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Review Article

RETINAL INFLAMMAGING: PATHOGENESIS AND PREVENTION

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ABSTRACT

Macula lutea, the yellow spot or fovea centralis in eye, serves the distinctive central vision in perceiving visual cues and contributing to task performance. Impaired visual acuity, in later years in life, compromises safety, productivity, and life quality. Carotenoid pigment content declines with cumulation of light-induced damage through aging process in the retina. The progression of resultant macular degeneration is aggravated by oxidative stress, inflammation, raised blood sugar, and vasculopathy associating aging. Senescent dry degeneration involves drusen (a compound of glycolipid and glycol-conjugate core) deposition that impairs metabolic connectivity of upper layers of retina with choroid. Degeneration of retinal pigment epithelium and photoreceptors thus results. The late more severe form of age-related macular degeneration (AMD), involves factors inducing choroidal neovascularization. Leaky neocapillaries speed degenerative process of the retina. Most age-related pathologies are initiated by metabolic disruptions and AMD shares features of systemic atherosclerosis. An aberrant tissue response to free radical stress, vasculopathy, and local ischemic underlies AMD pathogenesis. There is no specific treatment modality and prudent strategy in prophylaxis only. Early diagnosis and proper control of environmental and lifestyle factors are strived by newer biomedical understanding, which is briefly reviewed.

Keywords: Age-related macular degeneration, Inflammaging, Endothelial dysfunction, Retinopathy, Neovascularization.

INTRODUCTION

Prevalence of age-related macular degeneration (AMD), mainly responsible for post middle age loss of vision is found around 2-5% in people above 70 years age in India [1]. Global population above 50 year age constitutes only 20% but carries 80% of blind burden. Most of the blind people live in developing countries. 90% of all cases of AMD are made by dry atrophied form of disease and Caucxasian race is more vulnerable. The aggressive neovascularizing form makes minor 10% prevalence, but mostly responsible for blindness and has greater prevalence in underdeveloped parts of the world. AMD stands second to diabetes as a cause of severe vision loss from the 5th decade of life onward.

Both AMD and diabetic retinopathy involve breakdown of blood-retinal barrier (BRB). The diabetic retinopathy initially affects inner retinal layers of endothelium. Contrastingly, AMD initially affects outer retina at chorioretinal interface in the retinal pigment epithelium (RPE). Neovascularization in choriocapillaries may subsequently invade retina. The retinal tissue has a high metabolism and oxygen consumption, with abundant content of polyunsaturated fatty acids. Retina is exposed to light, a strong oxidizing factor. Typically, the macula area suffers photochemical damage with generation of excess of reactive oxygen species (ROS). Around 3% of diagnosed diabetes patients bear retinopathy but have much less incidence of AMD than non-diabetic population [2]. The damaged BRB of the inner layer in diabetics appears to signal upregulated transport function of outer layer BRB in RPE. This delays neovascularization that drives AMD progression [3].

Pathogenesis

Photochemical damage due to oxidative stress is the hallmark of AMD. Dry form of AMD is characterized by drusen deposits. These impair metabolic connectivity of choroid and upper layers of the macula, resulting in degeneration of RPE and photoreceptors (PR). Wet form of AMD involves choroid neovascularizing factors. The consequent increased fluid leaks injure RPE and PRs further. Lipids accumulate in the Bruch's membrane during the ordinary process of aging. The membrane thickens and is devoid of protective antioxidant enzymes. Lipids cause stimulation of accumulating macrophages toward production of vascular endothelial growth factor (VEGF). Inflammation sets choroidal neovascularization to eliminate molecules perceived as injurious to RPE and PRs. This proves counterproductive. Several bioactive mediators and alternate complement pathway sustain the chronic inflammation. The spread of Bruch's membrane leads to early and late forms of AMD. Derangements are implied in multiple physiological pathways [4].

Primary lesion appears in RPE where molecular debris accumulates straining cells. Extrusion of debris and accumulation in Bruch's membrane as drusen aggregates, as well as under basal lamina occur next. Progressive degeneration of RPE and PRs continues. Leakage from neovascularization membrane invading the debris worsens the pathology. New vessels arising from macular disc cause vitreous retraction. The pull may cause vitreous hemorrhages, retinal detachment, etc. Serous or hemorrhagic leaks elevate the neurosensory RPE, resulting in dysmorphic vision, scotoma, blurring, and decline of central vision.

PATHOGENIC DETERMINANTS IN AGING PHENOMENA

Aging disorders are cumulative outcome of multiple defective cellular mechanisms and metabolic pathways. Environmental and lifestyle factors are implicated as well. Metabolism is crucially linked to initiation of age-related maladies. The RPE is impacted adversely by oxidized cholesterol moieties. Mitochondrial function is deranged, increasing apoptosis. The complement system is activated, and there is increased expression of VEGF in endothelium. The complement system plays a role in drusen formation as well as neovascularization in AMD. The accompanying endothelial damage and dysfunction allow formation of atheromatous plaque in systemic atherosclerosis. Local and systemic complement activity plays role in both atherosclerosis and AMD. Specific polymorphism "Y402H" of complement inhibitor factor H is associated

with increased incidence of AMD and atherosclerosis [5-8]. The molecular composition of drusen is highly similar to an atheromatous plaque. Oxidant stress and local ischemia underlie the pathogenesis in both.

Endothelial dysfunction

Vascular endothelium supports integrity and stability of circulation homeostasis via production of various bioactive modulators and hormones [9,10]. Dysfunction of endothelium compromises the circulatory homeostasis and preservation of organ functions. AMD represents local manifestation of systemic vascular dysfunction. Sustained subclinical inflammation is triggered by ROS, generated in attempt to eliminate some persisting irritant in the system. The process of such inflammaging is obvious in AMD [11].

Endothelial dysfunction is indeed defensive activation. There is upregulated expression of pro-inflammatory molecules. Circulatory impedance during perturbed states is avoided by synthesis of nitric oxide (NO) from endothelial nitric oxide synthase (eNOS) enzyme. Excess oxidative stress uncouples function of eNOS, and the NO is transformed to peroxynitrite radical in combination with superoxide anions. Endothelial dysfunction is NO deficient state [12], inflicted by intracellular oxidant stress [13].

Chronic inflammatory state

Chronic inflammation occurring in drusen implicates cellular and humoral inflammatory and immune constituents [14]. Antioxidant defense is depleted in the aged, making them vulnerable to the occurrence of AMD [15]. Inflammatory cytokines in the aqueous humor are found increased through all stages of AMD. The persisting irritation, as well as pro-inflammatory mediator, contributes to endoplasmic reticulum (ER) stress in exposed vascular endothelium. The homeostatic cleansing and maintenance tasks of ER get compromised. ER stress promotes VEGF expression and angiogenesis, the basis for neovascularization [16].

Activation, injury, or apoptosis of vascular endothelial cells release submicron sized microparticles in circulation. These are seen in chronic cardiovascular, cerebrovascular, renal, and metabolic disorders as well as in AMD [17]. The particles are integral components of inflammation, vascular injury, angiogenesis, and thrombosis [18]. Levels of van Willebrands factor, fibrinogen, and plasminogen activator inhibitor type 1 are increased in atherosclerosis as well as in AMD [19,20]. Advanced glycation end-product levels are also elevated in AMD [21] as also lipid peroxide levels [22,23]. Both are causal to endothelial dysfunction. Raised plasma level of C-reactive protein (CRP) is a constant feature of AMD [24]. Intraocular inflammation in of neovascularized AMD is marked by elevated endothelin-1 levels [25]. Systemic atherosclerosis is characterized by generalized complement activation [6,7], which is established risk factor for AMD [8]. Retinal autoantibodies that occur normally in 10% population are elevated in most AMD patients [26]. Increased anticytomegalovirus IgG antibody titer is found to significantly associate with AMD [27]. Significant association of AMD with periodontal inflammation is reported as well [28]. All these suggest autoimmunity perspectives in pathogenesis.

Sustained inflammation is a crucial pathogenic determinant of AMD. CRP elevation is more than just inflammatory biomarker and inhibits eNOS expression depleting NO availability. CRP also increases angiotensin 1 receptor expression, and consequent increased ROS formation, with further inactivation of NO. The endothelial progenitor cell (EPC) number and activity are also compromised by CRP. Raised concentration of cellular adhesion molecule in drusen suggests activity of macrophages gathering around. The adhesion molecules also reveal choroidal vascular inflammatory disorder [29]. The risk factors that promote atherosclerosis and cardiovascular disease also contribute AMD risk [30]. Patients bearing AMD have increased the occurrence of stroke and myocardial infarction [31].

Oxidant stress

Normally, only 1% of oxygen destined for mitochondrial respiration leak out as superoxide. The proportion increases markedly with aging, amid depleted state of antioxidant protection. Same scenario manifests with heightened lipid peroxide burden and lowered NO availability in AMD [32]. Amid reduced ocular perfusion in the aged, RPE dysfunction leads to risk of AMD [33]. There is decline in EPC function, parallel with decreased the physical activity of the aged, which may be reversed as prevention strategy [34]. Critical to the occurrence of vascular impairment is the increased activity of transcription factor NF-kappa-B in the aged people [35]. The majority of AMD sufferers give positive family history. Smoking is singularly the most provocative lifestyle factor for AMD. Circulation disorders, arteriosclerosis, angina, myocardial infarction, and stroke are proven secondary risk factors for AMD. Decreased retinal perfusion implies altered pericyte function, increased blood viscosity, altered fibrinolytic activity. Vasoocclusion would cause tissue hypoxia upregulating the mechanisms for neovascularization [36]. Obesity, the leading component in metabolic syndrome, is independent risk factor for retinopathy [37]. The hyperleptinemia increases oxidant stress [38]. Oxidant stress causes overexpression of VEGF, the key neovascularizing molecule in AMD [39].

PREVENTION

Preventive measures against AMD have to target the shared mechanisms of chronic inflammatory diseases, e.g., cardiovascular disorders, obesity, diabetes, hypertension, etc. [40]. Lifestyle modification must include smoking cessation, which increases oxidant stress and blood coagulability and reduces protective high-density lipoprotein cholesterol [41,42]. Nicotine is detrimental to antiangiogenic factor production by RPE while stimulates VEGF formation directly [43]. Physical activity improves expression of eNOS and NO availability, as well as expression of antioxidant superoxide dismutase enzymes [44]. Dose-dependent reduction in AMD risk is reported following physical exercise [45]. Physical exercise also improves mitochondrial function and activity of EPC [46,47]. Both such consequences are good for vascular health.

Nutrients

Role of micro and macronutrients in modifying individual risk factors are widely studied. Carotenoids are present in macular pigment and exert antioxidant influence on PR cell layer through filtering blue light, which mediates light injury. Polyphenolic antioxidants contained in green vegetables and carotenoids in colored fruits and had shown good preventive promise. Carotenoid lutein suppresses NF-kappa-B activation and systemic inflammation, choroidal neovascularization, and retinal ischemia [48]. Lutein and zeaxanthin help filtering injurious blue light and quench free radicals [49]. Dietary intakes of lutein and zeaxanthin are found low in most AMD patients [50]. Supplementation of such carotenoids may be prudent preventive measure in the aging individuals.

High glycemic index foods increase formation of the advanced glycation end products (AGE), which accumulate in tissue causing the ER stress [51]. Avoidance of such foods appears to offer preventive benefit [52]. Weight reduction in overweight individuals reduces risk of AMD [53]. Calorie restriction to half of the *ad-libitum* intake, improves NO production and function, improved mitochondrial bioenergetics, and reduced ROS generation. The activity of silent information regulator 1 is also enhanced and the endothelial function is benefited via multiple ways. Calorie restriction thus has proven prevention value [54].

Favorable influence of Omega-3 fatty acids, rich in linseed, olive, and fish oil on vascular and other degenerative processes in chronic inflammatory state is well known. Peroxisome proliferator-activated receptor (PPAR) gamma receptor mechanisms, linked to lipid metabolism, also are found to mediate protection from AMD. This is apparent from the favorable effects of regular consumption of docosahexaenoic acid and eicosapentaenoic acid (fish oil) [55].

Increasing understanding on biological roles of vitamin D supplement in aging the individual is relevant also to prevention of AMD [56]. Folate deficiency is linked to the occurrence of hyperhomocysteinemia, with pro-inflammatory influence. Combined folate with vitamin B12, B6 supplement in elderly shows preventive benefits against AMD [57].

Zinc supplement offers excellent biological rationale [58]. That checks activation of the complement cascade, with established pathogenic role [59,60]. Dietary L-arginine supplement is used to boost NO production. It is shown to be relevant to AMD prevention [61,62]. Patients with AMD are deficient in coenzyme Q profile, and its supplementation helps delaying disease progression [63,64]. The unique, calorie restriction-mimetic potential of resveratrol, has generated interest in supplementation trials for preventing light-induced retinal damage and endothelial dysfunction in AMD [65,66]. The patients with AMD exhibit profoundly deficient profile of melatonin, compared to normal age-matched fellows [67,68]. Melatonin supports cell vitality via telomerase enzyme function in RPE. A boost to melatonin profile may be preventive for AMD.

PHARMACEUTICAL PREVENTION

Pharmacological prevention should aim at suppressing free radical stress, improving NO production and thus correcting endothelial dysfunction. This is systemic objective in prevention of aging-associated disorders [69]. Overactive renin-angiotensin-aldosteron system is implicated in pro-inflammatory state, and its control has prevention value [70]. Angiotensin receptor blockade (ARB) prevents choroidal neovascularization in AMD [71]. Telmisartan, an ARB also is stimulant to PPAR gamma, boosting the preventive beneficence [72]. Angiotensin receptors mediate nicotinamide adenine dinucleotide phosphate oxidase activation and critically enhance the generation of oxidant stress that may be suppressed specifically by ARB drugs [73-76].

3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitor lipid-lowering drugs, the statins, possess a variety of antiaging actions [77]. Statins correct the NO versus superoxide imbalance and thus improve endothelial function. They inhibit leukocyte-endothelium adhesion/interaction and that damages retina and repress angiogenesis. Patients with coronary artery disease are taking statin exhibit 5-fold reduced the risk of developing AMD [78]. Preventive potential of statins against AMD is proven [79,80].

Preventive promise is also shown by drugs inhibiting endothelial uptake of oxidized lipoproteins [81]. Trimetazidine, an agent, promoting preferential utilization of glucose over fat, for use as fuel, reduces oxidative stress and ischemic injury [82]. Novel newer beta-adrenoceptor blockers carvedilol and nebivolol, improve mitochondrial function [83]. PPAR gamma agonists also exhibit such effect [84]. Both these drug classes inhibit oxidant stress, improve NO availability and function. Current consensus favors the development of agents that share such actions, and additionally, may break the peroxynitrite radical [74].

Alagebrium, a drug breaking the AGEs may correct endothelial dysfunction [85]. An antagonist of endothelin, Bonestan, also inhibits neovascularization in AMD [25]. Novel pharmacological agents being evaluated for preventive potential against AMD include an antagonist of serotonin receptor 1a [86], an antagonist of tumor necrosis factor alfa [87], as well as well-known antioxidant n-acetylcysteine [88]. Critical significance of the activation of alternate complement pathway in chronic inflammation states has prompted testing of inhibitors toward stalling neovascularization and retinal damage in AMD [89].

PUBLIC HEALTH PERSPECTIVES

As per the WHO projection, AMD would comprise 7% and diabetic retinopathy 4% of blinding disorders of eye by 2020 [90]. Low power laser ablation conjunct with verteporfin (photosensitizer), render uncertain benefits in a very small fraction of AMD cases. Intravitrious injections of anti-VEGF agents are practically most demanding and again limited in benefit. Any surgical interventions would need services of highly skilled vitreoretinal surgeons, again promising no certain benefit. These are mostly indicated in the neovascularizing form of AMD, the late hopeless stage.

The available primary/secondary prevention through lifestyle options, nutraceuticals, and drugs deserves chance in persons above 50 years age and bearing cardiovascular risk factors. All individuals diagnosed as having AMD at any stage must receive proactive management with available remedies. As of now, preventive measures for healthy individuals are untested. People's education and awareness of modify able risk factors, e.g., avoidance of smoking, control of obesity appear very relevant. A survey revealed that 73% of diabetic retinopathy cases and 84% cases with AMD are simply unaware of their serious condition [91]. This raises serious public health concern, for regular eye checkups, for elderly complaining any deterioration in vision. Definitive referral mechanism for care must be available when AMD is detected in eye check-ups. Rehabilitation is indispensable need, and depression for vision loss must be timely addressed. Techniques for early diagnosis and delivery of requisite care, cost reduction in available treatment options in community contexts, are crying vistas to address by research and developmental health-care policy [92].

REFERENCES

1. Krishnan T, Ravindran RD, Murthy GV, Vashist P, Fitzpatrick KE, Thulasiraj RD, *et al*. Prevalence of early and late age-related macular degeneration in India: The INDEYE study. Invest Ophthalmol Vis Sci 2010;51(2):701-7.
2. Voutilainen-Kaunisto RM, Teräsvirta ME, Uusitupa MI, Niskanen LK. Age-related macular degeneration in newly diagnosed Type 2 diabetic patients and control subjects: A 10-year follow-up on evolution, risk factors, and prognostic significance. Diabetes Care 2000;23(11):1672-8.
3. Sander B, Larsen M, Moldow B, Lund-Andersen H. Diabetic macular edema: Passive and active transport of fluorescein through the blood-retina barrier. Invest Ophthalmol Vis Sci 2001;42(2):433-8.
4. Bhutto I, Lutty G. Understanding age-related macular degeneration (AMD): Relationships between the photoreceptor/retinal pigment epithelium/Bruch's membrane/choriocapillaris complex. Mol Aspects Med 2012;33(4):295-317.
5. Machalinska A, Kawa MP, Marlicz W, Machaliński B. Complement system activation and endothelial dysfunction in patients with age related macular degeneration (AMD): Possible relation between AMD and atherosclerosis. Acta Ophthalmol 2012;90(8):695-703.
6. Machalinska A, Dziedziejko V, Mozolewska-Piotrowska K, Karczewicz D, Wiszniewska B, Machalinski B. Elevated plasma levels of C3a complement compound in the exudative form of age-related macular degeneration. Ophthalmic Res 2009;42(1):54-9.
7. Reynolds R, Hartnett ME, Atkinson JP, Giclas PC, Rosner B, Seddon JM. Plasma complement components and activation fragments: Associations with age-related macular degeneration genotypes and phenotypes. Invest Ophthalmol Vis Sci 2009;50(12):5818-27.
8. Seddon JM, Gensler G, Milton RC, Klein ML, Rifai N. Association between C-reactive protein and age-related macular degeneration. JAMA 2004;291(6):704-10.
9. Verma S, Anderson TJ. Fundamentals of endothelial function for the clinical cardiologist. Circulation 2002;105(5):546-9.
10. Lerman A, Zeiher AM. Endothelial function: Cardiac events. Circulation 2005;111(3):363-8.
11. Fischer T. Comment on the human vascular system (Hungarian). Orv Hetil 2006;147:1145.
12. Marchesi C, Ebrahimian T, Angulo O, Paradis P, Schiffrin EL. Endothelial nitric oxide synthase uncoupling and perivascular adipose oxidative stress and inflammation contribute to vascular dysfunction in a rodent model of metabolic syndrome. Hypertension 2009;54(6):1384-92.
13. Yi L, Chen CY, Jin X, Zhang T, Zhou Y, Zhang QY, *et al*. Differential suppression of intracellular reactive oxygen species-mediated signaling pathway in vascular endothelial cells by several subclasses of flavonoids. Biochimie 2012;94(9):2035-44.
14. Colak E, Majkic-Singh N, Žoric L, Radosavljevic A, Kosanovic-Jakovic N. The impact of inflammation to the antioxidant defense parameters in AMD patients. Aging Clin Exp Res

2012;24(6):588-94.
15. Colak F, Mojkie-Singh N, Zoric L, Radosavljevic A, Kosanovic-Jakovic N. The role of CRP and inflammation in the pathogenesis of age related macular degeneration. Biochem Med (Zagreb) 2012;22(1):39-48.
16. Salminen A, Kauppinen A, Hyttinen JM, Toropainen E, Kaarniranta K. Endoplasmic reticulum stress in age-related macular degeneration: Trigger for neovascularization. Mol Med 2010;16(11-12):535-42.
17. Yong PJ, Koh CH, Shim WS. Endothelial microparticles: Missing link in endothelial dysfunction? Eur J Prev Cardiol 2013;20(3):496-512.
18. Chironi GN, Boulanger CM, Simon A, Dignat-George F, Freyssinet JM, Tedgui A. Endothelial microparticles in diseases. Cell Tissue Res 2009;335(1):143-51.
19. Wu KH, Tan AG, Rochtchina E, Favaloro EJ, Williams A, Mitchell P, *et al.* Circulating inflammatory markers and homeostatic factors in age related maculopathy: A population based case control study. Invest Ophthalmol Vis Sci 2007;48(5):1983-8.
20. Vischer UM. von Willebrand factor, endothelial dysfunction, and cardiovascular disease. J Thromb Haemost 2006;4(6):1186-93.
21. Tan KC, Chow WS, Ai VH, Metz C, Bucala R, Lam KS. Advanced glycation end products and endothelial dysfunction in Type 2 diabetes. Diabetes Care 2002;25(6):1055-9.
22. Evereklioglu C, Er H, Doganay S, Cekmen M, Turkoz Y, Otlu B, *et al.* Nitric oxide and lipid peroxidation are increased and associated with decreased antioxidant enzyme activities in patients with age-related macular degeneration. Doc Ophthalmol 2003;106(2):129-36.
23. Hennig B, Chow CK. Lipid peroxidation and endothelial cell injury: Implications in atherosclerosis. Free Radic Biol Med 1988;4(2):99-106.
24. Adali E, Kurdoglu M, Adoli F, Cim N, Yildizhan R, Kolusari A. The relationship between brachial artery flow mediated dilatation, high sensitivity CRP and uterine artery velocimetry with pre-eclampsia. J Clin Ultrasound 2011;39(4):191-7.
25. Cellini M, Strobbe E, Gizzi C, Balducci N, Toschi PG, Campos EC. Endothelin-1 plasma levels and vascular endothelial dysfunction in primary open angle glaucoma. Life Sci 2012;91(13-14):699-702.
26. Morohoshi K, Goodwin AM, Ohbayashi M, Ono SJ. Autoimmunity in retinal degeneration: Autoimmune retinopathy and age-related macular degeneration. J Autoimmun 2009;33(3-4):247-54.
27. Miller DM, Espinosa-Heidmann DG, Legra J, Dubovy SR, Sũner IJ, Sedmak DD, *et al.* The association prior cytomegalovirus infection with neovascular age-related macular degeneration. Am J Ophthalmol 2004;138(3):323-8.
28. Brzozowska A, Puchalska-Niedbal L. Oral status as a potential source of infection in AMD patients – Introductio. Klin Oczna 2012;114(1):29-32.
29. Jones JB, Tao Y, Neumaier M, Findeisen P. Monocyte chemotractant protein I, intracellular adhesion molecule 1 and vascular cell adhesion molecule 1 in exudative age-related macular degeneration. Arch Ophthalmol 2010;128(10):1281-6.
30. Connell PP, Keane PA, O'Neill EC, Altaie RW, Loane E, Neelam K, *et al.* Risk factors for age-related maculopathy. J Ophthalmol 2009;2009:360764.
31. Ikram MK, Mitchell P, Klein R, Sharrett AR, Couper DJ, Wong TY. Age-related macular degeneration and long-term risk of stroke subtypes. Stroke 2012;43(6):1681-3.
32. Totan Y, Cekiç O, Borazan M, Uz E, Sögüt S, Akyol O. Plasma malondialdehyde and nitric oxide levels in age related macular degeneration. Br J Ophthalmol 2001;85(12):1426-8.
33. Xu W, Grunwald JE, Metelitsina TI, DuPont JC, Ying GS, Martin ER, *et al.* Association of risk factors for choroidal neovascularization in age-related macular degeneration with decreased foveolar choroidal circulation. Am J Ophthalmol 2010;150(1):40-47.e2.
34. Xia WH, Li J, Su C, Yang Z, Chen L, Wu F, *et al*. Physical exercise attenuates age-associated reduction in endothelium-reparative capacity of endothelial progenitor cells by increasing CXCR4/JAK-2 signaling in healthy men. Ageing Cell 2012;11(1):111-9.
35. Fischer T. New possible strategy for prevention and preventive treatment of age-related macular degeneration resting on recent clinical and pathophysiological observations. CEMED 2009;3:415-30.
36. Shotliff K, Duncan G. Diabetes and the eye. In: Shaw KM, Cummings MH, editors. Diabetic Complications. Chichester, UK: John Wiley & Sons; 2005. p. 1-19.
37. Cheung N, Wong TY. Obesity and eye diseases. Surv Ophthalmol 2007;52(2):180-95.
38. Bouloumie A, Marumo T, Lafontan M, Busse R. Leptin induces oxidative stress in human endothelial cells. FASEB J 1999;13(10):1231-8.
39. Caldwell RB, Bartoli M, Behzadian MA, El-Remessy AE, Al-Shabrawey M, Platt DH, *et al.* Vascular endothelial growth factor and diabetic retinopathy: Role of oxidative stress. Curr Drug Targets 2005;6(4):511-24.
40. Ambati J, Ambati BK, Yoo SH, Ianchulev S, Adamis AP. Age-related macular degeneration: Etiology, pathogenesis, and therapeutic strategies. Surv Ophthalmol 2003;48(3):257-93.
41. Takagi H. Aging and retinal vascular diseases. Nippon Ganka Gakkai Zasshi 2007;111(3):207-30.
42. Chakravarthy U, Wong TY, Fletcher A, Piault E, Evans C, Zlateva G, *et al.* Clinical risk factors for age-related macular degeneration: A systematic review and meta-analysis. BMC Ophthalmol 2010;10:31.
43. Pons M, Marin-Castaño ME. Nicotine increases the VEGF/PEDF ratio in retinal pigment epithelium: A possible mechanism for CNV in passive smokers with AMD. Invest Ophthalmol Vis Sci 2011;52(6):3842-53.
44. Golbidi S, Laher I. Exercise and the cardiovascular system. Cardiol Res Pract 2012;2012:210852.
45. Willioms PT. Prospective study of incident age-related macular degeneration in relation to vigorous physical activity during a seven year follow up. Invest Ophthalmol Vis Sci 2009;50(1):101-6.
46. Wong IY, Koo SC, Chan CW. Prevention of age-related macular degeneration. Int Ophthalmol 2011;31(1):73-82.
47. King RE, Kent KD, Bomser JA. Resveratrol reduces oxidation and proliferation of human retinal pigment epithelial cells via extracellular signal-regulated kinase inhibition. Chem Biol Interact 2005;151(2):143-9.
48. Kijlstra A, Tian Y, Kelly ER, Berendschot TT. Lutein: More than just a filter for blue light. Prog Retin Eye Res 2012;31(4):303-15.
49. Mares JA, Voland RP, Sondel SA, Millen AE, Larowe T, Moeller SM, *et al.* Healthy lifestyles related to subsequent prevalence of age-related macular degeneration. Arch Ophthalmol 2011;129(4):470-80.
50. Olea JL, Aragón JA, Zapata ME, Tur JA. Characteristics of patients with wet age-related macular degeneration and low intake of lutein and zeaxanthin. Arch Soc Esp Oftalmol 2012;87(4):112-8.
51. Uchiki T, Weikel KA, Jiao W, Shang F, Caceres A, Pawlak D, *et al*. Glycation altered proteolysis as a pathologic mechanism that links dietary glycemic index, ageing and age related diseases (in nondiabetics). Aging cell 2012;11(1):1-13.
52. Chiu CJ, Taylor A. Dietary hyperglycemia, glycemic index and metabolic retinal diseases. Prog Retin Eye Res 2011;30(1):18-53.
53. Peters A, Magliano DJ, Stevens J, Duncan BB, Klein R, Wong TY. Changes in abdominal obesity and age-related macular degeneration: The atherosclerosis risk in communities study. Arch Ophthalmol 2008;126(11):1554-60.
54. Anderson RM, Weindruch R. The caloric restriction paradigm: Implications for healthy human aging. Am J Hum Biol 2012;24(2):101-6.
55. Augood C, Chakravarthy U, Young I, Vioque J, de Jong PT, Bentham G, *et al.* Oily fish consumption, dietary docosahexaenoic acid and eicosapentaenoic acid intakes, and associations with neovascular age-related macular degeneration. Am J Clin Nutr 2008;88(2):398-406.
56. Millen AE, Voland R, Sondel SA, Parekh N, Horst RL, Wallace RB, *et al.* Vitamin D status and early age-related macular degeneration in postmenopausal women. Arch Ophthalmol 2011;129(4):481-9.
57. Christen WG, Glynn RJ, Chew EY, Albert CM, Manson JE. Folic acid, pyridoxine, and cyanocobalamin combination treatment and age-related macular degeneration in women: The women's antioxidant and folic acid cardiovascular study. Arch Intern Med 2009;169(4):335-41.
58. Prasad AS. Zinc: An antioxidant and anti-inflammatory agent: Role of zinc in degenerative disorders of aging. J Trace Elem Med Biol 2014;28(4):364-71.
59. Semes LP. Recent evidence points to common pathways in AMD and vascular disease: Research supports dietary modification or supplementation to reduce risk. Prim Care Optom News 2012.
60. Zampatti S, Ricci F, Cusumano A, Marsella LT, Novelli G, Giardina E. Review of nutrient actions on age-related macular degeneration. Nutr Res 2014;34(2):95-105.
61. Jablecka A, Bogdanski P, Balcer N, Cieslewicz A, Skoluda A, Musialik K. The effect of oral L-arginine supplementation on fasting glucose, HbA1c, nitric oxide and total antioxidant status in diabetic patients with atherosclerotic peripheral arterial disease of lower extremities. Eur Rev Med Pharmacol Sci 2012;16(3):342-50.
62. Sharma A, Bernatchez PN, de Haan JB. Targeting endothelial dysfunction in vascular complications associated with diabetes. Int J Vasc Med 2012;2012:750126.
63. Blasi MA, Bovina C, Carella G, Genova ML, Jansen AM, Lenaz G, *et al.* Does coenzyme Q10 play a role in opposing oxidative stress in patients with age-related macular degeneration? Ophthalmologica 2001;215(1):51-4.
64. Nakajima Y, Inakuchi Y, Bishi M. Coenzyme Q10 protects retinal cells

against oxidative stress *in vitro* and *in vivo*. Brain Res 2008;1226:226-33.
65. Kubota S, Kunhara T, Ebinuma M, Kubota M, Yuki K, Sasaki M, *et al*. Resveratrol prevents light-induced retinal degeneration via suppressing activator protein-1 activation. Am J Pathol 2010;177(4):1725-31.
66. Lassaletta AD, Chu LM, Elmadhun NY, Burgess TA, Feng J, Robich MP, *et al.* Cardioprotective effects of red wine and vodka in a model of endothelial dysfunction. J Surg Res 2012;178(2):586-92.
67. Rastmanesh R. Potential of melatonin to treat or prevent age-related macular degeneration through stimulation of telomerase activity. Med Hypotheses 2011;76(1):79-85.
68. Rosen R, Hu DN, Perez V, Tai K, Yu GP, Chen M, *et al.* Urinary 6-sulfatoxymelatonin level in age-related macular degeneration patients. Mol Vis 2009;15:1673-9.
69. Münzel T, Gori T. Nebivolol: The somewhat-different beta-adrenergic receptor blocker. J Am Coll Cardiol 2009;54(16):1491-9.
70. Kurihara T, Ozhawa Y, Ishida S, Okano H, Tsubota K. Renin-angiotensin system hyperactivation can induce inflammation and retinal neural dysfunction. Int J Inflamm 2012;2012:Article ID: 581695, 14. Available from: http://www.dx.doi.org/10.1155/2012/581695.
71. Wright SA, O'Prey FM, McHenry MT, Leahey WJ, Devine AB, Duffy EM, *et al.* A randomised interventional trial of omega-3-polyunsaturated fatty acids on endothelial function and disease activity in systemic lupus erythematosus. Ann Rheum Dis 2008;67(6):841-8.
72. Pershadsingh HA, Moore DM. PPARgamma agonists: Potential as therapeutics for neovascular retinopathies. PPAR Res 2008;2008:164273.
73. López-Sendón J, Swedberg K, McMurray J, Tamargo J, Maggioni AP, Dargie H, *et al.* Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease. The task force on ACE-inhibitors of the European society of cardiology. Eur Heart J 2004;25(16):1454-70.
74. Ceriello A. New insights on oxidative stress and diabetic complications may lead to a "causal" antioxidant therapy. Diabetes Care 2003;26(5):1589-96.
75. Molavi B, Mehta JL. Oxidative stress in cardiovascular disease: Molecular basis of its deleterious effects, its detection, and therapeutic considerations. Curr Opin Cardiol 2004;19(5):488-93.
76. Asselbergs FW, van der Harst P, Jessurun GA, Tio RA, van Gilst WH. Clinical impact of vasomotor function assessment and the role of ACE-inhibitors and statins. Vascul Pharmacol 2005;42(3):125-40.
77. Ota H, Eto M, Kano MR, Kahyo T, Setou M, Ogawa S, *et al.* Induction of endothelial nitric oxide synthase, SIRT1, and catalase by statins inhibits endothelial senescence through the Akt pathway. Arterioscler Thromb Vasc Biol 2010;30(11):2205-11.
78. Hall NF, Gale CR, Syddall H, Phillips DI, Martyn CN. Risk of macular degeneration in users of statins: Cross sectional study. BMJ 2001;323(7909):375-6.
79. Kim KJ, Kim KS, Kim NR, Chin HS. Effects of simvastatin on the expression of heme oxygenase-1 in human RPE cells. Invest Ophthalmol Vis Sci 2012;53(10):6456-64.
80. Shahsuvaryan M. HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors: Evaluation of the role and actions in age-related macular degeneration. J Physiol Pathophysiol 2010;1(2):13-7.
81. Morawietz H. LOX-1 receptor as a novel target in endothelial dysfunction and atherosclerosis. Dtsch Med Wochenschr 2010;135(7):308-12.
82. Coyas A. The efficacy of trimetazidine in cochleovestibular disorders of ischemic origin. A crossover control versus placebo trial. Ann Otolaryngol Chir Cervicofac 1990;107 Suppl 1:82-7.
83. Wu TC, Chen YH, Leu HB, Chen YL, Lin FY, Lin SJ, *et al.* Carvedilol, a pharmacological antioxidant, inhibits neointimal matrix metalloproteinase-2 and - 9 in experimental atherosclerosis. Free Radic Biol Med 2007;43(11):1508-22.
84. Hwang J, Kleinhenz DJ, Rupnow HL, Campbell AG, Thulé PM, Sutliff RL, *et al.* The PPARgamma ligand, rosiglitazone, reduces vascular oxidative stress and NADPH oxidase expression in diabetic mice. Vascul Pharmacol 2007;46(6):456-62.
85. Zieman SJ, Melenovsky V, Clattenburg L, Corretti MC, Capriotti A, Gerstenblith G, *et al.* Advanced glycation end product crosslink breaker (alagebrium) improves endothelial function in patients with isolated systolic hypertension. J Hypertens 2007;25(3):577-83.
86. Thampi P, Rao HV, Mitter SK, Cai J, Mao H, Li H, *et al.* The 5HT1a receptor agonist 8-Oh DPAT induces protection from lipofuscin accumulation and oxidative stress in the retinal pigment epithelium. PLoS One 2012;7(4):e34468.
87. Mirshahi A, Hoehn R, Lorenz K, Kramann C, Baatz H. Anti-tumor necrosis factor alpha for retinal diseases: Current knowledge and future concepts. J Ophthalmic Vis Res 2012;7(1):39-44.
88. Hara R, Inomata Y, Kawaji T, Sagara N, Inatani M, Fukushima M, *et al.* Suppression of choroidal neovascularization by N-acetyl-cysteine in mice. Curr Eye Res 2010;35(11):1012-20.
89. Rohrer B, Long Q, Coughlin B, Wilson RB, Huang Y, Qiao F, *et al.* A targeted inhibitor of the alternative complement pathway reduces angiogenesis in a mouse model of age-related macular degeneration. Invest Ophthalmol Vis Sci 2009;50(7):3056-64.
90. WHO: Vision 2020. The Right to Sight-Global Initiative for the Elimination of Avoidable Blindness. Action Plan 2006-2011. Geneva: WHO; 2007.
91. Gibson DM. Diabetic retinopathy and age-related macular degeneration in the U.S. Am J Prev Med 2012;43(1):48-54.
92. WHO Consultation Report. Public Health Management of Chronic Eye Diseases. Geneva: WHO; 2011.