis I, Peter N. Early vascular aging and the role of central blood pressure. *Journal of Hypertension*. 2011; 29(10): 1847-53
22. Zekavat SM, Aragam K, Emdin C, Khera A, Klarin D, Zhao H, et al. Genetic association of finger photoplethysmography-derived arterial stiffness index with blood pressure and coronary artery disease. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2019; 39(6): 1253-61.
23. Golshiri K, Ataabadi EA, Rubio-Beltran E, Duthiel S, Yao W, Snyder GL, et al. Selective Phosphodiesterase 1 Inhibition Ameliorates Vascular Function, Reduces Inflammatory Response, and Lowers Blood Pressure in Aging Animals. *Journal of Pharmacology and Experimental Therapeutics*. 2021; 378(2): 173-83.
24. Ziemann SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2005; 25(5): 932-43.
25. Selzer F, Sutton-Tyrrell K, Fitzgerald SG, Pratt J, Tracy R, Kuller LH, et al. Comparison of risk factors for vascular disease in the carotid artery and aorta in women with systemic lupus erythematosus. *Arthritis & Rheumatism*. 2004; 50(1): 151-9.
26. Willmot M, Leonardi-Be J, Bath PM. High blood pressure in acute stroke and subsequent outcome: a systematic review. *Hypertension*. 2004; 43(1): 18-24.
27. Calder PC, Bosco N, Bourdet-Sicard R, Capuron L, Delzenne N, Franceschi C, et al. Health relevance of the modification of low grade inflammation in ageing (inflammageing) and the role of nutrition. *Ageing Research Reviews*. 2017; 40: 95-119.
28. Luca M, Luca A, Calandra C. The role of oxidative damage in the pathogenesis and progression of Alzheimer's disease and vascular dementia. *Oxidative Medicine and Cellular Longevity*. 2015; 2015(6): 1-8.
29. Csiszar A, Sosnowska D, Wang M, Lakatta EG, Sonntag WE, Ungvari Z. Age-associated proinflammatory secretory phenotype in vascular smooth muscle cells from the non-human primate *Macaca mulatta*: reversal by resveratrol treatment. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences*. 2012; 67(8): 811-820.
30. Ungvari Z, Csiszar A, Kaley G. Vascular inflammation in aging. *Herz*. 2004; 29(8): 733-40.
31. Mattson MP. Roles of the lipid peroxidation product 4-hydroxynonenal in obesity, the metabolic syndrome, and associated vascular and neurodegenerative disorders. *Experimental Gerontology*. 2009; 44(10): 625-33.
32. Strand BH, Grøholt E-K, Steingrimsdóttir OA, Blakely T, Graff-Iversen S, Næss Ø, et al. Educational inequalities in mortality over four decades in Norway: prospective study of middle aged men and women followed for cause specific mortality, 1960-2000. *British Medical Journal*. 2010; 340: 1-10.
33. Sader MA, McCredie RJ, Griffiths KA, Wishart SM, Handelsman DJ, Celmajer DS. Oestradiol improves arterial endothelial function in healthy men receiving testosterone. *Clinical Endocrinology*. 2001; 54(2): 175-81.
34. Moreau KL, Hildreth KL, Klawitter J, Blatchford P, Kohrt WM. Decline in endothelial function across the menopause transition in healthy women is related to decreased estradiol and increased oxidative stress. *GeroScience*. 2020; 42(6): 1699-714
35. Aversa A, Bruzziches R, Francomano D, Natali M, Gareri P, Spera G. Endothelial dysfunction and erectile dysfunction in the aging man. *International Journal of Urology*. 2009; 17(1): 38-47.
36. Buijs J, Musters M, Verrips T, Post JA, Braam B, Riel NV. Mathematical modeling of vascular endothelial layer maintenance: the role of endothelial cell division, progenitor cell homing, and telomere shortening. *American Journal of Physiology-Heart and Circulatory Physiology*. 2004; 287(6): 2651-8.
37. Levenson J, Pessana F, Garipey J, Armentano R, Simon A. Gender differences in wall shear-mediated brachial artery vasoconstriction and vasodilation. *Journal of the American College of Cardiology*. 2001; 38(6): 1668-74.
38. Sakabe K, Fukuda N, Fukuda T, Wakayama K, Nada T, Morishita S, et al. Gender differences in short-term effects of atorvastatin on lipid profile, fibrinolytic parameters, and endothelial function. *Nutrition, Metabolism and Cardiovascular Diseases*. 2008; 18(3): 182-8.
39. Moreau KL. Modulatory influence of sex hormones on vascular aging. *American Journal of Physiology-Heart and Circulatory Physiology*. 2019; 316(3): 522-6.
40. Moreau KL. Intersection between gonadal function and vascular aging in women. *Journal of Applied Physiology*. 2018; 125(6): 1881-7.
41. Moreau KL, Hildreth KL. Vascular aging across the menopause transition in healthy women. *Advances in Vascular Medicine*. 2014; 2014: 1-25.
42. Somani YB, Pawelczyk JA, De Souza MJ, Kris-Etherton P, Proctor D. Aging women and their

- endothelium: Probing the relative role of estrogen on vasodilator function. *American Journal of Physiology-Heart and Circulatory Physiology*. 2019; 317(2): 395-404.
43. Nyberg M, Seidelin K, Andersen TR, Overby NN, Hellsten Y, Bangsbo J. Biomarkers of vascular function in premenopausal and recent postmenopausal women of similar age: effect of exercise training. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*. 2014; 306(7): 510-7.
44. Yao F, Zhang Y, Huang Y, Ma H, Dong Y, Deng L, et al. Subclinical endothelial dysfunction and low-grade inflammation play roles in the development of erectile dysfunction in young men with low risk of coronary heart disease. *Heart*. 2011; 97(3): 653-659.
45. Wang C, Jackson G, Jones TH, Matsumoto A, Nehra A, Perelman M, et al. Low testosterone associated with obesity and the metabolic syndrome contributes to sexual dysfunction and cardiovascular disease risk in men with type 2 diabetes. *Diabetes Care*. 2011; 34(7): 1669-75.
46. Bar DZ, Arlt MF, Brazier JF, Norris W, Campbell SE, Chines P, et al. A novel somatic mutation achieves partial rescue in a child with hutchinson-gilford progeria syndrome. *Journal of Medical Genetics*. 2017; 54(3): 212-6.
47. Brassard JA, Fekete N, Garnier A, Hoesli CA. Hutchinson–gilford progeria syndrome as a model for vascular aging. *Biogerontology*. 2016; 17: 129-45.
48. Petrie JR and Salt IP. Diabetes and vascular disease. In: Touyz RM, Delles CH. *Textbook of Vascular Medicine*. Springer; 2019. p.429-37.
49. Kumar A, Patel DR, Wolski KE, Lincoff AM, Kashyap SR, Ruotolo G, et al. Baseline fasting plasma insulin levels predict risk for major adverse cardiovascular events among patients with diabetes and high-risk vascular disease: Insights from the ACCELERATE trial. *Diabetes and Vascular Disease Research*. 2019; 16(2): 171-7.
50. Groeneveld ON, van den Berg E, Johansen OE, Schnaidt S, Hermansson K, Zinman B, et al. Oxidative stress and endothelial dysfunction are associated with reduced cognition in type 2 diabetes. *Diabetes and Vascular Disease Research*. 2019; 16(6): 577-81.
51. Maamoun H, Abdelsalam SS, Zeidan A, Korashy HM, Agouni A. Endoplasmic reticulum stress: A critical molecular driver of endothelial dysfunction and cardiovascular disturbances associated with diabetes. *International Journal of Molecular Sciences*. 2019; 20(7): 1-21.
52. Maruhashi T, Higashi Y. Pathophysiological association between diabetes mellitus and endothelial dysfunction. *Antioxidants*. 2021; 10(8): 1306.
53. Toya T, Ahmad A, Attia Z, Cohen-Shelly M, OzcanI, Noseworthy PA, et al. Vascular aging detected by peripheral endothelial dysfunction is associated with ECG-derived physiological aging. *Journal of the American Heart Association*. 2021; 10(3): 018656.
54. Halim M, Halim A. The effects of inflammation, aging and oxidative stress on the pathogenesis of diabetes mellitus (type 2 diabetes). *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*. 2019; 13(2): 1165-72.
55. Chan HC, Chan HC, Liang CJ, Lee HC, Su H, Lee AS, et al. Role of low-density lipoprotein in early vascular aging associated with systemic lupus erythematosus. *Circulation*. 2019; 140(1).
56. Perna M, Roman MJ, Alpert DR, Crow M, Lockshin M, Sammaritano LR, et al. Relationship of asymmetric dimethylarginine and homocysteine to vascular aging in systemic lupus erythematosus patients. *Arthritis & Rheumatism*. 2010; 62(6): 1718-22.
57. Stortz M, Triantafyllias K, Schwarting A, Menke J. Vascular stiffness: influencing factors on carotid-femoral pulse wave velocity in systemic lupus erythematosus. *Clinical and Experimental Rheumatology*. 2020; 38(1): 74-81.
58. Dai L, Schurgers LJ, Shiels PG, Stenvinkel P. Early vascular ageing in chronic kidney disease: impact of inflammation, vitamin K, senescence and genomic damage. *Nephrology Dialysis Transplantation*. 2020; 35(2): 31-7.
59. Hobson S, Arefin S, Kublickiene K, Shiels P, Stenvinkel P. Senescent cells in early vascular ageing and bone disease of chronic kidney disease—a novel target for treatment. *Toxins*. 2019; 11(2): 1-13.
60. Singh MM, Kumar R, Tewari S, Agarwal S. No association of genetic markers with carotid intimal medial thickness in β -thalassemia major patients. *Journal of Pediatric Genetics*. 2018; 7(1): 19-22.
61. Adly AAM, ElSherif NHK, Ismail EAR, Ibrahim YA, Niazi G, Elmetwally SH. Ischemia-modified albumin as a marker of vascular dysfunction and subclinical atherosclerosis in β -thalassemia major. *Redox Report*. 2017; 22(6): 430-8.
62. Sweeney MD, Montagne A, Sagare AP, Nation D, Schneider LS, Chui HC, et al. Vascular dysfunction—the disregarded partner of Alzheimer's disease. *Alzheimer's & Dementia*. 2019; 15(1): 158-67.
63. Liesz A. The vascular side of Alzheimer's disease. *Science*. 2019; 365(6450): 223-4.
64. Cortes-Canteli M, Iadecola C. Alzheimer's Disease and vascular aging: JACC focus seminar. *Journal of the American College of Cardiology*. 2020; 75(8): 942-51.
65. Venturelli M. The Role of Nitric Oxide on vascular dysfunction during aging and Alzheimer's disease. In: Morbidelli L, Bonavida B, editor. *Therapeutic Application of Nitric Oxide in Cancer and Inflammatory Disorders*. Elsevier; 2019. p. 221-8.
66. Saeed S, Waje-Andreassen U, Fromm A, Øygarden H, Kokorina M, Naess H, et al. Early vascular aging in young and middle-aged ischemic stroke patients: the Norwegian Stroke in the Young Study. *PloS One*. 2014; 9(11): 1-6.
67. Hachinski V, Iadecola C, Petersen RC, Breteler M, Nyenhuis D, Black S, et al. National Institute of Neurological Disorders and Stroke—Canadian stroke

network vascular cognitive impairment harmonization standards. *Stroke*. 2006; 37(9): 2220-41.

68. Barton M. Obesity and aging: determinants of endothelial cell dysfunction and atherosclerosis. *Pflügers Archiv-European Journal of Physiology*. 2010; 460(5): 825-37.

69. Bailey-Downs LC, Sosnowska D, Toth P, Mitschelen M, Gautam T, Henthorn J, et al. Growth hormone and IGF-1 Deficiency exacerbate high-fat diet-induced endothelial impairment in obese lewis dwarf rats: implications for vascular aging. *The Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences*. 2012; 67(6): 553-64.

70. Bailey-Downs LC, Tucsek Z, Toth P, Sosnowska D, Gautam T, Sonntag WE, et al. Aging exacerbates obesity-induced oxidative stress and inflammation in perivascular adipose tissue in mice: a paracrine mechanism contributing to vascular redox dysregulation and inflammation. *The Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences*. 2013; 68(7): 780-92.

71. Ungvari Z, Parrado-Fernandez C, Csiszar A, Cabo R. Mechanisms underlying caloric restriction and lifespan regulation: implications for vascular aging. *Circulation Research*. 2008; 102(5): 519-28.

72. Georgiopoulos GA, Lambrinoudaki I, Athanasouli F, Armeni E, Rizos D, Kazani M, et al. Free androgen index as a predictor of blood pressure progression and accelerated vascular aging in menopause. *Atherosclerosis*. 2016; 247: 177-183.