EDITORIAL

Reversing Aging and Improving Health Span in Glaucoma Patients: The Next Frontier?

Tanuj Dada[1], Karthikeyan Mahalingam[2], Shibal Bhartiya[3]

Journal of Current Glaucoma Practice (2024): 10.5005/jp-journals-10078-1451

Introduction

Glaucoma is a chronic progressive optic neuropathy characterized by degeneration of retinal ganglion cells (RGC) and its axon causing optic nerve cupping and associated visual field defects.[1–9] In glaucoma, initially, there is the death of RGC associated with damage to the retinal nerve fiber layer (RNFL) and optic nerve head (structural changes), leading to visual field defects (functional changes). Many studies also suggest that the structural changes precede the visual field changes in glaucoma. Although intraocular pressure (IOP) control is the mainstay of treatment, glaucoma progression can occur even after adequate IOP control.[2–9]

Glaucoma is an age-related noncommunicable disease—part of the bouquet of diseases that affect some, but not all, elderly. While aging is an immutable, and irreversible deterioration in physiological homeostasis and function due to changes at the cellular level, it is exaggerated in the case of disease. The factors that may be responsible for the development of glaucoma at the cellular level include oxidative stress and mitochondrial dysfunction as well as protein misfolding. Possible alterations in cellular milieu that could contribute to glaucoma include excitotoxicity, altered neurotrophin signals, and hypoxic and ischemic injuries.[8]

Various neuroprotective strategies have been proposed to prevent RGC apoptosis, but IOP lowering is the only practical therapy.[10–16] As apart from glaucoma, the aging process can also contribute to the RNFL loss/optic nerve neurodegeneration, there is an unmet need to focus on therapies for slowing down this process.[7–9,17–22]

This is important for patients first detected with moderate/advanced damage and already have a low reserve of RGC. Even after adequate treatment, there is a downward slope of age-related progression, which may cause visual disability in their lifetime. Hence, a key question emerges—can antiaging therapies and lifestyle modifications reduce the rate of age-related decline of RGC/RNFL in glaucoma patients? Therapeutic strategies that may reverse or retard aging, will not decrease the incidence and morbidity due to age-related chronic diseases, but also prolong the healthy lifespan, improving the quality of life of the individual. In this article, we will briefly discuss the pathophysiology of age-related changes; the potential role, and new strategies to reverse, or at least, slow aging.

How Does Aging Impact Glaucoma Patients?

Aging and Ocular Stiffness

With advancing age, there are alterations in extracellular matrix (ECM) microstructure like increased ECM deposition, assembly, and subsequent crosslinking, leading to increased tissue stiffness.[23,24] It has been shown that ocular rigidity increases with increasing age.[25] There is age-related thickening or increased stiffness of trabecular meshwork (TM) and Schlemm's canal (SC) cells and tissues, leading to elevated IOP.[26]

In glaucoma, the lamina cribrosa of the optic nerve head is the principal site of RGC axonal damage. During aging, due to the accumulation of advanced glycation end products, profound changes are observed in the collagenous and noncollagenous components of ECM of lamina cribrosa causing stiffening and reduced compliance at the optic nerve head, leading to increased susceptibility to IOP-induced damage.[27] Like lamina cribrosa, age-related alterations in ECM of sclera and peripapillary sclera (thinning, stiffening) also have a significant impact on the biomechanics of optic nerve head.[28] Stiff sclera causes decreased optic canal expansion and increases ganglion cell loss.[29,30] Age-related structural changes may lead to a reduction of corneal hysteresis (a measure of the change in viscoelastic damping of the cornea) and corneal resistance factor.[31] Lower corneal hysteresis is associated with an increased risk for glaucoma progression.

Aging and Retinal Ganglion Cell Loss

Aging is known to be associated with the loss of RGC and their axons.[32,33] With increasing age, the proportion of neuronal tissue in the RNFL also decreases.[33]

In older age, the mechanical risk factors associated with retinal ganglion cell loss include a stiff sclera and decreased optic canal expansion.[30] Apart from these mechanical factors, age-related

[1]Department of Ophthalmology, Dr Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, Delhi, India

[2]Department of Ophthalmology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India

[3]Department of Ophthalmology and Community Outreach, Marengo Asia Hospitals, Gurugram and Faridabad, Haryana, India; Mayo Clinic, Jacksonville, Florida, United States

Corresponding Author: Tanuj Dada, Department of Ophthalmology, Dr Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, Delhi, India, Phone: +91 9873336315, e-mail: tanujdada@gmail.com

How to cite this article: Dada T, Mahalingam K, Bhartiya S. Reversing Aging and Improving Health Span in Glaucoma Patients: The Next Frontier? J Curr Glaucoma Pract 2024;18(3):87–93.

Source of support: Nil

Conflict of interest: None

biochemical alterations contribute to retinal ganglion cell loss. Most of these biochemical alterations are mediated by caspase-dependent apoptosis, histone lysine methylation, and histone acetylase (HAT)/histone deacetylase (HDAC) deacetylation.[34–36] Nuclear factor (erythroid-derived 2)- like 2 (NRF2), a transcription factor that regulates cellular redox homeostasis, declines with age.[37] Age-related alterations in redox homeostasis prevent reactive oxygen species (ROS) reduction. The increased ROS causes oxidative stress, damages mitochondrial deoxyribonucleic acid (DNA), and increases the optic nerve's neurodegenerative vulnerability.[37–39]

Why do We Age—Pathophysiology of Aging

Aging occurs mainly due to cumulative DNA damage and epigenetic dysregulation. The epigenome determines which genes are switched on (functional) or off (not functional), and this gets dysregulated as we age, leading to cell damage. There is a shortening of telomeres that caps and protects the DNA in our chromosomes. There is also an accumulation of protein due to loss of protein homeostasis related to this, an increase in crosslinked proteins that bind to each other—advanced glycation crosslinks and an increase in senescent cells which are harmful to healthy cells. There is a loss of energy production with a reduction in mitochondrial function and a loss of stem cells, which are responsible for cell rejuvenation or tissue repair. Chronic, low-grade inflammation, also called inflammaging, involves both cytokine and noncytokine mediate processes, and is central to immunosenescence.

There is also considerable evidence that lifestyle factors are the triggers for systemic physiological imbalances. The latter is a result of the underlying oxidative stress, insulin resistance, and hyperinsulinemia,[7] imbalances in the renin–angiotensin–aldosterone system, as well as autonomic and immunomodulatory dysregulation. In fact, insulin resistance has been shown to have a positive correlation with IOP, and the former, along with hyperinsulinemia may, thus, contribute to glaucoma. The interaction between the lifestyle style triggers and their resultant physiological malfunctions and individual genetic susceptibility is known to influence not only aging, but also several age-related diseases.[2,7–9]

Stress and Aging

With increasing age, there is a shortening of telomeres; thus, telomere length is a marker of cellular aging. Psychological stress can be associated with decreased telomere length.[40] Darrow et al., in their meta-analysis, reported that there is a shortening of telomere length in patients with psychiatric disorders (like depression, anxiety, posttraumatic stress disorder, etc.) compared to controls.[41] The underlying mechanisms for the association of chronic psychological stress and shorter telomere are poorly understood. During stressful events, the hypothalamic–pituitary–adrenal axis (HPA) is activated, causing a rapid (but transient) increase in glucocorticoid stress hormone.[42] There may be an increase in oxidative stress if repeated activation of the HPA axis occurs. The oxidizing molecule can affect telomeres, which leads to the hypothesis that increased glucocorticoids cause telomere shortening. Steptoe et al. reported that cortisol responsivity may partly mediate the relationship between psychological stress and cellular aging.[43] Jiang et al.'s meta-analysis also supported a relationship between cortisol reactivity and telomere shortening.[44] Animal experimental studies also suggested that exposure to chronic stress and glucocorticoids is associated with shortened telomeres, which may be partially reversible.[45] People who are exposed to chronic stress age rapidly due to telomere shortening.[46]

Antiaging Therapy

While aging, an organism experiences a series of progressively degenerative changes and becomes more sensitive to internal and external stimuli which leads to an aggravation of oxidative stress, accumulation of inflammation, apoptosis of cells, damage to structures and functions of cells/organs, and finally death.[47,48] There are some interventions in animal models or even in human studies that are known to have antiaging properties and can increase the lifespan.[49] Activation of the sirtuin can be a useful method for lifespan extension.[50] Quercetin can regulate the inflammatory response, oxidative stress, mitochondrial dysfunction, autophagy, and apoptosis by activating sirtuin 1 in aging-related diseases.[51–53] Many studies have shown that resveratrol has antiaging properties, can extend the lifespan, and also treat age-related diseases.[54–61] The mechanisms by which resveratrol causes antiaging effects include suppression of oxidative stress, inhibition of inflammation, improvement of mitochondrial function, and regulation of apoptosis.[62] In recent years, the role of hyperbaric oxygen therapy (HBOT–delivering 100% oxygen at atmospheric pressure) in antiaging therapy has been explored.[63–65] HBOT alters gene expression, delays cell senescence, assists in telomere length enhancement, and thus has the potential for regenerative and antiaging therapy.[64] Thus, vitamin D can act as a shield against aging. Due to the critical effect exerted by vitamin D, it can be considered a tool to tackle immunosenescence, oxi-inflammaging, and whole-body aging. However, there are significant limitations to translating knowledge into clinical practice.[66] Oleic acid, coenzyme Q10, alpha-lipoic acid, and nicotinamide mononucleotide (NMN) supplementation are gaining attention for antiaging therapy. Further studies must assess their potential benefit and safety.[67–72] NMN as a sirtuin-activating agent had protective effects against age-related ocular diseases such as dry eye, glaucoma, and macular degeneration.[73] Similarly, many strategies were tried to protect or regenerate the RGC Cells.[11,74–76] Skoufis and Segos reported that antiaging therapy could aid in glaucoma control, improving the ocular microcirculation.[77]

Epigenetic Reprogramming

It is proposed that during aging, the accumulation of epigenetic noise/loss of epigenetic information disrupts gene expression patterns, leading to decreases in tissue function and regenerative capacity.[78–80] Even though aging is thought to be a unidirectional process, there are some situations in which biological age can be reset entirely, such as in "immortal" jellyfish and when cloning an animal using nuclear transfer. If the mammalian cells had preserved a faithful copy of epigenetic information from an earlier stage of life, it might be possible to reverse aging by using that information.[81] Sinclair stated that restoring epigenetic information to reverse aging is similar to rebooting a malfunctioning computer.

Epigenetic reprogramming is the key to reversing aging and increasing longevity.[82] The epigenetic rejuvenation is achieved through transcription factor-mediated reprogramming or pharmacological interventions based on small molecules, like DNA methyltransferase inhibitors and HDAC inhibitors.

Transcription Factor-mediated Reprogramming

Almost all species have a decline in regenerative potential during aging. In mammals, the central nervous system (CNS) is among the first to lose regenerative potential.[83,84] RGC (part of CNS) can regenerate axons after damage during the embryonic or neonatal period, but this capacity is lost within days after birth.[83,85] The trio of genes Oct4, Sox2, and Klf4 (together named OSK), which are active in stem cells, can help to rewind the adult cells to an earlier state. Lu et al. showed that ectopic expression of OSK in mouse RGC can restore youthful DNA methylation patterns and transcriptomes, promote axon regeneration after injury, and reverse vision in mouse models of glaucoma and aged mice.[76] The DNA demethylases TET1 and TET2 are required for the beneficial effects of OSK-induced reprogramming in axon regeneration and vision restoration. It is a partial reprogramming that enables the epigenetic landscape of cells and DNA methylation patterns to be reset, allowing cells to rejuvenate and tissues to regenerate without reaching a pluripotency state, thus minimizing the risk of tumorigenesis.[86]

Deoxyribonucleic Acid Methyltransferase Inhibitors-mediated Reprogramming

With increasing age, there are alterations in DNA methylation like global hypomethylation and site-specific hypermethylation, which are linked to many age-related diseases like diabetes, cancer, cardiovascular diseases, neurodegenerative disorders, etc.[87] DNA methylation is catalyzed by DNA methyltransferases.[88] So, targeting DNA methyltransferases with specific inhibitors to delay or reverse the pathologies can be a potential antiaging strategy. FDA had approved DNA methyltransferase inhibitors like 5-azacitidine and decitabine as antitumor agents.[89,90] There is limited experimental evidence regarding the direct effects of DNA methyltransferase inhibitors on age-related diseases.

Histone Deacetylase Inhibitors-mediated Reprogramming

With increasing age, there are changes in histone acetylation, particularly alterations in specific histone marks and the expression of HDACs.[91] The opposing actions of histone acetyltransferases (HATs) and HDACs (whose activities are correlated with gene activation and gene silencing, respectively) control the acetylation of core histones.[92] HDAC inhibitors target epigenetic changes and, indirectly, the remaining hallmarks of aging and thus have shown promise in treating age-related chronic disorders.[93] HDAC inhibitors reprogram chromatin through modulating p53, p300/CREB binding protein, p300/CBP-associated factor and thus promoting neuroprotection.[33,94,95] HDAC inhibitors like RGFP966 or conditional knockout of the *Hdac3* gene (encodes HDAC3), offer protection to the RGC.[74,75]

Current Challenges in Epigenetic Reprogramming

Epigenetic reprogramming can reverse aging and increase longevity, but several challenges hinder these strategies. Despite progress, there is an incomplete understanding of the intricate processes regulating gene expression and cellular reprogramming.[96] After attaining youthful characteristics, sustaining them and preventing their reversion to an aged state over extended periods is complex and requires continuous monitoring and optimization of reprogramming. Delivery of transcription factors for reprogramming by the viral vectors can lead to pathological insertional mutagenesis and reactivation of reprogramming factors.[97] Reprogramming factors like OSKM genes may be associated with the risk of neoplastic development in reprogrammed cells.[98] Most of these reprogramming has been successful only in rejuvenating animal tissues. New technologies and further research are needed to apply these findings in humans.

Lifestyle Modifications for Antiaging

Several lifestyle factors like physical activity, smoking, drinking, nutrition, sleep, stress, etc. can be associated with age-related diseases and death. Lifestyle modifications can be beneficial to prevent aging and age-related diseases. Most of these aim at reducing the allostatic overload which results in physiological dysregulation due to chronic stress.[2,7–9,99–129]

Stress Management

Meditation-based interventions have been shown to reduce stress and improve general health.[101,102] Our previous studies have shown that meditation-based interventions can also reduce stress and improve the quality of life in patients with glaucoma.[14,103–105] A recent meta-analysis by Schutte et al. suggested that meditation-based interventions may prevent telomere attrition or increase telomere length.[106] In long-term meditators, telomere length correlates with DNA methylation.[107] Tolahunase et al. studied the impact of yoga and meditation-based lifestyle intervention (YMLI) on cellular aging in apparently healthy individuals.[108] In their study, a 12-week course of YMLI significantly reduced the mean levels of 8-hydroxy-2′-deoxyguanosine, ROS, cortisol, and IL-6. It also significantly increased the mean levels of total antioxidant capacity, telomerase activity, β-endorphin, BDNF, and sirtuin-1. The mean level of telomere length was increased (but the finding was not significant $p = 0.069$). They concluded that YMLI can reduce the rate of cellular aging. Similarly, Dasanayaka et al. studied the associations of meditation with telomere dynamics in healthy adults and reported that meditation has multilevel benefits in telomere dynamics (compared to nonmeditators, meditators had longer relative telomere length, higher relative expression of hTERT and hTR genes and significantly lower methylation level of the promoter region of hTERT gene) with potential to promote healthy aging.[109] Thus, meditation can aid in healthy aging by appropriate telomere dynamics.[110–112]

Avoid Smoking and Alcohol Consumption

Cigarette smoking is an important accelerator of the aging process both directly (complex mechanisms mediated by excessive free radical formation) and indirectly (by favoring the appearance of various pathologies).[113,114] Smokers have a significantly higher biological age than chronological age and a higher percentage of fat tissue than nonsmokers.[115] Nonsmokers can delay the aging process and the appearance of diseases. Chronic alcohol consumption accelerates and exacerbates the age-related diseases.[116] Alcohol consumption can increase oxidative stress and inflammation, influencing telomere length.[117] Wang et al. reported that the long-term average alcohol consumption is associated with acceleration of biological age.[118] Thus, avoiding smoking and alcohol consumption will aid in healthy aging.

Improving Physical Activity

Physical activity/regular exercise can limit the prevalence of various cardiometabolic and neurodegenerative diseases by reducing mitochondrial dysfunction.[119] It prevents the decline in mitochondrial respiration, mitigates aging-related loss of

muscle mass, and enhances insulin sensitivity.[120] It can maintain blood pressure, control blood sugar and body weight, reduce dyslipidemia, and improve bone and muscle health. Thus, exercise/physical activity can promote healthy aging.

Diet Modification

Appropriate nutrition intake is crucial to prevent or delay the development of diseases, boost longevity, and promote healthy aging.[121,122] One should consume diets rich in vegetables, fruits, nuts, cereals, fish, unsaturated fats, antioxidants, potassium, and omega-3, choose a low carbohydrate diet, reduce intake of red meat, and ultraprocessed foods. Calorie restriction has also been shown to improve lifespans in some model organisms.[123] It works by neutralizing the harmful effects of ROS and oxidative damage.[124]

Sleep Quality and Quantity

Sleep is integral to the health of metabolic and physiological systems, endocrine function, immune response, and retardation of senescence. Poor sleep is known to accelerate aging, and age-related diseases, like Alzheimer's disease, hematopoietic stem cell dysfunction, and coronary artery disease.[125–131] Numerous studies have reported that improving the quantity and quality of sleep can be considered as an antiaging treatment that can prevent, slow, or even. Similarly, the chronobiological effects of melatonin include a reversal of the cellular degeneration associated with aging. Melatonin, and its metabolites, N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK) and N1-acetyl-5-methoxykynuramine (AMK), have neuroprotective, anti-inflammatory, immunomodulatory, and oncostatic properties.[125–130]

Increased HIF-1α protein levels, higher oxidative stress markers 8-OHdG and TNF-α, and a decrease in pyruvate dehydrogenase kinase-1 protein were noted in rats with chronic intermittent hypoxia, induced by obstructive sleep apnea-like models. These are like the oxidative stress, inflammation, and upregulation of HIF-1α in the retina, seen in early-stage glaucoma.[129] Obstructive Sleep Apnea (OSA), however, appears to be an aggravating factor, rather than an independent risk factor for glaucoma, even though there is a significant association between OSA, glaucoma, and higher eye pressures.[130,131]

Conclusion

To conclude, aging can cause or accelerate the loss of RGC either by mechanical or biochemical alterations. Several research studies have attempted to stop or reverse aging and age-related diseases, with promising results. However, there are several challenges to using them in clinical practice at the present time. Future research could provide a valuable intervention to halt or reverse age-related loss of RGC and be a helpful armamentarium in treating glaucoma. At present, lifestyle modifications could be considered as adjuvant therapy in glaucoma patients, with an aim to evaluate and reduce the allostatic load, to restore the physiological balance.[9] That these may also have a potentially beneficial or protective effect on other age-related noncommunicable diseases is an added advantage. It is important to establish a new target in glaucoma patients other than the target IOP for "reversing aging" or "slowing the aging process" to mitigate the age-related retinal ganglion cell loss. An interesting research question for the future would be to evaluate glaucoma "fast progressors" for "accelerated aging" and evaluate if lifestyle interventions can slow/reverse both.

References

1. Weinreb RN, Khaw PT. Primary open-angle glaucoma. Lancet 2004;363(9422):1711–1720. DOI: 10.1016/S0140-6736(04)16257-0
2. Gc K, Mahalingam K, Gupta V, et al. Stress and allostatic load in patients with primary open angle glaucoma. J Glaucoma 2024;33(2):87–93. DOI: 10.1097/IJG.0000000000002332
3. Alencar LM, Medeiros FA. The role of standard automated perimetry and newer functional methods for glaucoma diagnosis and follow-up. Indian J Ophthalmol 2011;59(Suppl 1):S53–S58. DOI: 10.4103/0301-4738.73694
4. Wollstein G, Kagemann L, Bilonick RA, et al. Retinal nerve fibre layer and visual function loss in glaucoma: the tipping point. Br J Ophthalmol 2012;96(1):47–52. DOI: 10.1136/bjo.2010.196907
5. Kerrigan-Baumrind LA, Quigley HA, Pease ME, et al. Number of ganglion cells in glaucoma eyes compared with threshold visual field tests in the same persons. Invest Ophthalmol Vis Sci 2000;41(3):741–748.
6. Wollstein G, Schuman JS, Price LL, et al. Optical coherence tomography longitudinal evaluation of retinal nerve fiber layer thickness in glaucoma. Arch Ophthalmol 2005;123(4):464–470. DOI: 10.1001/archopht.123.4.464
7. Dada T. Is glaucoma a neurodegeneration caused by central insulin resistance: diabetes type 4? J Curr Glaucoma Pract 2017;11(3):77–79. DOI: 10.5005/jp-journals-10028-1228
8. Kopp W. Aging and "age-related" diseases—what is the relation? Aging Dis2024 . DOI: 10.14336/AD.2024.0570
9. Dada T, Mahalingam K, Gupta V. Allostatic load and glaucoma: are we missing the big picture? J Curr Glaucoma Pract 2020;14(2):47–49. DOI: 10.5005/jp-journals-10078-1280
10. Sena DF, Lindsley K. Neuroprotection for treatment of glaucoma in adults. Cochrane Database Syst Rev 2013;2:CD006539. DOI: 10.1002/14651858.CD006539.pub3
11. Mahalingam K, Chaurasia AK, Gowtham L, et al. Therapeutic potential of valproic acid in advanced glaucoma: a pilot study. Indian J Ophthalmol 2018;66(8):1104–1108. DOI: 10.4103/ijo.IJO_108_18
12. Dada T, Lahri B, Mahalingam K, et al. Beneficial effect of mindfulness based stress reduction on optic disc perfusion in primary open angle glaucoma: a randomized control trial. J Tradit Complement Med 2021;6:581–586. DOI: 10.1016/j.jtcme.2021.06.006
13. Vasudevan SK, Gupta V, Crowston JG. Neuroprotection in glaucoma. Indian J Ophthalmol 2011;59(Suppl 1):S102–S113. DOI: 10.4103/0301-4738.73700
14. Gagrani M, Faiq MA, Sidhu T, et al. Meditation enhances brain oxygenation, upregulates BDNF and improves quality of life in patients with primary open angle glaucoma: a randomized controlled trial. Restor Neurol Neurosci 2018;36(6):741–753. DOI: 10.3233/RNN-180857
15. Dada T, Ramesh P, Shakrawal J. Meditation: a polypill for comprehensive management of glaucoma patients. J Glaucoma 2020;29(2):133–140. DOI: 10.1097/IJG.0000000000001406
16. Dada T, Gagrani M. Mindfulness meditation can benefit glaucoma patients. J Curr Glaucoma Pract 2019;13(1):1–2. DOI: 10.5005/jp-journals-10078-1239
17. Coleman-Belin J, Harris A, Chen B, et al. Aging effects on optic nerve neurodegeneration. Int J Mol Sci 2023;24(3):2573. DOI: 10.3390/ijms24032573
18. Hondur G, Göktaş E, Al-Aswad L, et al. Age-related changes in the peripheral retinal nerve fiber layer thickness. Clin Ophthalmol 2018;12:401–409. DOI: 10.2147/OPTH.S157429
19. Parikh RS, Parikh SR, Sekhar GC, et al. Normal age-related decay of retinal nerve fiber layer thickness. Ophthalmology 2007;114(5):921–926. DOI: 10.1016/j.ophtha.2007.01.023
20. Celebi ARC, Mirza GE. Age-related change in retinal nerve fiber layer thickness measured with spectral domain optical coherence tomography. Invest Ophthalmol Vis Sci 2013;54(13):8095–8103. DOI: 10.1167/iovs.13-12634
21. Jeong D, Sung KR, Jo YH, et al. Age-related physiologic thinning rate of the retinal nerve fiber layer in different levels of myopia. J Ophthalmol 2020;2020:e1873581. DOI: 10.1155/2020/1873581

22. Guedes G, Tsai JC, Loewen NA. Glaucoma and aging. Curr Aging Sci 2011;4(2):110–117. DOI: 10.2174/1874609811104020110
23. Kohn JC, Lampi MC, Reinhart-King CA. Age-related vascular stiffening: causes and consequences. Front Genet 2015;6:112. DOI: 10.3389/fgene.2015.00112
24. Akhtar R, Sherratt MJ, Cruickshank JK, et al. Characterizing the elastic properties of tissues. Mater Today (Kidlington) 2011;14(3):96–105. DOI: 10.1016/S1369-7021(11)70059-1
25. Pallikaris IG, Kymionis GD, Ginis HS, et al. Ocular rigidity in living human eyes. Invest Ophthalmol Vis Sci 2005;46(2):409–414. DOI: 10.1167/iovs.04-0162
26. Liu B, McNally S, Kilpatrick JI, et al. Aging and ocular tissue stiffness in glaucoma. Surv Ophthalmol 2018;63(1):56–74. DOI: 10.1016/j.survophthal.2017.06.007
27. Albon J, Purslow PP, Karwatowski WS, et al. Age-related compliance of the lamina cribrosa in human eyes. Br J Ophthalmol 2000;84(3):318–323. DOI: 10.1136/bjo.84.3.318
28. Sigal IA, Yang H, Roberts MD, et al. IOP-induced lamina cribrosa displacement and scleral canal expansion: an analysis of factor interactions using parameterized eye-specific models. Invest Ophthalmol Vis Sci 2011;52(3):1896–1907. DOI: 10.1167/iovs.10-5500
29. Geraghty B, Jones SW, Rama P, et al. Age-related variations in the biomechanical properties of human sclera. J Mech Behav Biomed Mater 2012;16:181–191. DOI: 10.1016/j.jmbbm.2012.10.011
30. Steinhart MR, Cone-Kimball E, Nguyen C, et al. Susceptibility to glaucoma damage related to age and connective tissue mutations in mice. Exp Eye Res 2014;119:54–60. DOI: 10.1016/j.exer.2013.12.008
31. Kamiya K, Shimizu K, Ohmoto F. Effect of aging on corneal biomechanical parameters using the ocular response analyzer. J Refract Surg 2009;25(10):888–893. DOI: 10.3928/1081597X-20090917-10
32. Dolman CL, McCormick AQ, Drance SM. Aging of the optic nerve. Arch Ophthalmol 1980;98(11):2053–2058. DOI: 10.1001/archopht.1980.01020040905024
33. Harwerth RS, Wheat JL, Rangaswamy NV. Age-related losses of retinal ganglion cells and axons. Invest Ophthalmol Vis Sci 2008;49(10):4437–4443. DOI: 10.1167/iovs.08-1753
34. Thomas CN, Berry M, Logan A, et al. Caspases in retinal ganglion cell death and axon regeneration. Cell Death Discov 2017;3:17032. DOI: 10.1038/cddiscovery.2017.32
35. Rao RC, Tchedre KT, Malik MTA, et al. Dynamic patterns of histone lysine methylation in the developing retina. Invest Ophthalmol Vis Sci 2010;51(12):6784–6792. DOI: 10.1167/iovs.09-4730
36. Pelzel HR, Schlamp CL, Nickells RW. Histone H4 deacetylation plays a critical role in early gene silencing during neuronal apoptosis. BMC Neurosci 2010;11:62. DOI: 10.1186/1471-2202-11-62
37. Schmidlin CJ, Dodson MB, Madhavan L, et al. Redox regulation by NRF2 in aging and disease. Free Radic Biol Med 2019;134:702–707. DOI: 10.1016/j.freeradbiomed.2019.01.016
38. Eells JT. Mitochondrial dysfunction in the aging retina. Biology (Basel) 2019;8(2):31. DOI: 10.3390/biology8020031
39. Auten RL, Davis JM. Oxygen toxicity and reactive oxygen species: the devil is in the details. Pediatr Res 2009;66(2):121–127. DOI: 10.1203/PDR.0b013e3181a9eafb
40. Mathur MB, Epel E, Kind S, et al. Perceived stress and telomere length: a systematic review, meta-analysis, and methodologic considerations for advancing the field. Brain Behav Immun 2016;54:158–169. DOI: 10.1016/j.bbi.2016.02.002
41. Darrow SM, Verhoeven JE, Révész D, et al. The association between psychiatric disorders and telomere length: a meta-analysis involving 14,827 persons. Psychosom Med 2016;78(7):776–787. DOI: 10.1097/PSY.0000000000000356
42. Costanzo A, Ambrosini R, Parolini M, et al. Telomere shortening is associated with corticosterone stress response in adult barn swallows. Curr Zool 2021;68(1):93–101. DOI: 10.1093/cz/zoab020
43. Steptoe A, Hamer M, Lin J, et al. The longitudinal relationship between cortisol responses to mental stress and leukocyte telomere attrition. J Clin Endocrinol Metab 2017;102(3):962–969. DOI: 10.1210/jc.2016-3035
44. Jiang Y, Da W, Qiao S, et al. Basal cortisol, cortisol reactivity, and telomere length: a systematic review and meta-analysis. Psychoneuroendocrinology 2019;103:163–172. DOI: 10.1016/j.psyneuen.2019.01.022
45. Lee RS, Zandi PP, Santos A, et al. Cross-species association between telomere length and glucocorticoid exposure. J Clin Endocrinol Metab 2021;106(12):e5124–e5135. DOI: 10.1210/clinem/dgab519
46. Yegorov YE, Poznyak AV, Nikiforov NG, et al. The link between chronic stress and accelerated aging. Biomedicines 2020;8(7):198. DOI: 10.3390/biomedicines8070198
47. Pyo IS, Yun S, Yoon YE, et al. Mechanisms of aging and the preventive effects of resveratrol on age-related diseases. Molecules 2020;25(20):4649. DOI: 10.3390/molecules25204649
48. Lagouge M, Argmann C, Gerhart-Hines Z, et al. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. Cell 2006;127(6):1109–1122. DOI: 10.1016/j.cell.2006.11.013
49. Grabowska W, Sikora E, Bielak-Zmijewska A. Sirtuins, a promising target in slowing down the ageing process. Biogerontology 2017;18(4):447–476. DOI: 10.1007/s10522-017-9685-9
50. Wątroba M, Szukiewicz D. The role of sirtuins in aging and age-related diseases. Adv Med Sci 2016;61(1):52–62. DOI: 10.1016/j.advms.2015.09.003
51. Xu D, Hu MJ, Wang YQ, et al. Antioxidant activities of quercetin and its complexes for medicinal application. Molecules 2019;24(6):1123. DOI: 10.3390/molecules24061123
52. Han X, Xu T, Fang Q, et al. Quercetin hinders microglial activation to alleviate neurotoxicity via the interplay between NLRP3 inflammasome and mitophagy. Redox Biol 2021;44:102010. DOI: 10.1016/j.redox.2021.102010
53. Hu Y, Gui Z, Zhou Y, et al. Quercetin alleviates rat osteoarthritis by inhibiting inflammation and apoptosis of chondrocytes, modulating synovial macrophages polarization to M2 macrophages. Free Radic Biol Med 2019;145:146–160. DOI: 10.1016/j.freeradbiomed.2019.09.024
54. Chandrashekara KT, Shakarad MN. Aloe vera or resveratrol supplementation in larval diet delays adult aging in the fruit fly, Drosophila melanogaster. J Gerontol A Biol Sci Med Sci 2011;66(9):965–971. DOI: 10.1093/gerona/glr103
55. Yu X, Li G. Effects of resveratrol on longevity, cognitive ability and aging-related histological markers in the annual fish *Nothobranchius guentheri*. Exp Gerontol 2012;47(12):940–949. DOI: 10.1016/j.exger.2012.08.009
56. Khusbu FY, Zhou X, Roy M, et al. Resveratrol induces depletion of TRAF6 and suppresses prostate cancer cell proliferation and migration. Int J Biochem Cell Biol 2020;118:105644. DOI: 10.1016/j.biocel.2019.105644
57. Zhao M, Ko S, Garrett IR, et al. The polyphenol resveratrol promotes skeletal growth in mice through a sirtuin 1-bone morphogenic protein 2 longevity axis. Br J Pharmacol 2018;175(21):4183–4192. DOI: 10.1111/bph.14477
58. Liu M, Yin Y, Ye X, et al. Resveratrol protects against age-associated infertility in mice. Hum Reprod 2013;28(3):707–717. DOI: 10.1093/humrep/des437
59. Wang N, Luo Z, Jin M, et al. Exploration of age-related mitochondrial dysfunction and the anti-aging effects of resveratrol in zebrafish retina. Aging (Albany NY) 2019;11(10):3117–3137. DOI: 10.18632/aging.101966
60. Olesen J, Ringholm S, Nielsen MM, et al. Role of PGC-1α in exercise training- and resveratrol-induced prevention of age-associated inflammation. Exp Gerontol 2013;48(11):1274–1284. DOI: 10.1016/j.exger.2013.07.015
61. Sin TK, Tam BT, Yu AP, et al. Acute treatment of resveratrol alleviates doxorubicin-induced myotoxicity in aged skeletal muscle through SIRT1-dependent mechanisms. J Gerontol A Biol Sci Med Sci 2016;71(6):730–739. DOI: 10.1093/gerona/glv175
62. Zhou DD, Luo M, Huang SY, et al. Effects and mechanisms of resveratrol on aging and age-related diseases. Oxid Med Cell Longev 2021;2021:9932218. DOI: 10.1155/2021/9932218

63. Wang S, Chen B, Yuan M, et al. Enriched oxygen improves age-related cognitive impairment through enhancing autophagy. Front Aging Neurosci 2024;16:1340117. DOI: 10.3389/fnagi.2024.1340117
64. Gupta M, Rathored J. Hyperbaric oxygen therapy: future prospects in regenerative therapy and anti-aging. Front Aging 2024;5:1368982. DOI: 10.3389/fragi.2024.1368982
65. Hadanny A, Sasson E, Copel L, et al. Physical enhancement of older adults using hyperbaric oxygen: a randomized controlled trial. BMC Geriatr 2024;24(1):572. DOI: 10.1186/s12877-024-05146-3
66. Fantini C, Corinaldesi C, Lenzi A, et al. Vitamin D as a shield against aging. Int J Mol Sci 2023;24(5):4546. DOI: 10.3390/ijms24054546
67. Schürmanns L, Hamann A, Osiewacz HD. Lifespan increase of *Podospora anserina* by oleic acid is linked to alterations in energy metabolism, membrane trafficking and autophagy. Cells 2022;11(3):519. DOI: 10.3390/cells11030519
68. Nadeeshani H, Li J, Ying T, et al. Nicotinamide mononucleotide (NMN) as an anti-aging health product—promises and safety concerns. J Adv Res 2021;37:267–278. DOI: 10.1016/j.jare.2021.08.003
69. Hou Y, Lautrup S, Cordonnier S, et al. NAD+ supplementation normalizes key Alzheimer's features and DNA damage responses in a new AD mouse model with introduced DNA repair deficiency. Proc Natl Acad Sci USA 2018;115(8):E1876–E1885. DOI: 10.1073/pnas.1718819115
70. de Barcelos IP, Haas RH. CoQ10 and aging. Biology 2019;8(2):28. DOI: 10.3390/biology8020028
71. Du G, Qiao Y, Zhuo Z, et al. Lipoic acid rejuvenates aged intestinal stem cells by preventing age-associated endosome reduction. EMBO Rep 2020;21(8):e49583. DOI: 10.15252/embr.201949583
72. de Bengy AF, Decorps J, Martin LS, et al. Alpha-lipoic acid supplementation restores early age-related sensory and endothelial dysfunction in the skin. Biomedicines 2022;10(11):2887. DOI: 10.3390/biomedicines10112887
73. Tsubota K. Anti-aging approach for ocular disorders: from dry eye to retinitis pigmentosa and myopia. Nippon Ganka Gakkai Zasshi 2017;121(3):232–248.
74. Schmitt HM, Schlamp CL, Nickells RW. Role of HDACs in optic nerve damage-induced nuclear atrophy of retinal ganglion cells. Neurosci Lett 2016;625:11–15. DOI: 10.1016/j.neulet.2015.12.012
75. Schmitt HM, Schlamp CL, Nickells RW. Targeting HDAC3 activity with RGFP966 protects against retinal ganglion cell nuclear atrophy and apoptosis after optic nerve injury. J Ocul Pharmacol Ther 2018;34(3):260–273. DOI: 10.1089/jop.2017.0059
76. Lu Y, Brommer B, Tian X, et al. Reprogramming to recover youthful epigenetic information and restore vision. Nature 2020;588(7836):124–129. DOI: 10.1038/s41586-020-2975-4
77. Skoufis EA, Segos J. Contemporaneous concept of anti aging therapy as new valuable paradigm on ocular blood flow enhancement in glaucoma. Adv Ophthalmol Vis Syst 2017;6(3):00181. DOI: 10.15406/aovs.2017.06.00181
78. Sinclair DA, Mills K, Guarente L. Accelerated aging and nucleolar fragmentation in yeast sgs1 mutants. Science 1997;277(5330):1313–1316. DOI: 10.1126/science.277.5330.1313
79. Imai S, Kitano H. Heterochromatin islands and their dynamic reorganization: a hypothesis for three distinctive features of cellular aging. Exp Gerontol 1998;33(6):555–570. DOI: 10.1016/s0531-5565(98)00037-0
80. Oberdoerffer P, Michan S, McVay M, et al. SIRT1 redistribution on chromatin promotes genomic stability but alters gene expression during aging. Cell 2008;135(5):907–918. DOI: 10.1016/j.cell.2008.10.025
81. Sinclair DA, LaPlante MD. Lifespan: Why We Age—and Why We Don't Have To. Simon and Schuster; 2019.
82. Pereira B, Correia FP, Alves IA, et al. Epigenetic reprogramming as a key to reverse ageing and increase longevity. Ageing Res Rev 2024;95:102204. DOI: 10.1016/j.arr.2024.102204
83. Goldberg JL, Klassen MP, Hua Y, et al. Amacrine-signaled loss of intrinsic axon growth ability by retinal ganglion cells. Science 2002;296(5574):1860–1864. DOI: 10.1126/science.1068428
84. Yun MH. Changes in regenerative capacity through lifespan. Int J Mol Sci 2015;16(10):25392–25432. DOI: 10.3390/ijms161025392
85. Laha B, Stafford BK, Huberman AD. Regenerating optic pathways from the eye to the brain. Science 2017;356(6342):1031–1034. DOI: 10.1126/science.aal5060
86. Puri D, Wagner W. Epigenetic rejuvenation by partial reprogramming. Bioessays 2023;45(4):e2200208. DOI: 10.1002/bies.202200208
87. Luo X, Hu Y, Shen J, et al. Integrative analysis of DNA methylation and gene expression reveals key molecular signatures in acute myocardial infarction. Clin Epigenetics 2022;14(1):46. DOI: 10.1186/s13148-022-01267-x
88. Xiao FH, Wang HT, Kong QP. Dynamic DNA methylation during aging: a "prophet" of age-related outcomes. Front Genet 2019;10:107. DOI: 10.3389/fgene.2019.00107
89. Kaminskas E, Farrell AT, Wang YC, et al. FDA drug approval summary: azacitidine (5-azacytidine, Vidaza) for injectable suspension. Oncologist 2005;10(3):176–182. DOI: 10.1634/theoncologist.10-3-176
90. Dhillon S. Decitabine/cedazuridine: first approval. Drugs 2020;80(13):1373–1378. DOI: 10.1007/s40265-020-01389-7
91. Lee Y, Shin MH, Kim MK, et al. Increased histone acetylation and decreased expression of specific histone deacetylases in ultraviolet-irradiated and intrinsically aged human skin in vivo. Int J Mol Sci 2021;22(4):2032. DOI: 10.3390/ijms22042032
92. Al-Mansour F, Alraddadi A, He B, et al. Characterization of the HDAC/PI3K inhibitor CUDC-907 as a novel senolytic. Aging (Albany NY) 2023;15(7):2373–2394. DOI: 10.18632/aging.204616
93. McIntyre RL, Daniels EG, Molenaars M, et al. From molecular promise to preclinical results: HDAC inhibitors in the race for healthy aging drugs. EMBO Mol Med 2019;11(9):e9854. DOI: 10.15252/emmm.201809854
94. Gaub P, Tedeschi A, Puttagunta R, et al. HDAC inhibition promotes neuronal outgrowth and counteracts growth cone collapse through CBP/p300 and P/CAF-dependent p53 acetylation. Cell Death Differ 2010;17(9):1392–1408. DOI: 10.1038/cdd.2009.216
95. Lebrun-Julien F, Suter U. Combined HDAC1 and HDAC2 depletion promotes retinal ganglion cell survival after injury through reduction of p53 target gene expression. ASN Neuro 2015;7(3):1759091415593066. DOI: 10.1177/1759091415593066
96. Wang K, Liu H, Hu Q, et al. Epigenetic regulation of aging: implications for interventions of aging and diseases. Signal Transduct Target Ther 2022;7(1):374. DOI: 10.1038/s41392-022-01211-8
97. Chen W, Wang C, Yang ZX, et al. Reprogramming of human peripheral blood mononuclear cells into induced mesenchymal stromal cells using non-integrating vectors. Commun Biol 2023;6(1):393. DOI: 10.1038/s42003-023-04737-x
98. Taguchi J, Shibata H, Kabata M, et al. DMRT1-mediated reprogramming drives development of cancer resembling human germ cell tumors with features of totipotency. Nat Commun 2021;12(1):5041. DOI: 10.1038/s41467-021-25249-4
99. Bhatti GK, Reddy AP, Reddy PH, et al. Lifestyle modifications and nutritional interventions in aging-associated cognitive decline and Alzheimer's disease. Front Aging Neurosci 2020;11:369. DOI: 10.3389/fnagi.2019.00369
100. Lee HW, Rhyu HS. Antiaging strategy considering physiological characteristics. J Exerc Rehabil 2019;15(3):346–350. DOI: 10.12965/jer.1938214.107
101. Goyal M, Singh S, Sibinga EMS, et al. Meditation programs for psychological stress and well-being: a systematic review and meta-analysis. JAMA Intern Med 2014;174(3):357–368. DOI: 10.1001/jamainternmed.2013.13018
102. Woodyard C. Exploring the therapeutic effects of yoga and its ability to increase quality of life. Int J Yoga 2011;4(2):49–54. DOI: 10.4103/0973-6131.85485
103. Dada T, Gwal RS, Mahalingam K, et al. Effect of "365 breathing technique" on intraocular pressure and autonomic functions in patients with glaucoma: a randomized controlled trial. J Glaucoma 2024;33(3):149–154. DOI: 10.1097/IJG.0000000000002356
104. Dada T, Bhai N, Midha N, et al. Effect of mindfulness meditation on intraocular pressure and trabecular meshwork gene expression: a randomised controlled trial. Am J Ophthalmol 2021;223:308–321. DOI: 10.1016/j.ajo.2020.10.012

105. Dada T, Mondal S, Midha N, et al. Effect of mindfulness-based stress reduction on intraocular pressure in patients with ocular hypertension: a randomized control trial. Am J Ophthalmol 2022;239:66–73. DOI: 10.1016/j.ajo.2022.01.017
106. Schutte NS, Malouff JM, Keng SL. Meditation and telomere length: a meta-analysis. Psychol Health 2020;35(8):901–915. DOI: 10.1080/08870446.2019.1707827
107. Mendioroz M, Puebla-Guedea M, Montero-Marín J, et al. Telomere length correlates with subtelomeric DNA methylation in long-term mindfulness practitioners. Sci Rep 2020;10(1):4564. DOI: 10.1038/s41598-020-61241-6
108. Tolahunase M, Sagar R, Dada R. Impact of yoga and meditation on cellular aging in apparently healthy individuals: a prospective, open-label single-arm exploratory study. Oxid Med Cell Longev 2017;2017:7928981. DOI: 10.1155/2017/7928981
109. Dasanayaka NN, Sirisena ND, Samaranayake N. Associations of meditation with telomere dynamics: a case-control study in healthy adults. Front Psychol 2023;14:1222863. DOI: 10.3389/fpsyg.2023.1222863
110. Jamil A, Gutlapalli SD, Ali M, et al. Meditation and its mental and physical health benefits in 2023. Cureus 2023;15(6):e40650. DOI: 10.7759/cureus.40650
111. Aghajanyan V, Bhupathy S, Sheikh S, et al. A narrative review of telomere length modulation through diverse yoga and meditation styles: current insights and prospective avenues. Cureus 2023;15(9):e46130. DOI: 10.7759/cureus.46130
112. Sung MK, Koh E, Kang Y, et al. Three months-longitudinal changes in relative telomere length, blood chemistries, and self-report questionnaires in meditation practitioners compared to novice individuals during midlife. Medicine (Baltimore) 2022;101(41):e30930. DOI: 10.1097/MD.0000000000030930
113. Nicita-Mauro V, Basile G, Maltese G, et al. Smoking, health and ageing. Immun Ageing 2008;5:10. DOI: 10.1186/1742-4933-5-10
114. Nicita-Mauro V, Lo Balbo C, Mento A, et al. Smoking, aging and the centenarians. Exp Gerontol 2008;43(2):95–101. DOI: 10.1016/j.exger.2007.06.011
115. Radmilović G, Matijević V, Mikulić D, et al. The impact of smoking on estimated biological age and body fat composition: a cross-sectional study. Tob Induc Dis 2023;21:161. DOI: 10.18332/tid/174663
116. White AM, Orosz A, Powell PA, et al. Alcohol and aging—an area of increasing concern. Alcohol 2023;107:19–27. DOI: 10.1016/j.alcohol.2022.07.005
117. Topiwala A, Taschler B, Ebmeier KP, et al. Alcohol consumption and telomere length: mendelian randomization clarifies alcohol's effects. Mol Psychiatry 2022;27(10):4001–4008. DOI: 10.1038/s41380-022-01690-9
118. Wang M, Li Y, Lai M, et al. Alcohol consumption and epigenetic age acceleration across human adulthood. Aging (Albany NY) 2023;15(20):10938–10971. DOI: 10.18632/aging.205153
119. Barbieri E, Agostini D, Polidori E, et al. The pleiotropic effect of physical exercise on mitochondrial dynamics in aging skeletal muscle. Oxid Med Cell Longev 2015;2015:917085. DOI: 10.1155/2015/917085
120. Cartee GD, Hepple RT, Bamman MM, et al. Exercise promotes healthy aging of skeletal muscle. Cell Metab 2016;23(6):1034–1047. DOI: 10.1016/j.cmet.2016.05.007
121. Yeung SSY, Kwan M, Woo J. Healthy diet for healthy aging. Nutrients 2021;13(12):4310. DOI: 10.3390/nu13124310
122. Leitão C, Mignano A, Estrela M, et al. The effect of nutrition on aging—a systematic review focusing on aging-related biomarkers. Nutrients 2022;14(3):554. DOI: 10.3390/nu14030554
123. Flanagan EW, Most J, Mey JT, et al. Calorie restriction and aging in humans. Annu Rev Nutr 2020;40:105–133. DOI: 10.1146/annurev-nutr-122319-034601
124. Civitarese AE, Carling S, Heilbronn LK, et al. Calorie restriction increases muscle mitochondrial biogenesis in healthy humans. PLoS Med 2007;4(3):e76. DOI: 10.1371/journal.pmed.0040076
125. Li Y, Tian X, Luo J, et al. Molecular mechanisms of aging and anti-aging strategies. Cell Commun Signal 2024;22(1):285. DOI: 10.1186/s12964-024-01663-1
126. Gao X, Huang N, Guo X, et al. Role of sleep quality in the acceleration of biological aging and its potential for preventive interaction on air pollution insults: findings from the UK biobank cohort. Aging Cell 2022;21(5):e13610. DOI: 10.1111/acel.13610
127. Bocheva G, Bakalov D, Iliev P, et al. The vital role of melatonin and its metabolites in the neuroprotection and retardation of brain aging. Int J Mol Sci 2024;25(10):5122. DOI: 10.3390/ijms25105122
128. Cortese R. Epigenetics and aging: relevance for sleep medicine. Curr Opin Pulm Med 2024. DOI: 10.1097/MCP.0000000000001109
129. Donkor N, Gardner JJ, Bradshaw JL, et al. Ocular inflammation and oxidative stress as a result of chronic intermittent hypoxia: a rat model of sleep apnea. Antioxidants (Basel) 2024;13(7):878. DOI: 10.3390/antiox13070878
130. Meurisse PL, Onen F, Zhao Z, et al. Primary open angle glaucoma and sleep apnea syndrome: a review of the literature. J Fr Ophtalmol 2024;47(2):104042. DOI: 10.1016/j.jfo.2023.104042
131. Zoh Y, Yun JM. Association between obstructive sleep apnea and glaucoma. Korean J Fam Med 2024. DOI: 10.4082/kjfm.23.0162