

THE AGE-RELATED MACULAR DEGENERATION AS A VASCULAR DISEASE: CONTRIBUTIONS TO THE NON- PHARMACOLOGICAL INTERVENTIONS AND PHARMACOLOGICAL THERAPY ARISING FROM ITS PATHOGENESIS.

Dr. Tamas Fischer M.D.

Article Received on
23 Jan 2016,

Revised on 13 Feb 2016,
Accepted on 07 March 2016

DOI: 10.20959/wjpr20164-5661

***Correspondence for
Author**

Dr. Tamás Fischer, M. D.

ABSTRACT

It has a great therapeutic significance that the disorder of the vascular endothelium, which supplies the affected ocular structures, plays a major role in the development of age-related macular degeneration. Chronic inflammation is closely linked to diseases associated with endothelial dysfunction and age-related macular degeneration is accompanied by a general inflammatory response. The vascular wall including those in chorioids may be activated by several repeated and/or prolonged mechanical, physical, chemical, microbiological,

immunologic and genetic factors causing a protracted host defence response with a consequent vascular damage, which leads to age- related macular degeneration. Based on this concept, age-related macular degeneration is a local manifestation of the systemic vascular disease. This recognition should have therapeutic implications because restoration of endothelial dysfunction can stabilize the condition of chronic vascular disease including age-related macular degeneration, as well. Restoration of endothelial dysfunction by non pharmacological or pharmacological interventions may prevent the development or improve endothelial dysfunction resulting in prevention or improvement of age-related macular degeneration.

Nonpharmacological interventions which may have beneficial effect in endothelial dysfunction include (1) *smoking cessation*; (2) *reduction of increased body weight*; (3) *adequate physical activity*; (4) *appropriate diet* (a) proper dose of *flavonoids, polyphenols* and *curcumin*; (b) *omega-3 long-chain polyunsaturated fatty acids: docosahexaenoic acid and eicosapentaenoic acid*; (c) *carotenoids, lutein and zeaxanthins*, (d) *management of dietary*

glycemic index, (e) *caloric restriction*, and (5) of stressful lifestyle. Non-pharmacological interventions should be preferable even if medicaments are also used for the treatment of endothelial dysfunction.- It is of great therapeutic significance that *disordered function of the vascular endothelium* which supply the affected ocular structures plays a major role in the pathogenesis and development of age-related macular degeneration. *Chronic inflammation* is closely linked to diseases associated with *endothelial dysfunction*, and age-related macular degeneration is accompanied by a *general inflammatory response*. According to current concept, age-related macular degeneration is a local *manifestation of systemic vascular disease*. This recognition could have therapeutic implications because *restoration of endothelial dysfunction can restabilize the condition of chronic vascular disease* including age-related macular degeneration as well. *Restoration of endothelial dysfunction by pharmacological or non pharmacological interventions may prevent the development or improve endothelial dysfunction, which result in prevention or improvement of age related macular degeneration as well.*

Pharmacological interventions (medicines) including (1) *inhibitors of the renin-angiotensin system* ([a] *converting enzyme inhibitors*, [b] *angiotensin-receptor blockers* and [c] *renin inhibitors*), (2) *statins*, (3) *acetylsalicylic acid*, (4) *trimetazidin*, (5) *third generation beta-blockers*, (6) *peroxisome proliferator-activated receptor gamma agonists*, (7) *folate*, (8) *vitamin D*, (9) *melatonin*, (10) *advanced glycation end-product* (11) *crosslink breaker alagebrium*, (12) *endothelin-receptor antagonist bosentan*, (13) *coenzyme Q10*; (14) “causal” *antioxidant vitamins*, (a) *FP015 metalloporphyrin compound* (b) *INO-1001*; (15) *N-acetyl-cysteine*, (16) *resveratrol*, (17) *L-arginine*, (18) *serotonin receptor agonists* [5-HT(1A) receptor agonists] *8-Oh DPAT*, (19) *tumor necrosis factor-alpha blockers*, (20) *curcumin* and (21) *doxycyclin* all have beneficial effects on endothelial dysfunction. *Restoration of endothelial dysfunction can restabilize chronic vascular disease including age-related macular degeneration as well.* Considering that the human vascular system is consubstantial, medicines listed above should be given to patients (1) who have no macular degeneration but have risk factors for the disease and are older than 50 years; (2) who have been diagnosed with unilateral age-related macular degeneration in order to prevent damage of the contralateral eye; (3) who have bilateral age-related macular degeneration in order to avert deterioration and in the hope of a potential improvement. However, *randomised prospective clinical trials are still needed* to elucidate the potential role of these drug treatments in the prevention and treatment of age-related macular degeneration.

KEYWORDS: age-related macular degeneration, endothelial dysfunction, oxidative stress, risk factors, primary and secondary prevention, non-pharmacological intervention, pharmacological intervention, lifestyle modifications.

Abbreviations

ACE I = angiotensin converting enzyme inhibitor; ADMA = asymmetrical dimethyl arginine; AGE = advanced glycation end-products; AMD = age-related macular degeneration; AMDRFs = AMD risk factors; Ang-1 = angiopoietin-1; Ang-II = angiotensin II; AO = antioxidant; AOVs = antioxidant vitamins; aPL = antiphospholipid antibody levels; ARB = angiotensin II receptor blocker; ASA = acetylsalicylic acid; AS = atherosclerosis; ATP = adenosine triphosphate; AT1R = AT1 receptor of angiotensin II; BMI = body mass index;; CAD = coronary artery disease; CD 40 = cluster of differentiation 40; CFH = complement factor H; CR = caloric restriction; CI = confidence interval; CNV = choroidal neovascularisation; COX-2 = cyclooxygenase-2; CRP = C-reactive protein; CV = cardiovascular; CVD = cardiovascular disease; hTERT = catalytic subunit of telomerase; DHA = docosahexaenoic acid; DR = diabetic retinopathy; ER = endoplasmic reticulum; EA = endothelial activation; ED = endothelial dysfunction; EDHF = endothelium-derived hyperpolarizing factor; EDNO = endothelial-derived nitric oxide; EF = endothelial function; EMP generation = endothelial microparticle generation; EPCs = endothelial progenitor cells; ET-1 = endothelin 1; eNOS = endothelial nitric oxide synthetase; Fib = fibrinogen; FMD = flow-mediated dilatation; GCC = glaucomatocyclitic crisis; GLP-1 = glucagon like peptide-1 receptor; GI = glycaemic index; GR = glutathione reductase; GS = glycativ stress; HDL-C = high density lipoprotein cholesterol; HMGCoA = hydroxy-methylglutaryl-coenzyme A; hsCRP = high sensitivity C-reactive protein; Hsps = heat shocks proteins; ICAM=intracellular adhesion molecule; immunoglobulin superfamily = IgSF; IL-6 = interleukin 6; LDL-C = low density lipoprotein cholesterol; LP = lipid peroxidation; Lp(a) = lipoprotein (a); LCPUFAs = long-chain polyunsaturated fatty acids; MHC-2 = major histocompatibility antigen complex 2; MCP-1 = monocyte chemotactic protein-1; NAD⁺ = nicotinamide adenine dinucleotide, oxidized form; NADPH = nicotinamide adenine dinucleotide, reduced form; Nrf2 = nuclear factor-E(2)-related factor-2; NF-kappaB = nuclear factor kappa B; OR = odds ratio; OS = oxidative stress; OSEs = oxidation specific epitopes; ox = oxidized; PAF = platelet-activation factor; PAI-1 = plasminogen activator inhibitor 1; PEDF = pigment epithelium derived factor; PARP = poly (ADP-ribose) polymerase; pp = postprandial; PPAR= peroxisome proliferator-activated receptor; PGI₂ = prostacyclin; PRA =

plasma renin activity; PRR = (pro)renin receptor; PUFA = polyunsaturated fatty acid; RAAS = renin-angiotensin-aldosterone system; RF = risk factor; RAPS = receptor-associated prorenin system; SyGS = systemic glycation stress; SIRT1 = silent information regulator 1; SOD = superoxide dismutase; STAT-3 = signal transducer and activator of transcription; aMT6s = 6-sulfatoxymelatonin levels; TAS = total antioxidant status; TF = tissue factor; TM = thrombomodulin; TNF- α = tumor necrosis factor- α ; tPA = tissue plasminogen activator; Th-1 = proinflammatory T-helper; Th-2 = antiinflammatory T-helper; TXA₂ = thromboxane-A₂; TRLs = triglyceride-rich lipoproteins; UPR = unfolded protein response; -VCAM = vascular cell adhesion molecule 1; VD = vascular disease; VEGF = vascular endothelial growth factor; vWF = von Willebrand factor; += overlap between CV and AMD risk factors.

Regarding the *treatment, preventive therapy of AMD*, despite intense research efforts, the enigma that is AMD continues to present daunting challenges for effective therapeutic/preventive therapeutic intervention. The lack of AMD-modifying therapies may, in part, be attributable to the narrow research focus employed to understand this very complex disease. Most human and animal studies in the AMD field reflect a "local/ophthalmic" and not „non-systematic/holistic view”: one should make an alteration in this usual/habitual orthodox approach/attitude(!).

(I) Non-medicinal therapy, preventive treatment of AMD/lifestyle modifications of patient with AMD

Aside from a few exceptions, restoration, healing of ED will ensue upon interventions resulting in a reduction of CV events; this fact provides further support for the theory that restoration of ED can re-stabilize the condition of chronic vascular disease including age-related macular degeneration (AMD) as well.

There is an excellent clinician author, who – with reason – criticizes the everyday, accepted practice of focusing mainly and primarily on the *pharmacological* normalization of the risk factors of cardiovascular diseases (CVD) instead of facing up the true driving force, and to preclude, eliminate *chronic stress due to civilized lifestyle*. After having accepted this as correct, we have to prefer – opposite to the pharmacological interventions – the nonpharmacological actions (against the disadvantageous lifestyle/habits): certainly, our state of health will be shaped mainly depending on our lifestyle. It is very important to identify the risk factors which can be influenced, in order to reduce the occurrence of CV/AMD events and to prevent the progression to an advanced stage. Although there are very promising

pharmacological interventions aimed at reducing and delaying the occurrence of vascular events, the evidence-based *first and most important intervention to be recommended should include the elimination, change of inappropriate habits.*

Preventive medicine for AMD which have lifestyle-related diseases as a systemic background, has attracted growing attention.^[1] Several modifiable aspects of lifestyle have been related to a lower occurrence of AMD, including not smoking, physical activity, and certain aspects of diet. Also, AMD is sometimes observed to be more common in people with a history of chronic diseases or conditions that can also be modified by lifestyle choices, such as cardiovascular disease, diabetes, hypertension, obesity, and diseases of inflammation or elevated markers of inflammation^[2] The *lifestyle modifications of AMD patient* is of indispensable importance, indeed, our health also depends on our *lifestyle choice*. It is very important to identify *modifiable risk factors (lifestyle risk factors)* that may *reduce disease occurrence or prevent progression to advanced stages*. Lifestyle risk factors, including *bad dietary habits, physical inactivity, smoking, and adiposity, stressful lifestyle* strongly influence the established vascular risk factors (a stressful lifestyle, also is a well-known risk factor for the development and progression of vascular injury) and also *affect novel pathways of risk such as inflammation/oxidative stress, endothelial function, thrombosis/coagulation, and modest alterations of these lifestyle risk factors are achievable and have substantial effects on (cardio)vascular risk.*

Modifying lifestyles behaviours of *diet, smoking, physical activity and stressful lifestyle* might reduce the risk for early AMD as much as 3-fold (with 71% lower odds for AMD), therapeutic lifestyle interventions, including dietary habits and exercise training improves vascular endothelial function and vascular structure. The three-fold lowering of odds was associated with having a combination of healthy lifestyles which included healthy diets, physical activity and not smoking: The three-fold lowering of odds for AMD among women with a combination of healthy, compared with unhealthy, lifestyles suggests that a combination of healthy lifestyle practices might be more important in reducing AMD risk than a focus on one. These changes, collectively, may contribute to lowering of oxidative stress, inflammation, blood pressure and improving blood lipids all of which are thought to be pathogenic mechanisms which promote AMD^[2] (139): smoking increases oxidative stress,, and stopping smoking lessens it; physical activity can also up-regulate antioxidant protection enzyme systems, so that it reduces oxidative stress; improvements in diet and physical

activity alone or in conjunction with a reduction in obesity can lessen oxidative stress as well; healthy lifestyles may lower AMD risk by lowering systemic inflammation which contributes to AMD pathogenesis; healthy diet patterns and physical activity relates to lower blood levels of CRP, a marker of systemic inflammation; healthy lifestyles may lower AMD risk by lowering systemic inflammation; healthy diet patterns and physical activity lowers blood levels of CRP, a marker of systemic inflammation. Very important are genetic, behavioral, and sociodemographic risk factors for second eye progression in age-related macular degeneration, jointly.^[3]

(1) **Smoking cessation** is of vital importance, established causative factor for AMD is smoking, which has been linked to increased oxidative stress, platelet aggregation, higher fibrinogen level, and reduced plasma high-density lipoprotein and diminished antioxidant levels. Cigarette smoking increases inflammation, thrombosis, and oxidation of low-density lipoprotein cholesterol. Cigarette smoke exposure increases oxidative stress as a potential mechanism for initiating vascular dysfunction. Both the gas and tar phases of cigarette smoke deliver a high concentration of oxidizing chemicals, including reactive oxygen species (ROS), nitric oxide (NO), peroxynitrite and free radicals that can get into the bloodstream and cause macromolecular damage in the vascular cells.^[4,5] Smoking reduces the concentration of antioxidant in the blood and probably also the function of antioxidant enzymes in the macula. Additionally, Factor H being an important element of the pathogenesis of AMD shows an age-dependent increase of the plasma level and a decrease in smokers.^[6] NT upregulates pro-angiogenic vascular endothelial growth factor (VEGF) and downregulated anti-angiogenic pigment epithelium derived factor (PEDF) expression through nicotinic acetylcholine receptors (nAChR) in retinal pigment epithelium (RPE): NT increased VEGF to PEDF ratio in RPE, plays a key role in the progression to wet AMD in passive smokers.^[7]

(2) **Reduction of body weight (slimming)** significantly reduces the risk of development and/or progression of AMD. Middle-aged persons who had a 3% or greater reduction in waist-hip ratio (WHR), a measure of abdominal obesity, over time were less likely to have AMD, particularly among those who were initially obese.^[8] Higher body mass index (BMI) significantly increased the progression the risk for advanced forms of AMD.

(3) It is most desirable making the patients to perform **regular, appropriate physical activity** (*increased shear-stress by physical exercise → improvement of ED!*). Although pharmacological interventions to delay vascular injury/events show promise, the main

intervention that could be recommended now to human on the basis of evidence is regular exercise physical exercise prevents and restores age-associated loss in endothelial function in humans (one of the most potent stimuli for NO production is increased laminar shear stress induced by an increase in blood flow during exercise).^[9] Physical activity increases vascular expression of eNOS, the exercise-induced up-regulation of vascular eNOS expression is closely related to the intensity of physical forces within the vasculature, especially shear stress. Increased NO synthesis secondary to amplified shear stress induces extracellular superoxide dismutase (SOD) expression so as to inhibit the degradation of NO by ROS. The risk of AMD significantly decreases with higher doses of exercise (independent of weight, cardiorespiratory fitness, and cigarette use). Physical activity raises high-density lipoprotein cholesterol, lowers low-density lipoprotein cholesterol and triglycerides, lowers blood pressure, improves fasting and postprandial glucose-insulin homeostasis, induces and maintains weight loss, improves physiological well-being, and likely lowers inflammation (also diminishes the level of inflammatory markers, namely pro-inflammatory cytokines, C-reactive protein), improves endothelial function and facilitates smoking cessation. Herculean efforts are not required: *great benefit is achieved with modest activity*, e.g. 30 minutes of brisk walking on most day^[10] Appropriate habitual physical activity is proving to strongly benefit health and longevity in humans, including a reduced risk of vascular disease, likely due, at least in part, to its direct vasoprotective effects: the mechanisms of vasoprotection conferred by exercise are likely complex but *includes a significant improvement of endothelial function, possibly by augmenting NO bioavailability and attenuating oxidative stress*, and by temporary increases in shear stress, which are known to modulate gene expression in endothelial cells. Furthermore, *exercise confers anti-inflammatory actions*, such as suppression of TNF α , and thereby may offer protection against TNF α -induced vascular impairment (regular exercise reduces CRP, IL-6, and TNF- α levels and also increases antiinflammatory substances such as IL-4 and IL-10). *regular exercise also promotes mitochondrial health, induces mitochondrial biogenesis, and upregulates mitochondrial antioxidant systems*, which also may contribute to its vasoprotective properties^[11] (146). Finally, there is evidence that exercise exerts a positive influence on the number and/or function of EPCs^[12]: physical exercise attenuates age-associated reduction in endothelium-reparative capacity of EPCs by increasing CXCR4/JAK-2 signaling Physical activity might contribute to greater macular pigment density by reducing inflammation and oxidative stress directly or by reducing obesity, exercise training restores the endothelial

progenitor cells number and function: a physically active, hearthealthy lifestyle prevents the earliest manifestation of AMD.

(4) Prescribing a *d i e t* which assures the intake of an appropriate dose the of most important *polyunsaturated fatty acid (PUFA)* is of primary significance (the ethyl ester of *eicosapentaenoic acid (EPA)* inhibits/prevents the evelopment of choroidal neovascularisation [CNV].^[13, 14] and contains flavonoids (*polyphenols*), *natural antioxidants* in abundance, is *rich in vegetables and fruits*, cacao and green tea has beneficial effects on endothelial function.^[15]

--- *Dietary flavonoids* are a large family of *polyphenols* ubiquitously expressed in plants. Flavonoids possess several anti-inflammatory activities due to their ability to scavenge reactive oxygen and nitrogen species (ROS and RNS), to inhibit the pro-inflammatory activity of ROS-generating enzymes including cyclooxygenase (COX), lipoxygenase (LOX) and inducible nitric oxide synthase (iNOS) and to modulate different intracellular signaling pathways from NF-κB to mitogen-activated protein kinases (MAPKs) through perturbation of redox-sensible networks in immune cells. Dietary polyphenols may counteract oxidative stress in vascular and inflammatory diseases by modulating key redox sensitive gene transcription *via* NF-κB. Epidemiological evidence suggests that diets containing high amounts of natural antioxidants afford protection against vascular disease.

--- *Inorganic nitrite*

Aging is the major risk factor for cardiovascular diseases (CVD). This is attributable primarily to adverse changes in arteries, notably, increases in large elastic artery stiffness and endothelial dysfunction mediated by inadequate concentrations of the vascular-protective molecule, nitric oxide (NO), and higher levels of oxidative stress and inflammation. Inorganic nitrite is a promising precursor molecule for augmenting circulating and tissue NO bioavailability because it requires only a one-step reduction to NO. Nitrite also acts as an independent signaling molecule, exerting many of the effects previously attributed to NO. nitrite may be effective in the treatment of vascular aging. In old mice, short-term oral sodium nitrite supplementation reduces aortic pulse wave velocity, the gold-standard measure of large elastic artery stiffness, and ameliorates endothelial dysfunction, as indicated by normalization of NO-mediated endothelium-dependent dilation. Increasing nitrite levels via dietary intake of nitrate appears to have similarly beneficial effects in many of the same physiological and clinical settings.^[16] ietary supplementation with micronutrient inorganic

nitrit (with dietary nitrate upplementation (with sodium nitrate 150 M mol/kg body weight, dissolved in drinking water; dose equivalent to a portion [300 g] of spinach). improves endothelial dysfunction and vascular stiffness and reduces SBP in the elderly with moderately increased cardiovascular risk: this finding provides evidence that dietary modulation with micronutrients improves vascular dysfunction, and might prevent or delay development of ES, respestiuevely.^[17]

-- *Curcumin* is a low-molecular-weight *phenolic compound* originating from *turmeric* (*Curcuma longa*): curcumin possesses a wide variety of biological activities, including antioxidant, anti-inflammatory and anti-angiogenic properties, the underlying mechanisms of these effects involve the regulation of various inflammation-related molecular targets and cellular targets, including those, which can be crucial to the pathogenesis of CNV. Due to its efficacy, ability to affect multiple targets and to its known safety for human use, curcumin has potent therapeutic value in the prevention and treatment of various chronic and acute inflammatory diseases (e.g., curcumin has been shown to be as effective as corticosteroids for chronic anterior uveitis). The therapeutic value of curcumin in the treatment of of laserinduced CNV: curcumin can effectively suppress the experimental CNV. Curcumin can decrease VEGF production in the early phase of laser-induced CNV (it can be explained at least in part by effectively inhibiting the infiltration of macrophages secreting VEGF), curcumin significantly inhibits the protein levels of TNF- α , MCP-1, and ICAM-1 in the RPEchoroid complexes with CNV: collectively, the curcumin-mediated suppression of CNV formation is attributable to the inhibition of multiple inflammatory and angiogenic steps including the activation of NF- κ B, infiltration of macrophages and granulocytes, and upregulation of inflammatory and angiogenic molecules. Therefore, the curcumin may serve as a therapeutic approach to the treatment of CNV in AMD.^[18]

--- *Omega-3 long-chain polyunsaturated fatty acids (LCPUFAs)* may act in a protective role against ischemia-, oxygen-, inflammatory-, and age-associated pathology of the choroidal vasculature and vascular and neural retina.^[19] *Eicosapentaenoic acid-* (EPA-) rich diet results in significant suppression of CNV and CNV-related inflammatory molecules (interceellular adhesion molecule [ICAM]-1, monocyte chemotactic protein [MCP]-1, interleukin [IL]-6), and vascular endothelial growth factor (VEGF) - *eicosapentaenoic acid* prevents inflammation and oxidative impairment by inhibiting inflammatory and oxidative stress response PUFAs can attenuate retinal NV formation directly, PUFAs intervention

decreases the neovascular activity (one of the retina, also) via PPAR-dependent reduction of inflammatory mediators and attenuation of EC activation. The *PPAR-dependent effect of 3-PUFAs on CNV formation is large and comparable to anti-VEGF treatment(!)*.^[20,21]

Age-related macular degeneration is caused by a series of metabolic and histological changes in the retina and underlying tissues, which culminate in the most severe form, neovascularisation. Abnormal blood vessel growth *begins in the vascular choroid*, which gradually invades the outer retina, and the accompanying leak of blood and fluid *secondarily damage the photoreceptor cells*.

--- Dietary supplementation with *omega-3 fish oils* also improves endothelial function and reduces oxidative stress and may therefore confer vascular - choroid-vascular, also - benefits: besides modulating inflammatory mediators, 3-PUFAs can directly attenuate activation of endothelial cells via PPAR-gamma. Prospective data from a large population of women with no prior diagnosis of AMD indicate that regular consumption of *docosahexaenoic acid (DHA)* and *EPA* and *fish* significantly reduced the risk of incident AMD.^[22] Age-related macular degeneration (AMD) may be partially prevented by dietary habits, especially when the diet contained low levels of LA, as suggested from epidemiological data. Foveal macula pigment depression (the MP foveal dip phenomenon) is associated with a suboptimal Holman RBC omega III EPA/DHA fatty acid index and Vitamin D status. (findings concerning the central macular pigment [MP] “foveal dip” phenomenon reported to occur with greater frequency with aging, in smokers and patients with AMD). The anti-inflammatory property of EPA may lead not only to prevention of CNV, but also to prophylactic improvement of background conditions related to AMD (systemic inflammation is predisposing background of AMD: omega-3 fatty acids may reduce up-regulation of CRP).

Dietary intake of omega-3 fatty acid can reduce the risk of both early and late AMD, the *omega-3 fatty acid metabolites* resolvins and protectins function as endogenous antiinflammatory compounds: resolvins and protectins mediate their beneficial effects by preventing NF-kappaB signaling. The *risk of taking omega-3 fatty acids* either from dietary fish or fish oil supplements is *low*, and the potential benefits outweighs the risks.-

----- Carotenoid concentrations relate inversely to vascular disease incidence: individuals with higher concentrations of sum of carotenoids, generally had lower risk for future vascular

disease. AMD has features of a chronic low-grade systemic inflammatory response, and the carotenoid *lutein* affects immune responses and inflammation, it diminishes the inflammation, choroidal neovascularization, retinal ischemia, suppresses NF kappa-B activation (possible systemic anti-inflammatory function).^[23] Carotenoids could have an antioxidant-mediated tempering influence on endothelial function and inflammation, thereby reducing the risk of vascular injury. The *carotenoids* composing macular pigment can block the frequencies of blue light that are known to damage the retina directly; they may also quench reactive oxygen species that form as a result of the light- and oxygen-rich environment. Dietary intake of *zeaxanthin* and carotenoids lutein (carrot juice is a carotene-rich food, spinach powder is a lutein- and zeaxanthin-rich food) is significantly related with a reduction in risk of late AMD, and a statistically significant association was observed between *lutein and zeaxanthin intake* and neovascular AMD risk, seventy-nine per cent of the patients with wet AMD have a deficient daily intake in lutein-zeaxanthin (the optimal dose of *lutein and zeaxanthin* for the prevention or treatment of AMD has not yet been defined).^[24]

--- *AREDS 1 supplements*

It is a potential validity of *food factor supplements* as a therapeutic strategy for preventing the retinal and choroidal pathologies driven by RAS-induced inflammatory and angiogenic molecules. *Food factors including lutein* (in yellow-green vegetables), the *omega-3 polyunsaturated fatty acid eicosapentaenoic acid* (purified from fish oil), *red pigment astaxanthin* from salmon and shrimp may inhibit the expression of inflammatory molecules including VEGF, ICAM-1, and MCP-1^[1], and *zinc* may play a protective role by interrupting the complement cascade.^[25]

e) Management of **dietary glycemic index (GI)** (glycemic index indicates how fast blood glucose is raised after consuming a carbohydrate-containing food) appears to be an effective intervention for the prevention of metabolic diseases, specifically AMD.

Epidemiological evidence indicates positive associations between GI and risk for diabetes, vascular diseases, and more recently, age-related macular degeneration: a low GI diet may be beneficial in reducing vascular disease risk. Dietary hyperglycemia is etiologically related to human aging and diseases, including diabetic retinopathy (DR) and AMD^[26] The risks for major age-related debilities including coronary heart disease, diabetes, and age-related macular degeneration (AMD) are diminished in people who consume lower glycemic index (GI) diets, in contrast to this consuming a *higher GI diet promotes AMD-like lesions*.

Consuming higher GI diets was associated with > 3 fold higher accumulation of *advanced glycation end products (AGEs)* in retina, suggesting that higher GI diets induce *systemic glycativ stress (SyGS)* that is etiologic for these lesions.^[27]

(5) Caloric restriction (CR) is a dietary regimen confers vasoprotection in aging and pathological conditions: reduction of caloric intake to 30–50% below ad libitum levels can delay the onset of age-related diseases, improve stress resistance, and decelerate functional decline.^[28] The potential therapeutic strategies to improve mitochondrial function in aging and cardiovascular diseases: antioxidants, calorie restriction, calorie restriction mimetics, and exercise training.

The mechanisms underlying the beneficial vascular effects of CR are undoubtedly multifaceted and may include improvement of systemic risk factors for vascular diseases, such as decreases in serum cholesterol, triglycerides, fasting glucose and fasting insulin levels, and reduction of systolic and diastolic blood pressure as well as direct antiaging effects exerted on the vasculature per se. The molecular mechanism by which CR promotes a beneficial endothelial phenotype includes upregulation and activation of eNOS, which results in increased bioavailability of NO and improves endothelial function, in part, via activating silent information regulator 1 (SIRT1). Improved NO bioavailability by CR may prevent vascular energetic dysfunction, which is likely to contribute to vascular pathological functional alterations.- Unrestricted food consumption, unrestricted eating, respectively in humans accelerates most, if not all, diseases of aging: so we can conclude that CR delays all diseases of aging, and in this manner, CR extends life span in almost all organisms: CR deactivates the TOR pathway, thus slowing aging and delaying diseases of aging, CR increases both maximal and healthy lifespan in humans. however, humans benefit from medical care, which prolongs lifespan despite accelerated aging in non-restricted individuals, and therefore in humans the effect of CR may be somewhat blunted. CR is the most potent environmental intervention that delays the onset of aging and extends life span in diverse experimental organisms: these novel insight will allow the development of novel treatments and preventive measures for age-associated diseases and disorders.^[29]

(6) Elimination/discontinuance of the stressful lifestyle (2) Mental stress can have marked effects on endothelium-dependent, flow-mediated vasodilation: reduction in flow-mediated vasodilation was seen during mental stress. A stressful lifestyle, is also a well-known risk factor for the development and progression of vascular injury: *modifications/elimination*

/discontinuance of the stressful lifestyle of patient with AMD are of indispensable importance, in all likelihood: Stressful habits are associated with high risk of stroke. Number of stressful life events, stressfulness significantly associates with myocardial infarct (MI).

Acute and chronic psychological stressors are associated with acute coronary syndromes (ACSs): acute stressful events, independent of traditional risk factors, can have a triggering effect on ACS occurrence.

(II) Medicinal therapy, medicinal preventive treatment of AMD

The above contributions/facts indicate that age-related macular degeneration may be a vascular disease (or part of a systemic vasculopathy): the recognition could have therapeutic implications because restoration of endothelial dysfunction may prevent the development or improve vascular disease resulting in prevention or improvement of age related macular degeneration as well (!).

The evolution of ED decisively affects the further course of the disease - improvement, stagnation, deterioration -. The beneficial effect of a favourable influence on ED, its successful medicinal therapy established fact in cardiovascular (CV) diseases, and the treatment of ED is an inherent part of the therapy of "underlying disease". As the human vascular system is an uniform entity, all – central and peripheral – parts of it are consubstantial physiologically and pathophysiologically as well as with regard to their ability to react, to avert (i.e. also from a therapeutic aspect), therefore treatment of ED should become an integral part of AMD therapy, because both primary and secondary prevention of AMD could be realised by this way.^[30]

Medical treatment of vascular dysfunction should be aimed not only at increasing levels of NO but also at reducing those of vascular superoxid and peroxinitrit: substances that simply deliver NO will worsen rather than improve endothelial dysfunction via further peroxinitrite formation. In the setting of endothelial dysfunction and high oxidative stress the ideal compound should stimulate NO production and simultaneously reduce oxidative stress within vascular tissues.^[31]

Concerning the favourable medicinal influencing of dysfunction the following statement can be made: Development and progression of vascular disease (CVD) takes years and occurs as a continuum. The RAAS is centrally involved in cardiovascular (CV) function along this

ontinuum and chronic activation of RAAS produces adverse pathophysiologic effects. Therefore, **RAAS blockade** has become a pivotal strategy to reduce adverse effects of RAAS activation. The renin-angiotensin system (RAS) is becoming well recognized as a proinflammatory mediator, *RAS pathway elements are also produced intrinsically*, making it possible to respond more dynamically to systemic or local cues. While RAS is important for controlling normal inflammatory responses, *hyperactivation of this pathway (reninangiotensin system hyperactivation) can induce/cause chronic inflammation (and oxidative stress) which are establishwd risk factors for age-related macular degeneration, and retinal neural dysfunction.*

The renin-angiotensin system (RAS) contributes to the processes of accelerated aging caused by lifestyle-related diseases from visceral obesity in the early stage to late-onset organ damage. Vision-threatening age-related macular degeneration (AMD), associated with lifestyle-related diseases as risk factors for progression, develop retinal and choroidal neovascularization (CNV), respectively, in their advanced stages. **Tissue RAS** is activated in the pathogenesis of CNV, leading to angiotensin type 1 receptor(AT1-R)-mediated expression of inflammation-related molecules.^[32] In fact, increasing evidence suggests that **RAS inhibition** may actually prevent progression of AMD: therefore, *RAS inhibition may be a pro mising therapeutic approach to prevent or treat AMD.*

The modern **RAAS-inhibiting**

(1) angiotensin converting enzyme ihibitors (ACE-inhibitors – ACEIs) (captopril, enalapril, perindopril, ramipril, etc.) and

(2) angiotensinreceptor blockers (ARBs) with great tissue affinity (candesartan, irbesartan, losartan, telmisartan, valsartan, etc.) exert their multifaceted (pleiotropic), beneficial effect independently of their antihypertensive activity.^[33, 34, 35, 36, 37, 38, 39, 40, 41] They *improve endothelial function (EF)*; they *substantially reduce ED*; they *act against the oxidative stress (OS)*; they *significantly relieve inflammation*, and they *inhibit thrombogenesis*, and both an angiotensin-converting enzyme inhibitor and an AT1 receptor antagonist have been shown to prevent the aging-related endothelial dysfunction.

Ad (1) Angiotensin converting enzym inhibitors (ACEIs)

ACE inhibition attenuated the superoxide-generating effects of angiotensin II, impaired thebreakdown of bradykinin, and increased the production of edothelium-derived nitric oxide

(EDNO). Angiotensin converting enzyme inhibitors (ACEIs) *facilitates nitrogen monoxide production* causing vasodilatation. EDNO besides inhibits aggregation of platelets, inhibits adhesion of monocytes and leukocytes to the endothelium, inhibits smooth muscle cell proliferation and inhibits oxidation of LDL also, *reduces vascular inflammation*^[35], and counteracts endothelial cell senescence via *facilitating nitrogen monoxide (NO) production*^[42], and plays a key role to maintain the vascular wall, healthy in a quiescent NO-dominated, endothelial phenotype.

Ad (2) Angiotensin-receptor-blockers (ARBs)

At the same time *AR-blockers/AT1-receptor antagonists (ARBs) act against the unfavourable, harmful vascular effects of angiotensin II exerted on the AT1 receptors, and significantly inhibit them: AT1-receptor antagonists (ARBs) increase/enhance the expression of AT2 receptors, and the so indirectly stimulated AT2 receptors, prevent/stall all unfavourable effects of angiotensin II to be realised on the AT1 receptors ("receptor switching phenomenon")*. Lifestyle-related diseases cause macro- and microangiopathies in the major organs including the eye: vision-threatening age-related macular degeneration (AMD) associates with lifestyle-related diseases as risk factors for development and progression of choroidal neovascularization (CNV), in their advanced stages. The *renin-angiotensin system (RAS) contributes to the processes of accelerated aging caused by lifestyle-related diseases*, and the role of renin-angiotensin-aldosterone system (RAAS) – through the AT1 receptor-mediated inflammatory activity of angiotensin II – is of key importance in the genesis and development of choroidal neovascularisation (CNV). Tissue RAS is activated in the pathogenesis of CNV, leading to angiotensin type 1 receptor (AT1-R)-mediated expression of inflammation-related molecules including vascular endothelial growth factor (VEGF), intercellular adhesion molecule (ICAM)-1, and monocyte chemotactic protein (MCP)-1. The blockade of AT1 receptors (executed by an ARB product) leads to significant suppression of CNV.^[36] The *AT1 receptor blocker telmisartan*, by putting peroxisome proliferator-activated receptor gamma (PPARgamma) effects into operation, inhibits the development of choroidal neovascularisation (CNV), and clinically beneficially influences, improves CNV.^[43]

Telmisartan is an angiotensin receptor blocker - with PPARgamma-agonistic properties, and without serious side-effects of PPARgamma agonist specifics - enhances number and beneficial function of the circulating endothelial progenitor cells (EPCs) as well as EPC

migratory capacity, inhibits TNF α -induced EPC apoptosis and reduces oxidative stress: i.e., re-endothelization is significantly enhanced by telmisartan.^[44, 45]

Angiotensin II activates the AT1 receptor resulting in superoxide anion generation, oxidative stress, and endothelial dysfunction. ACE inhibitors and ARBs diminish production of intracellular superoxide anions. ACE-inhibitors significantly inhibit the formation of Ang-II that activates the NADPH-oxidase enzyme which is the main source of vascular OS: the unfavourable effects of Ang-II manifesting on the AT1 receptors, also activating the NADPH oxidase enzyme, are prevented by ARB products. It is clear from the above facts that ACEIs and ARBs separately, but particularly when given concomitantly, can drastically reduce superoxide production/oxidative stress (OS).^[38, 45, 46, 47] Most probably, concomitant therapeutic administration of ACEI and ARB may be the most expedient^[48]: one of the agents ensures the benefits of elevated bradykinin level, while the other drug inhibits the unfavourable effects of angiotensin II exerted on the AT1 receptor. ACE inhibition also improves the life and death cycle of the endothelium, and ACE inhibition can also improve the production and mobilisation of endothelial progenitor cells [EPCs] from bone marrow^[49] (184).- RAS is becoming widely recognized as a proinflammatory mediator: *AS inhibition* may prevent various diseases including AMD, RAS inhibition may actually prevent progression of AMD. Another *a direct renin inhibitor (RAS inhibitor) aliskiren* may mediate more robust vascular protection than either ACEI or ARB.

(3) *Direct renin inhibitors*

Recently the armamentarium of clinical medicine has included an orally acting *direct renin inhibitor (aliskiren)* (a RAS blocker). We can reasonably presume that the inhibition of renin will be a better strategy than the currently existing ACEI and ARB medicines. This is related to the effect exerted on angiotensin II production as well as to its potential effects on renin and prorenin activity bound to the (pro)renin receptor. *Aliskiren* is a potent inhibitor of renin; it significantly reduces plasma renin activity (PRA), and the suppression of PRA, down on the cascade, also *results in the suppression of A-II production*. As the direct renin inhibitor *aliskiren* blocks the deleterious microvascular effects of renin and prorenin occurring upon their binding to the (pro)renin receptors, this may mean a considerable therapeutic advantage in comparison to ACE-inhibitors and AR-blockers, and it may actually mediate more robust vascular protection than either ACEI or ARB.^[50] Renin inhibitors and angiotensin receptor blockers act according to pharmacological mechanisms which are separated and favour each

other: PRA increases when valsartan is given in monotherapy, however when is given in ombination with aliskiren, the PRA will decrease, i.e. the inhibition of RAAS becomes more cmplete.

Receptor for prorenin [(pro)renin receptor - PRR] is expressed in the eye, in the icrovascular endothelial cells of the retina. Prorenin binds to the receptor that causes dual activation of its intracellular signaling and tissue RAS by binding to (pro)renin (aliskiren odulates tissue and intracellular RAS), PRR activates renin's enzymatic activity inherent in rorenin leading to the generation of angiotensin II (AngII) by a traditional RAS pathway at he cell/tissue level, and by (pro)renin binding to PRR initiates a cascade of signaling events hat are associated with profibrotic and proliferative actions, independent of AngII – this athogenic mechanism is termed *receptor-associated prorenin system [RAPS]* -. It wasdemonstrated the contribution of RAPS to the pathogenesis of CNV and dual regulation of EGF by signal transduction via (pro)renin receptor (PRR) and AT1-R. *RAPS contributes to he pathogenesis of CNV and dual regulation of VEGF and MCP-1* by signal transduction via pro) renin receptor and AT1-R (170). However, definitive proof is still lacking by showing mprovement of disease by administration of a *specific PRR antagonist* (this is due to lack of a reliable and selective PRR antagonist[!]).

A peptide segment of the prorenin prosegment, called *handle-region-peptide (HRP)*, has ained significant interest as a PRR antagonist: in the eye, HRP has been shown to be eneficial in preventing ocular inflammation as well as in pathological angiogenesis. Resolving these issues would be critical: HRP and PRR could be considered as a target for therapeutic interventions in eye (retinal) pathophysiology. The putative (pro)renin receptor blocker, the handle region peptide (HRP), exerts effects on top of the blood pressurelowering and cardioprotective effects of the renin inhibitor aliskiren.^[51] The renin-angiotensin system (RAS) contributes to the processes of accelerated aging caused by lifestyle-related diseases from visceral obesity in the early stage to late-onset organ damage. Vision-threatening age-related macular degeneration (AMD) may be associated with lifestyle-related diseases as risk factors for progression, developing retinal and choroidal neovascularization (CNV), respectively, in their advanced stages. Tissue RAS is activated in the pathogenesis of CNV, leading to angiotensin type 1 receptor(AT1-R)-mediated expression of inflammation-related molecules.^[52]

(4) Statins (HMGCoA)

Age-related macular degeneration (AMD) is a progressive late onset disorder of the macula affecting central vision. Age-related macular degeneration is the leading cause of blindness in people over 65 years in industrialized countries. Recent epidemiologic, genetic, and pathological evidence has shown AMD shares a number of risk factors with atherosclerosis, leading to the hypothesis that statins may exert protective effects in AMD. The pathogenesis of AMD remains indeterminate and is likely to be multifactorial, and the disease is related to well-known risk factors, that are shared with atherosclerosis and consequently with increased risk of cardiovascular disease (CVD). Similar susceptibility genes exist for CVD and AMD, such as complement factor H loci, therefore, a modification in atherosclerotic changes with lipid-lowering medications may exert a preventive effect in AMD development by prevention of lipid deposits at the level of Bruch's membrane. Statins are hydroxymethylglutarylcoenzyme A (HMG Co-A) reductase inhibitors, which are capable of reducing serum lipoprotein levels and are primarily used to treat dyslipidemia and reduce cardiovascular mortality. Of the anti-lipemic products, the up-to-date *hydroxymethylglutaryl-coenzyme A (HMGCoA) reductase inhibitor statins* (simvastatin, lovastatin, atorvastatin, resuvastatin, fluvastatin, etc.) exert their multifaceted favourable effects due to their pleiotropic properties including antiinflammatory, anti-endothelial dysfunction, anti-angiogenic, and antioxidant activities - independently of the reduction of total and LDL cholesterol levels.^[53, 54, 55, 56, 57, 58, 59, 60,] They *improve endothelial function (EF)* and substantially *reduce ED*. This is independent of the cholesterol lowering effect of these drugs. They *increase the bioavailability/usability of NO and increase flow-mediated dilatation (FMD)* that depends on the endothelium. They increase and *enhance the activity of endothelial nitric oxide synthetase (eNOS)* also indirectly by reducing the serum level of CRP. By increasing the synthesis and release of NO, they also *enhance retinal blood supply*. Property of statins is preservation of ischemic vasculature: the activation of a protein kinase results in an increased production of nitric oxide that results in an improved choroidal blood flow and a reduced capillary drop out. Endothelium-derived nitric oxide (NO) besides inhibits aggregation of platelets, inhibits adhesion of monocytes and leukocytes to the endothelium, inhibits smooth muscle cell proliferation and inhibits oxidation of LDL also *inhibits vascular inflammation* by suppressing the expression and activity of adhesion molecules and chemokines. Many studies demonstrated a significant increase in vasodilatation of retinal arterioles and venules after statin therapy in patients with hypercholesterolaemia indicating *pleiotropic beneficial effects of statins on the retinal microcirculation* which seem to be

mediated by the endothelium-dependent, NO-mediated pathway. Statins *promote the process of restoring endothelial injuries* and actively participate in it by increasing the number and improving the function of endothelial progenitor cells (EPCs) of bone marrow origin: statin therapy *accelerates reendothelialization* as well as they mobilise the endothelial progenitor cells to the site of injury (“*homing*”).^[61] Treatment with **statins** inhibits endothelial senescence and that enhancement of *SIRT1* plays a critical role in *prevention of endothelial senescence* through the Akt pathway, a direct target of statin.^[62]

They *inhibit thrombus formation*: by inhibiting RhoA/Rho kinase. Statins reduce thrombosis via multiple pathways, including inhibiting platelet activation and reducing the pathologic expression of the procoagulant protein tissue factor. Many of the antithrombotic effects of statins are attributed to inhibiting prenylation of RhoA and effects on other intracellular signaling molecules such as NF- κ B and KLF2. These antithrombotic activities of statins likely contribute to the ability of statins to reduce the incidence of cardiovascular death.^[63]

They significantly *mitigate inflammation as they stimulate the expression of peroxisome proliferator-activated receptor-gamma (PPARgamma)*. They also decrease the amount of inflammatory cells and cytokines (IL-1, IL-6) activating thrombocytes and other proteins regulating immunological processes. They effectively inhibit leukocyte-endothelium interaction also in the retina. and they significantly decrease the expression of P-selectin and ICAM-1 so that they protect neuronal cells of the retina from being perished.^[58] They inhibit the expression of major histocompatibility antigen complex 2 (MHC-II) on macrophages and endothelial cells that leads in turn to a reduction of T-cell proliferation and differentiation and by this way to the decrease of the release of inflammatory cytokines^[59] (195). Statins *reduces endothelial cell apoptosis* by confining inflammation, by increasing the bioavailability of nitric oxide, and through their anti-oxidative effects^[56] (192). Statins lower accumulation of lipids in Bruch membrane: drusen is a key pathophysiologic pathway for AMD development neovascular membranes associated with AMD include macrophages, which may respond to statins. *Statin specifics reduce the increased CRP level or may normalise it. By inhibiting the RhoA/Rho kinase pathway - ensuring unhindered endothelial function -, statins avert/inhibit the harmful effects of CRP, in patients with CAD: where serum CRP levels significantly decreased upon statin medication (≤ 2 mg/L) the number of events has significantly decreased and considerable improvement ensued*^[64] (200). *Recovery of endothelial function occurs in response to strategies known to reduce vascular events, and this adds support to the concept*

that restoration of endothelial function can restabilize the vascular disease process. Neovascularisation is a major complication in AMD, therefore, angiogenesis is potential point of statin modulation^[65] a retrospective study of 326 patients with age-related macular degeneration reported a 49% reduction in the rate of choroidal neovascularization in statin-treated patients ($P = 0.01$). Statins ameliorate a number of vascular diseases: statin inhibits vascular endothelial growth factor (VEGF) levels (71%) in the treated group compared with the control group. The inflammatory component, as assessed by tumor necrosis factor- α (TNF- α) level was also decreased, statin may be able to decrease nitric oxide (NO) production: fluvastatin demonstrates an inhibitory effect on the production of NO in inflammatory angiogenesis of newly formed vascular tissue (statin was also able to decrease nitric oxide (NO) production, detected with an NO-sensitive electrode. To our knowledge this is the first study demonstrating an inhibitory role of fluvastatin on the production of NO in inflammatory angiogenesis of newly formed fibrovascular tissue.^[66]

Another retrospective study suggests a possible beneficial effect of statin intake for the prevention of AMD in individuals 68 years of age or older: Individuals 68 years of age or older who were classified as long-term users of statins had statistically significant less self-reported AMD (odds ratio (OR) 0.64, 95% confidence interval (CI) 0.49–0.84; $P=0.002$), after adjusting for potential confounding variables. No significant association was found between the prevalence of AMD and statin consumption among subjects between 40 and 67 years of age (OR 1.61, 95% CI 0.85–3.03; $P=0.137$).^[67]

In the study of Hall et al. AMD developed in only 4% of patients with coronary artery disease (CAD) who underwent coronary intervention procedure and took statin for years, compared to 22% in those who received no statin therapy: the difference was shown to be strongly significant^[54]. As indirect evidence for a statin effect preventing the development or appearance of AMD can be considered another clinical study where 550 patients with AMD were compared with 5500 subjects without AMD with regard to the use of lipid-lowering medication. Among those who took a statin (atorvastatin, cerivastatin, fluvastatin, pravastatin, or simvastatin) there was a significantly lower likelihood of developing AMD (OR 0.30; 95% CI: 0.030–0.062). There was also a significant decrease in the chance for developing AMD among those who received combined statin+non-statin (fibrate and nicotinic acid) medication (OR 0.20; 95% CI: 0.06–0.64), while no significant correlation was observed in those taking only non-statin lipid-lowering medicines.-

Statin and aspirin therapy are associated with *decreased rates of choroidal neovascularization* among patients with age-related macular degeneration.^[68, 69] Many have recently advocated the use of statins, in retinal eye disease, based on their antiapoptotic, anti-proliferative effects, besides lipid-lowering and anti-inflammatory properties, and they presented evidence for the role of heat shocks proteins (Hsps) as target of statin-mediated neuroprotective effects in ocular disease. Statin users at baseline and at the five-year follow-up had a 67% lowered risk of indistinct soft drusen, a key late AMD precursor lesion, at 10-year examination.^[71] Oxidized low-density lipoproteins (LDL) play a major role in the pathogenesis of atherosclerosis. Inhibition of cholesterol synthesis by statins has several protective effects but is not sufficient to prevent the uptake of oxidized LDL and the development of ED. For this reason a selective pharmacological inhibition of the uptake of oxidized LDL (oxLDL) in endothelial cells is a therapeutic approach. An important novel target molecule is the endothelial lectin-like oxLDL receptor LOX-1: this makes the LOX-1 receptor a novel and interesting target molecule in endothelial dysfunction. This makes the LOX-1 receptor a novel and interesting target molecule in endothelial dysfunction.

(5) Ezetimibe

Postprandial hyperlipemia is significantly associated with transient endothelial dysfunction: *ezetimibe* improves postprandial hyperlipemia and *lipemia-induced endothelial dysfunction*. *Combination therapy with low-dose simvastatin and ezetimibe* preserved post-fat load endothelial function contrary to high-dose simvastatin monotherapy: both statins and ezetimibe have beneficial effects on postprandial hyperlipemia and lipemia-induced endothelial dysfunction, and combining a low-dose statin with ezetimibe may provide similar beneficial effects on endothelial function as high-dose statin, possibly due to *direct antiinflammatory and anti-oxidant effects* as well as the lipid-lowering actions of the drugs.^[71]

(6) Fenofibrat

Non-lipid-related mechanisms are currently regarded as the most plausible explanation for the beneficial effect of fibrate on vascular injury. Fibric acid derivatives possess independent anti-inflammatory and antioxidant properties mediated by their proliferator-activated receptor- α (PPAR- α) agonist activity. Inflammation is decreased via inhibition of enhanced nuclear transcription factor-kappaB (NF-Kb) activity, thus preventing interleukin (IL)-1-induced expression of IL-6 and cyclo-oxygenase-2 and in turn preventing any increase in

capillary permeability. Fibrin acid can also downregulate the expression of vascular endothelial growth factor receptor a key regulator of vascular regrowth in response to hypoxia, thus avoiding an excess neovascularisation. Fibrates, by virtue of their PPAR- α agonist properties, can induce the expression of nitric oxide synthase and decrease cellular adhesion molecules, thereby inhibiting NF-Kb and suppressing the genes that encode adhesion molecules^[72]

Topical application of fenofibrate has therapeutic potential in preventing retinal and choroidal NV formation, amelioration retinal inflammation, and reduction of retinal NV leakage^[73]

(7) *Acetylsalicylic acid (ASA)*

Considering that cardiovascular diseases were possible risk factors and chronic inflammation was a hypothetical mechanism of AMD, aspirin which could decrease the incidence of cardiovascular events and the relationship between aspirin use and incidence of AMD needed further considerations. We have more and more evidence showing that *acetylsalicylic acid (ASA) (aspirin)* acts not only by inhibiting platelet aggregation, but just by *restoring the balance of endothelium* (regarding its vasodilating, antiadhesive, antithrombotic, and *antiinflammatory* functions): the significant effects of aspirin which have a pleiotropic activity include *inhibition of angiotensin II*, and ASA exerts that through its potent *antioxidant (i.e. anti-ED)* properties by *inhibiting vascular superoxide production*^[74, 75]. ASA inhibits cyclooxygenase, which is responsible for arachidonic acid metabolism and prostaglandin production. Aspirin mitigates resistin-induced endothelial dysfunction via modulation of reactive oxygen species (ROS) generation.^[76] Aspirin is associated with decreased rates of CNV among AMD patients.^[69] Several studies were conducted to evaluate the association between aspirin use and incidence of AMD, while no concordant conclusions were drawn.^[77]

(8) *Trimetazidine*

In *organ failure* (or tissue failure) *including insufficient retinal function*, induced by damage the extent of glucose oxidation decreases and the oxidation of free fatty acids becomes intensified, increasing the amount of oxygen needed for the formation of one molecule of ATP. A reduction in the available quantity of ATP is an inherent decisive factor in the development and progression of this pathological condition, creating an abnormal metabolic constellation which can be characterised as “hunger for energy”. *Trimetazidine (TMZ)* (1-[2,3,4-trimethoxybenzyl] piperazine, dihydrochloride) exerts its beneficial effect just by influencing the substrate use of the organ/tissue, by shifting metabolism from the fatty acids

towards glucose oxidation, and by this way stimulating complete glucose utilisation including both glycolysis and glucose oxidation. Namely, during glucose oxidation less oxygen is needed for the production of one mol of adenosine triphosphate: so glucose oxidation is more favourable for the tissue with insufficient function and supply than fatty acid oxidation.

Trimetazidine attains its beneficial effect by partial inhibition of fatty acid oxidation and substantial *mitigation/reduction of damage due to free radicals (including endothelial dysfunction)*. Trimetazidine substantially *mitigates oxidative stress* (it significantly decreases malonyl aldehyde production) and it protects/maintains the functioning capacity of endogenous antioxidant enzyme system.^[78] Treatment with TMZ, improves cardiac and endothelial dysfunction. Ameliorating of ED by TMZ treatment involved beneficial changes in antioxidative and anti-inflammatory properties, which are cell-specific effects on either survival or apoptosis.^[79,80] There are known good results attained by adjuvant trimetazidine therapy in both latent and overt cardiac failure as well as in cochleovestibular syndrome caused by insufficient cerebral circulation^[81,82] (217, 218). It would certainly be reasonable to use the drug also in AMD, as an adjuvant therapy at insufficient retinal function (the original summary of the product characteristics has highlighted the beneficial effect of trimetazidine on the insufficiently functioning tissues of the sense organs.

Trimetazidine *protects the retina against ischemic damage*^[83]: TMZ has a beneficial effect on retinal lipid peroxidation and changes due to ischemic injury.^[84] TMZ treatment involved changes in antioxidative and anti-inflammatory properties, which are cell-specific effects on either survival or apoptosis. The specific actions and physiological effects of TMZ

(9) Third generation beta blockers and (10) PPARgamma agonist

The *third generation beta blockers: carvedilol, nebivolol*^[85] and the *peroxisome proliferator-activated receptor-gamma (PPARgamma) agonist* pioglitazone and rosiglitazone^[86] exert their vascular protective effects exactly *via their mitochondrial antioxidant activity*. Third generation beta blocker directly effects on the endothelial L-arginine/NO pathway.^[87] PPARgamma agonists reduce the expression of NADPH oxidase and vascular oxidative stress, they suppress inflammatory processes which play a key role in the pathogenesis of AM.^[88] They directly inhibit the activation of vascular endothelial growth factor (VEGF), the main promoter of the development of choroidal neovascularisation (CNV). PPAR γ agonists increase endothelial NO release without altering endothelial NO synthase expression, they also stimulate both activity and expression of Cu/Zn-SOD: these findings illuminate

additional molecular mechanisms by which PPAR γ agonists may directly alter vascular endothelial function, to advantage.^[43] AMD involves the abnormal retinal pigment epithelium (RPE), drusen formation, photoreceptor atrophy, and choroidal neovascularization. Peroxisome proliferator-activate receptor- γ (PPAR- γ) play an important role in immune regulation, regulation of reactive oxygen species (ROSs), as well as regulation of vascular endothelial growth factor (VEGF), matrix metalloproteinase-9 (MMP-9), and docosahexaenoic acid (DHA), in addition, PPAR gamma is expressed in RPE, an essential cell in photoreceptor regeneration. These molecules have all been implicated in the pathogenesis of AMD.

(11) Folate improves endothelial dysfunction by reducing the serum levels of homocysteine (elevated levels of homocysteine promote endothelial dysfunction by their toxic effects on the endothelium, probably mediated by an increase in oxidative stress and inhibition of NO production). The plasma concentration of Hcy in AMD patients had significantly increased: daily supplementation with folic acid (2,5 mg/d), pyridoxine (50 mg/d), and cyanocobalamin (1 mg/d) may reduce the risk of AMD.^[89]

(12) Vitamin D status may significantly beneficial affect odds of early AMD: vitamin D - because of its *anti-inflammatory, immune modulating properties* - may *suppress* the cascade of destructive *inflammation* that occurs at the level of the RPE-choroid interface in early stages of AMD.. The *increase of circulating 25(OH) (vitamin D)* results in a significant decrease of the systemic inflammation biomarkers, hsCRP, serum amyloid antigen (SAA), TNF- α and IL-6 (anti-inflammatory effects of cholecalciferol!), vitamin D has been shown to have anti-angiogenic properties.^[89] The „symptomatic” *antioxidant vitamins (AOVs) (vitamin C, E)* used for preventing, conventionally, OS (174) did not really live up to the hopes placed in them: the activity of AOVs against OS is limited only to scavenging the already formed oxidative products. That is why they are called (in an not completely proper way) “symptomatic” and not “causal” antioxidants (AO) protecting the integrity of cellular mitochondria.

(14) Cysteine pro-drug L-2-oxothiazolidine-4-carboxylic acid (OTC) Oxidant- and inflammation-induced damage to retinal pigment epithelial (RPE) cells is central to the pathogenesis of age-related macular degeneration (AMD). Inflammation is a common consequence of increased oxidative stress in RPE cells and the retina, and once initiated, inflammation further potentiates reactive oxygen species (ROS) production in this cell and

tissue type. OTC treatment significantly inhibits the expression and secretion of IL-6 and Ccl2: cellular and molecular markers of inflammation were significantly suppressed in the retina: OTC has a robust antioxidant and cell-protective properties on human RPE cells.- L-2-oxothiazolidine-4-carboxylic acid attenuates oxidative stress and inflammation in retinal pigment epithelium.

(15) The clinical development of *“causal” AOVs products with “mitochondrial” activity* (SOD and catalase mimetics, t-propionyl carnitine, LY3335311, PJ3 and *FP15 metalloporphyrin* as well as the *PAP-inhibitor INO-1001* are in progress. The inhibition of the reaction pathway peroxynitrite → DNA damage → PARP by rapid catalytic breakdown of peroxynitrite with the help of the FP015 metalloporphyrin compound, showing great promise, or by the inhibition of PARP with the drug INO-1001 may open a new possibility in the treatment of OS induced vascular dysfunction in several pathologic conditions ^[45] including AMD. *Nevertheless, we have excellent therapeutic possibilities also until then: statins, ACEIs ARBs, ASA (aspirin), trimetazidin, third generation beta blockers, PPARgamma agonists .*

(16) **Melatonin** may play a causal role in the occurrence of age-related macular degeneration (AMD). Melatonin is a strong antioxidant and can induce the expression of various antioxidant enzymes by activation of melatonin receptors. Long-term melatonin treatment may prevent the age-dependent mitochondrial oxidative stress: the beneficial effects of melatonin administration against these conditions are due to its direct free radical scavenger activity, its indirect antioxidant properties and its anti-inflammatory effects. Melatonin inhibits leukocyte-endothelial interaction, the first step of the inflammatory process. Decrease of melatonin production in aged persons may cause a reduction of antioxidant activity.

Replicative capacity and response to injury in the retinal pigment epithelium (RPE) is compromised during aging. Prevention of telomere shortening by antioxidants may be a useful approach for reducing the cumulative effects of oxidative stress in RPE cells. Antiinflammatory and antioxidative properties of melatonin are also involved in the protection against vascular disease. Melatonin has been shown to have the capacity to control eye pigmentation and thereby regulate the amount of light reaching the photoreceptors, to scavenge hydroxyl radicals and to protect retinal pigment epithelium (RPE) cells from oxidative damage. Melatonin, a well known antioxidant, which acts advantageously as an amphiphilic agent, may benefit AMD patients. No significant side effects were observed: melatonin's virtual absence of toxicity makes possible its long-term use. Melatonin may

exerts additional benefit through down-regulating hTERT (catalytic subunit of telomerase) expression and stimulated telomerase activity in RPE, which subsequently helps to prevent or treat AMD. 6-sulfatoxymelatonin levels (aMT6s), the major metabolite of melatonin in urine: *urinary aMT6s level in AMD patients was 40% lower than in age- and gender-matched controls suggesting that AMD is associated with a greater decrease of melatonin than typically seen with the normal aging process.*^[90-91] Administration of exogenous melatonin reduces the tissue concentration of vascular endothelial growth factor (VEGF): 3 mg melatonin given orally each night at bedtime for 3 months to AMD patients may reduce pathologic macular changes: melatonin seems to protect the retina and to delay macular degeneration.

(17) AMD is accompanied by enhanced systemic ***advanced glycation end products (AGE)*** accumulation, and increased serum concentrations of AGE is associated with ED. ***Alagebrium, an AGE crosslink breakers*** enhances peripheral artery endothelial function, improves ED^[92], improves overall impedance, AGE-crosslink breakers may reduce central arterial stiffness and vascular remodeling.

(18) Increased ***plasma ET-1*** level was a statistically significant risk factor for development of neovascular AMD: elevated plasma *ET-1* may be an important *risk factor* in the development of neovascular AMD. This suggests that an ***ET-1 receptor antagonist Bosentan*** might offer a new therapeutic approach to this disease: dual inhibition of endothelin receptors increases ocular blood flow *ET receptor antagonist bosentan* may improve microvascular endothelial function through several potential mechanisms including direct effects on the vasoconstriction caused by ET-1 activity, decrease in oxidative stress and inflammation, improvement in metabolic characteristics, attenuation of vascular injury and augmentation of nitric oxide pathways.^[93]

(19) ***Resveratrol (RSV) (3,5,4'-trihydroxystilbene)***, a diet-derived *polyphenol* (polyphenolic phytoalexin), and later found to be an anti-hyperlipidemic medicinal component of grapes and red wine, also extracted from dried roots of the common weed *Polygonum cuspidatum*. was reported to *mimic many respect of caloric restriction (CR)* and to exert vasoprotective effects, attenuating OS, *improving endothelial function, inhibiting vascular inflammation, and decreasing the rate of endothelial apoptosis.*^[94] Like the flavonoids, resveratrol bears good *antioxidant, antiinflammatory, vasoactive, and pro-survival effects*, making it a

candidate to counteract the common stress factors for age-related neurological disorders (three age-related neurodegenerative diseases: Alzheimer's disease (AD), Parkinson's disease (PD), and age-related macular degeneration [AMD]). Resveratrol directly scavenges hydroxyl radicals, superoxide, and DPPH. radicals, and inhibits H₂O₂- or lipid peroxidation of membrane lipids. RV has *anti-inflammatory effects*, and is a nonspecific COX-1 and COX-2 inhibitor.^[95] RSV exerts various bioactivities in addition to its classical antioxidant property: the molecular mechanism of resveratrol-mediated vasoprotection involve a direct inhibition of NF-kappaB, upregulation of eNOS and antioxidant enzymes, induction of mitochondrial biogenesis, and prevention oxidative stress-induced apoptosis. RSV as a molecule that acts by mimicking the beneficial effects of dietary restriction, and may share common downstream targets with rapamycin and metformin, although those molecules do not reveal all the secrets of the fountain of youth, they may help us maintaining the quality of life in the old age.^[96] RV is cardio-protective between 175 and 350 mg human equivalent dose (HED) in rodents, and cytotoxic (cell killing) at 10-times higher dose (between 1750 mg and 3500 mg HED). Resveratrol reduces oxidation and proliferation of human retinal pigment epithelial cells via extracellular signal-regulated kinase inhibition: resveratrol confers endothelial protective effects which are mediated by the activation of nuclear factor-E(2)-related factor-2 (Nrf2). Retinal activator protein-1 activation, up-regulated following light exposure, was significantly reduced by application of resveratrol: use of resveratrol as a therapeutic agent to prevent retinal degeneration related to light damage.

Using an oral resveratrol (RV) called Longevinex® or L/RV (Resveratrol Partners, LLC, Las Vegas, NV, USA) for 3 AMD patients who progressed on AREDS II type supplements refused intra-vitreous anti-VEGF injections or failed to respond to anti-VEGF treatment. Authors observed *dramatic short-term anti-VEGF type effect including anatomic restoration* of retinal structure with a suggestion of *improvement in abnormal/diseased choroidal blood flow*. The visual function improvement mirrors the effect seen anatomically. The effect is bilateral with the added benefit of better RPE function. Effects have lasted for one year or longer when taken daily. Unanticipated systemic benefits were observed. A component of red wine, independent of ethanol, possibly a polyphenol such as *resveratrol*, may confer vasculoprotection (improvement in *microvessel function*!): resveratrol and phytochemicals in red wine can suppress the development of vascular injury without affecting plasma lipid levels). by normalizing endothelial dysfunction.

(20) ***L-arginine supplementation*** is a reasonable method to increase endothelium NO production and lower free radicals formation: dietary supplementation (7g/day) of arginine reverses endothelial dysfunction associated with major vascular risk factors and ameliorates many common vascular disorders. L-arginine supplementation was able to restore endothelial-dependent vasodilation by augmenting cGMP production.^[98]

(21) ***Coenzyme Q10 (CoQ10) supplementation*** is associated with significant improvement in endothelial function (120 mg/day): this evidence supports a role for CoQ10 supplementation in patients with endothelial dysfunction.^[99] CoQ improves endothelial function via reversal of mitochondrial dysfunction. CoQ10 is a potent antioxidant: presence of adequate tissue concentrations of CoQ may be important in limiting oxidative and nitrosative damage, and a critical intermediate of the electron transport chain: exerts neuroprotective effects against retinal damage^[100] Coenzyme Q10 (CoQ10) levels were determined in plasma from exudative AMD patients and age-matched controls, and most patients had lower plasma CoQ10 content than most controls: coenzyme Q10 protects retinal cells against oxidative stress.

(22) Age-related macular degeneration (AMD) is associated with oxidative stress, lipofuscin accumulation and retinal degeneration: ***5-HT(1A) agonists*** can reduce lipofuscin accumulation, increase antioxidant protection, *protects the retina from oxidative damage and mitochondrial dysfunction*: 5-HT(1A) receptor agonists 8-OH DPAT protects against oxidative stress by increasing antioxidant protection, reducing lipofuscin levels which, in turn, reduces the generation of ROS and prevents mitochondrial damage). 5-HT(1A) receptor agonists 8-OH DPAT offer a therapeutic option for retinal degenerations such as AMD^[101] 5-HT1A agonist, 8-hydroxy-2-(di-*n*-propylamino)-tetralin (8-OH DPAT), is able to reduce the accumulation of lipofuscin, to increase antioxidant protection and to reduce oxidative damage in human RPE cells as well as being able to reduce lipofuscin accumulation and improve visual function in AMD.^[102]

(23) ***Tumor necrosis factor alpha (TNF- α)*** is a pro-inflammatory cytokine produced by macrophages and T-cells and it plays role in the pathogenesis of inflammatory, edematous, neovascular and neurodegenerative disorders (in AMD also): studies suggest a positive effect of intravenously administered ***TNF- α blockers***, mainly infliximab, for treating refractor

neovascular age-related macular degeneration^[103]: Tumor necrosis factor- α inhibition improves endothelial function and decreases arterial stiffness.^[104]

(24) Studies on the pathogenesis of AMD indicate that inflammation is a fundamental component of the disease process and that the alternative pathway (AP) of complement plays a critical role in driving the inflammatory response: a targeted *inhibitor specific for the A of complement* significantly reduces CNV and the physiological consequences of CNV on retina function.^[105]

(25) A potent antioxidant *N-acetyl-cysteine (NAC)* inhibits indicators of oxidative stress and the activation of NF- κ B, and, consequently, suppresses macrophage and neutrophil infiltration and the development of CNV: this suggests novel preventative and interventional therapeutic strategies for age-related macular degeneratio.^[106] NAC also inhibited the overexpression of p-STAT3 and VEGF in CNV and in RPE cells: antioxidant supplementation (NAC also!) helps attenuate the development of CNV. Thus, NAC reveals a potential strategy for the treatment and prevention of diseases involving CNV. (NAC is a potent antioxidant that is known to be a precursor of glutathione (GSH), and NAC acted directly as free radical scavengers and is independent of its ability to enhance GSH synthesis.) signal transducer and activator of transcription (STAT3) signalling may activated by ROS in RPE cells and participate in the development of CNV: NAC was found to suppressed the level of p-STAT3 and VEGF overexpression in vivo.

(26) *Treprostinil* have following pharmacological action: namely vasodilatation, prevention of smooth muscle cell proliferation, and antithrombotic properties/effects. Prostaglandin I₂ analog treprostinil exerts anti-inflammatory effects by suppressing TNF- α expression via the IP receptor-cyclic adenosine monophosphate pathways and by inhibiting the expression of costimulatory molecules on human monocyte-derived DCs (MDDCs), and treprostinil has the potential to serve as a therapeutic option to protect the tissues against ischaemia/reperfusion(I/R) injury.^[107]

(27) *Adiponectin peptide I (APNpI)*

The mutualistic symbiotic relationship within the photoreceptor / RPE / BrMb / CC complex is lost in AMD, loss of this functionally integrate relations results in dysfunction all of the components in the complex. Restoration of the relationship can be accomplished therapeutically by targeting the initial insult: control of inflammation could

prevent loss of CC and increase blood flow in supply blood vessels to the CC, reduction in oxidative stress could have positive effects on CC and RPE death. Anti-VEGF therapies are already having a profound effect on progression of wet AMD, but better delivery or longer lasting agents are needed to avoid monthly injections of the therapy into the eye.

Wet type of AMD is characterized by extensive growth of new vessels (CNV), and one of the effective strategies in treatment of AMD in humans is to limit choroidal neovascularization (CNV) by acting on VEGF related signaling pathway. *Intravitreal-used anti-VEGF drugs* are successfully being applied for inhibition of CNV, however, these drugs *have some serious side effects*: endophthalmitis, retinal detachment, retinal tear, uveitis, and *vitreal hemorrhage*. *Therefore development of new drugs which may be more effective and have fewer side effects is necessary* as an alternative to current treatments: ***adiponectin peptide I (APNpI)*** inhibited formation of new vessels in CNV by decreasing VEGF, VEGF-R2 expression and cell proliferation. Thus, APNpI may have potential therapeutic use for AMD treatment.^[108]

(28) Eicosapentaenoic acid (EPA) / docosahexaenoic acid (DHA)

DHA, EPA and fish significantly reduced the risk of incident AMD: compared with the lowest quartile, there was a significant trend for decreased odds with increasing quartiles of either DHA or EPA. ORs in the highest quartiles were 0.32 (95% CI: 0.12, 0.87; P = 0.03) for DHA and 0.29 (95% CI: 0.11, 0.73; P = 0.02) for EPA. Eating oily fish at least once per week compared with less than once per week was associated with a halving of the OR for NV-AMD.^[109]

(30) Habitual coffee consumption has been associated with improved endothelial function in elderly. The improvement in endothelial function may in part account for the associations of moderate coffee intake (about 2 to 4 cups daily) with lower risks for coronary heart disease and stroke. Indeed, even in the setting of endothelium damage, coffee has the ability to prevent arterial thrombus formation, a benefit that is independent of its content).^[110]

(31) Luteolin

Luteolin is capable of inhibiting endothelial dysfunction induced by Ang II by *suppressing the upregulation of Nox4, p-Akt and VEGF*^[111], thereby restraining the proliferation and migration of SMCs induced by injured ECs.

(32) **Doxycyclin** ameliorates hypertension-induced *endothelial dysfunction* by inhibiting oxidative stress generation and improving NO bioavailability, in addition to its inhibitory effects on MMP activity: low-dose oral doxycycline monohydrate can slow the deterioration of, or improve, retinal function or induce regression or slow the progression of retinopathy.^[112]

(III) Elimination of chronic stress due to civilized lifestyle.^[113]

Aside from a few exceptions, restoration, healing of ED will ensue upon interventions resulting in a reduction of CV events; this fact provides further support for the theory that *restoration of ED can re-stabilize the condition of chronic vascular disease including age-related macular degeneration (AMD) as well.*^[114]

There are an excellent clinician authors, who – with reason – criticizes the everyday, accepted practice of focusing mainly and primarily on the *pharmacological* normalization of the risk factors of cardiovascular diseases (CVD) instead of facing up the true driving force, and to preclude, eliminate *chronic stress due to civilized lifestyle*). After having accepted this as correct, *we have to prefer* – opposite to the pharmacological interventions – the *non-pharmacological actions (against the disadvantageous lifestyle/habits)*: certainly, *our state of health will be shaped mainly depending on our lifestyle.*

Although there are very promising *pharmacological* interventions aimed at reducing and delaying the occurrence of vascular events, the evidence-based *first and most important intervention to be recommended should include the elimination, change of inappropriate habits/lifestyle.*^[115] It is very important to identify the risk factors which can be influenced, in order to reduce the occurrence of CV events and to prevent the progression to an advanced stage.

(IV) Elimination of all risk factors of AMD

Furthermore, obviously, we have to strive for the possibly complete *elimination, aversion of all risk factors of AMD (elimination of all ASRFs, respectively!)* which induce OS and consequential ED. It is reasonable to *intervene modifiable risk factors*, for the prevention of AMD.

CONCLUSIONS^[116, 117, 118]

The *endothelial system* assures unhindered functioning and stability of the internal milieu maintaining vascular health and protecting against vascular injury, noxa. by producing, synthesising and excreting various substances: vasodilators and vasoconstrictors, growth factors and their inhibitors, pro-inflammatory and antiinflammatory agents, pro-thrombotic and fibrinolytic factors, and by keeping them in a strict equilibrium. *Endothelial dysfunction* is the change of these properties, what is inappropriate with regard to the preservation of organ function.

In the genesis and later development of age-related macular degeneration (AMD), endothelial dysfunction (ED) has a crucial determining role. *AMD-risk factors* often are identical with the *risk factors of (cardio)vascular (CV) diseases*, so the two conditions have a similar pathogenesis. These risk factors lead to vascular injury through the same mechanism of actions, by inducing *oxidative stress* (OS → ED!): *harm (noxa, i.e. [AMD] risk factors) → oxidative stress [OS] → endothelial activation [EA], endothelial dysfunction [ED], respectively → vascular injury, vascular disease*. Disordered function of endothelium in the vessels supplying the affected ocular structures with blood (ED) have a key role in the genesis and development of age-related macular degeneration.

Wall of blood vessels including those in choroids may be triggered by several repeated and/or *prolonged mechanical, physical, chemical, microbiological, immunologic, and genetic influences-impacts-stimuli (noxa)*, against which protracted response, the so-called *host defense response* may develop, and in consequence of this, vascular damage pathological consecutive changes ending in AMD, ultimately, may develop: all this goes to show that *AMD is a local manifestation of systemic vascular disease*.

As the human *vascular system is uniform and consubstantial*, the undermentioned following medicines/non-medicinal methods beneficial in ED also exert a favourable effect on the vessels of the eye, in the choroid / retina. Consequently, it seems logical to presume that, as a part of our primary and secondary preventive activity,

(A) such *medicines discussed above* - exerting a favourable effect on the vessels of the eye, in the choroid/retina - should be given to:

- (a) *patients who* have no macular degeneration, but *have risk factors of AMD* including patients who carry one or more complement-related gene polymorphisms predisposing to the disease, naturally, inducing OS and consecutive ED, and are older than 50 years;
- (b) patients who have been diagnosed *with unilateral AMD*, in order to prevent the damage of the contralateral eye due to macular degeneration;
- (c) and finally patients who have been diagnosed *with bilateral AMD*, in order to avert deterioration and in the hope of a potential improvement.

(B) In addition *lifestyle modifications* of AMD patients (non-medicinal therapy, nonmedicinal preventive treatment of AMD, respectively) - exerting a favourable effect on the vessels of the eye, in the choroid/retina -: smoking cessation; reduction of bodyweight (slimming); regular, appropriate physical activity; prescribing a *d i e t* flavonoids, polyphenols, respectively; omega-3 long-chain polyunsaturated fatty acids (LCPUFAs): docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA); carotenoids (lutein and zeaxanthin); management of dietary glycemic index (GI); caloric restriction (CR); *eliminaion/discontinuance of the stressful lifestyle*) is of indispensable importance.

(C) We have to *prefer the non-pharmacological actions* (against the disadvantageous *lifestyle/habits*): the evidence-based first and most important intervention to be recommended should include the elimination of inappropriate habits/lifestyle.

(D) We have to face up the true driving force, and to preclude, *eliminate chronic stress* due to civilized lifestyle: long-term stress leads to endothelial dysfunction.

(E) We should strive to completely *eliminate the risk factors* of macular degeneration (and ones of the CV disease) which induce OS and consequential ED, in addition.

(F) Of course, the performance of randomised, prospective, multicentric *clinical trials* is necessary.

REFERENCES

1. Pascal W. Hasler and Josef Flammer: Predictive, preventive and personalised medicine for age-related macular degeneration. EPMA J., 2010; 1(2): 245–251.
2. Mares, J. A., Volland, R. P., Sondel, S. A.: Healthy lifestyle related to subsequent prevalence of age-related macular degeneration. Arch. Ophtalmol., 2011; 129(4): 470-480.

3. Lechanteur, Y. T., van der Ven, J. P., Smailhodzic, D. : Genetic, behavioral, and sociodemographic risk factors for second eye progression in age-related macular degeneration. *Invest. Ophthalmol. Vis. Sci.*, 2012; 53(9): 5846-52.
4. Parmeggiani F, Sorrentino FS, Romano MR, Costagliola C.: Mechanism of inflammation in age-related macular degeneration: an up-to-date on genetic landmarks. *Mediators of Inflammation*, 2012, (2012), Article ID 546786, 16 pages doi:10.1155/2012/546786
5. Tagaki, H.: Aging and retinal vascular diseases. *Nippon Ganka Gakkai Zasshi*, 2007; 111(3): 207-230. Vol 3, Issue 6, 2014. 281.
6. Esparza-Gordillo J, Soria JM, Buil A, Souto JC, Almasy L, Blangero J.: Genetic determinants of variation in the plasma levels of the C4b-binding protein (C4BP) in Spanish families. *Immunogenetics*. 2003; 54(12): 862-6.
7. Pons, M., Marin-Castano, M. E.: Nicotine increases 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. doi: 10.1167/iovs.10-6254.
8. Peeters, A., Magliano, D. J., Stevens, J.: Changes in abdominal obesity and age-related macular degeneration: the Atherosclerosis Risk in Communities Study. *Arch. Ophthalmol.*, 2008; 126(11): 1554-60.
9. Werner C, Furster T, Widmann T.: Physical exercise prevents cellular senescence in circulating leukocytes and in the vessel wall. *Circulation*, 2009; 120: 2438–2447.
10. Williams PT: Prospective study of incident age-related macular degeneration in relation to vigorous physical activity during a 7-year follow-up. *Invest Ophthalmol Vis Sci.*, 2009; 50(1): 101-6. doi: 10.1167/iovs.08-2165.
11. Ian Yat Hin Wong, Simon Chi Yan Koo, Clement Wai Nang Chan: Prevention of age-related macular degeneration. *Int. Ophthalmol.*, 2011; 31(1): 73–82.
12. King, R. E., Kent, K. D., Bomser, J. A.: Resveratrol reduces oxidation and proliferation of human retinal pigment epithelial cells via extracellular signal-regulated kinase inhibition. *Chem. Biol. Interact.*, 2005; 151(2): 143-149.
13. Mozaffarian, D., Wilson, P. W. F., Kannel, W. B.: Beyond established and novel risk factors. Lifestyle risk factors and vascular disease. *Circulation*, 2008; 117: 3031-3038.
14. Ungvari, Z., Kaley, G., de Cabo, R.: Mechanism of vascular aging: New perspectives. *J. Gerontol. A. Biol. Sci. Med. Sci.*, 2010; 65(10): 1028-1041.
15. Landberg, R., Naidoo, N., van Dam, R.M.: Diet and endothelial function: from individual components to dietary patterns. *Curr. Opin. Lipidol.*, 2012; 23(2): 147-55.

16. Rammos C1, Hendgen-Cotta UB, Sobierajski J, Bernard A, Kelm M, Rassaf T.: Dietary nitrate reverses vascular dysfunction in old adults with moderately increased cardiovascular risk. *J Am Coll Cardiol.* 2013 Aug 14. pii: S0735-1097(13)03869-2. doi: 10.1016/j.jacc.2013.08.691. [Epub ahead of print]
17. Amy L. Sindler, Allison E. DeVan, Bradley S. Fleenor, and Douglas R. Seals: Inorganic nitrite supplementation for healthy arterial aging. *J. Appl Physiol.*, 2014; 116: 463–477.
18. Xie P, Zhang W, Yuan S, Chen Z, Yang Q, Yuan D, Wang F, Liu Q.: Suppression of experimental choroidal neovascularization by curcumin in mice. *PLoS One.*, 2012; 7(12): e53329. doi: 10.1371/journal.pone.0053329.
19. Koto, T., Nagai, N., Mochimaru, H.: Eicosapentaenoic acid is anti-inflammatory in preventing chorioidal neovascularisation in mice. *Invest. Ophthalmol. Vis. Sci.*, 2007; 48: 4328-4334.
20. Augood, C., Chakravarthy, U., Young, I.: Oily fish consumption, dietary docosahexaenoic acid and eicosapentaenoic acid intakes, and association with neovascular age-related macular degeneration. *Am. J. Clin. Nutr.*, 2008; 88(2): 398-406.
21. Augood, C., Chakravarthy, U., Young, I.: Oily fish consumption, dietary docosahexaenoic acid and eicosapentaenoic acid intakes, and association with neovascular age-related macular degeneration. *Am. J. Clin. Nutr.*, 2008; 88(2): 398-406.
22. Wight, S. A., O'Prey, F. M., McHenry, M. T.: A randomized interventional trial of omega-3-polyunsaturated fatty acids on endothelial function and disease activity in systemic lupus erythematosus. *Ann. Reum. Dis.*, 2008; 67(6): 841-8.
23. Kijlstra, A., Tian, Y., Kelly, E. R.: Lutein: More than just a filter for blue light. *Prog Retin Eye Res.*, 2012; 31(4): 303-15. doi: 10.1016/j.preteyeres.
24. Olea, J. L., Aragón, J. A., Zapata, M. ED.: Characteristics of patients with wet age-related macular degeneration and low intake of lutein and zeaxanthin. [Article in English, Spanish.] *Arch. Soc. Esp. Oftalmol.*, 2012; 87(4): 112-118.
25. Age-Related Eye Disease Study Research Group (AREDS Group): A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch. Ophthalmol.*, 2001; 119(10): 1417-36.
26. Chiu, C. J., Taylor, A.: Dietary hyperglycemia, glycemic index and metabolic retinal diseases. *Prog. Retin. Eye Res.*, 2011; 30(1): 18-53

27. Uchiki, T., Weikel, K. A., Jiao, W.: Glycation-altered proteolysis as a pathobiologic mechanism that links dietary glycemic index, aging, and age-related disease (in nondiabetics). *Aging Cell*, 2012; 11(1): 1-13; doi: 10.1111/j.1474-9726.2011.00752.x.
28. Merino, J., Megias-Rangil, I., Ferré R., Plana, N.: Body weight loss by very-low-calorie diet program improves small artery reactive hyperemia in severely obese patients. 165. *Obes Surg.*, 2013 Jan; 23(1): 17-23. doi: 10.1007/s11695-012-0729-6.
29. Dai DF¹, Rabinovitch PS, Ungvari Z.: Mitochondria and cardiovascular aging. *Circ Res.*, 2012 Apr 13; 110(8): 1109-24. doi: 10.1161/CIRCRESAHA.111.246140.
30. Fischer T.:The Age-Related Macular Degeneration (AMD) may be Vascular Disease, Part of Vasculopathy, respectively. Novel Considerations on AMD Arising from the Newest Pathophysiological, Clinical and Clinical-Pharmacological Observations (Preliminary Communication). *Journal of Neuroscience and Behavioural Health*, 2012; 4(5): 42-49, DOI:10.5897/JNBH11.042; ISSN 2141-2286 ©2012 Academic Journals.
31. Muenzel, T., Gori, T.: Nebivolol. the somewhat-different beta-adrenergic receptor blocker. *J. Am. Coll. Cardiol.*, 2009; 54: 1491-1499.
32. Ishida, S.: Lifestyle-related diseases and anti-aging ophthalmology: suppression of retinal and choroidal pathologies by inhibiting renin-angiotensin system and inflammation [Article in Japanese]. *Nihon Ganka Gakkai Zasshi*, 2009; 113(3): 403-22.
33. Heagerty, A. M.: Effect of AT1-receptor blockade on vascular structure and function. *Eur. Heart J.*, 2004; 6(Suppl. H): H17–H21.
34. Jackson, E. K.: Renin and angiotensin: drugs affecting renal and cardiovascular function. In: Goodman and Gilman's Pharmacologic Basis of Therapeutics. Ed.: Brunton, L. L., Lazo, J. S., Parker, K. L., McGraw-Hill, N.Y., 2005; 789–808.
35. Kwang Kon Koh, Michael J. Quon, Seung Hwan Han et al: Distinct vascular and metabolic effects of different classes of anti-hypertensive drugs. *Int J Cardiol.*, 2010; 140(1): 73–81.
36. Lonn, E., Gerstein, H. C., Smieja, M.: Mechanism of cardiovascular risk reduction of ACE inhibitor ramipril: insights from HOPE and HOPE substudies. *Eur. Heart J.*, 2003; 5(Suppl. A): A43-A48.
37. Soehnlein, O., Schmeisser, A., Cicho, J.: ACE inhibition lowers angiotensin-II-induced monocyte adhesion to HUVEC by reduction of p65 translocation and ATI expression. *J. Vasc. Res.*, 2005; 42: 399–407.

38. López-Sendón J, Swedberg K, McMurray J, Task Force of ACE-Is of European Society of Cardiology: Expert consensus document on angiotensin converting enzyme inhibitor in vascular disease. *Eur. Heart J.*, 2004; 25: 1454–147..
39. Wassman, S., Laufs, N., Bauner, A. T.: Inhibition of geranygeranylation reduces angiotensin II-mediated free radical production in vascular smooth muscle cells. *Mol. Pharmacol*, 2001; 59: 649–654.
40. Wassman, S., Nickenig, G.: The role of AT1-receptor in the cardiovascular continuum. *Eur. Heart J.*, 2004; 6(Suppl. H): H3-H9.
41. Landmesser, M., Harrison, D. G.: Oxidant stress as a marker for cardiovascular events. Ox marks the spot. *Circulation*, 2001; 104: 2638–2640.
42. Erusalimsky, J. D.: Vascular endothelial senescence: from mechanism to pathophysiology. *J. Appl. Physiol.*, 2009; 106(1): 326-332.
43. Pershadsingh, H.A., Moore, D.M.: PPAR gamma agonist: Potential therapeutics for neovascular retinopathies. *PPAR Res.*, 2008; 2008: 164–273.
44. Steinmetz, M., Brouwers, C., Nickenig, G.: Synergistic effects of telmisartan and simvastatin on endothelial progenitor cells. *J. Cell Mol. Med.*, 2010; 14(6B0): 1645-1656.
45. Ceriello, A.: New insights on oxidative stress and diabetic complication may lead to a „causal” antioxidant therapy. *Diabetes Care*, 2003; 25: 1589–1596.
46. Molavi, B., Metha, H. L.: Oxidative stress in cardiovascular disease: molecular basis of its deleterious effect, its detection, and therapeutic consideration. *Curr. Opin. Cardiol.*, 2004; 19: 477–493.
47. Asselberg, F. W., van der Harst, P., Jessurun, G. A. J.: Clinical impact of vasomotor assessment and role of ACE-inhibitors and AR-blockers. *Vasc. Pharmacol.*, 2005; 42: 125–140.
48. McMurray, J., Solomon, S., Piepera, K.: The effect of valsartan, captopril or both on arteriosclerotic events after acute myocardial infarction. *J. Am. Coll. Cardiol.*, 2006; 47: 726–733.
49. Ferrari, R., M Guardigli, G., Ceconi, C.: Secondary prevention of CAD with ACE inhibitors: a struggle between life and death of the endothelium. *Cardiovasc. Drugs Ther.*, 2010; 24(4): 331-.339.
50. Wilkinson-Berka, J. L., Miller, A. G., Fletcher, E. L.: Prorenin and the (pro)renin receptor: do they have a pathogenic role in the retina? *Front. Biosci. (Elite Ed.)*, 2010; 2: 1054-1064.

51. Lu, X., Danser, A. H., Meima, M. E.: HRP and prorenin: focus on the (pro)renin receptor and vacuolar H⁺-ATPase. *Front. Biosci. (Schol Ed.)*, 2011; 3: 1205-15.
52. Ishida, S.: Lifestyle-related diseases and anti-aging ophthalmology: suppression of retinal and choroidal pathologies by inhibiting renin-angiotensin system and inflammation [Article in Japanese]. *Nihon Ganka Gakkai Zasshi*, 2009; 113(3): 403-22.
53. Almutti, K., Rimawi, R., Spevack, D.: Effects of statins beyond lipid lowering: Potential for clinical benefits. *Internat. J. Cardiol.*, 2006; 109: 7–15.
54. Hall, N.F., Gale, C.R., Sudall, H.: Risk of macular degeneration in users of statins: cross-sectional study, *BMJ*, 2001; 323: 375–376.
55. 191. Niessen, S. E., Tuzcu, E. M., Crowe, T.: Statin-therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *N. Eng. J. Med.*, 2005, 352, 28–38.
56. Ray, K., Cannon, C. D.: The potential relevance of the multiple lipid-independent (pleiotropic) effects of the statins. *J. Am. Coll. Cardiol.*, 2005; 46: 1425–1433.
57. Wydlanski, M. E., Gokce, N., Keane, J. E.: The clinical implication of endothelial dysfunction. *J. Am. Coll. Cardiol.*, 2003; 42: 1149–1160.
58. Honjo, M., Tanihara, H., Nishijima, K.: Statins inhibit leukocyte-endothelial interaction and prevent neuronal death induced by ischemia-reperfusion injury in the rat retina. *Arch. Ophthalmol.*, 2002; 120: 1707–1713.1
59. Palinsky, W., Tsimiskas, S.: Immunomodulatory effects of statins. *J. Am. Soc. Nephrol.*, 2002; 13: 1673–1681.
60. McGwin, G., Owsley, C., Curcio, C. A.: The association between statin use and age related macular degeneration. *Br. J. Ophthalmol.*, 2003; 87: 1121–1125.
61. Asselberg, F. W., van der Harst, P., Jessurun, G. A. J.: Clinical impact of vasomotor assessment and role of ACE-inhibitors and AR-blockers. *Vasc. Pharmacol.*, 2005; 42: 125–140.
62. Ota, H., Eto, H., Kano, M. R.: 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): 2205-2211.
63. Owens AP 3rd1, Mackman N: The antithrombotic effects of statins. *Annu Rev Med.* 2014; 65: 433-45. doi: 10.1146/annurev-med-051812-145304.
64. Fassett RG, Robertson IK, Ball MJ, Geraghty DP, Coombes JS.: Effects of atorvastatin on biomarkers of inflammation in chronic kidney disease. *Clin Nephrol.* 2014 Feb;81(2):75-85. doi: 10.5414/CN108090.

65. Kubota, S., Kurihara, T., Ebinuma, M.: Resveratrol prevents light-induced retinal degeneration via suppressing activator protein-1 activation. *Am. J. Pathol.*, 2010, 177(4), 1725-1731.
66. Araújo FA, Rocha MA, Capettini LS, Campos PP, Ferreira MA, Lemos VS, Andrade SP.: 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (fluvastatin) decreases inflammatory angiogenesis in mice. *APMIS.*, 2013; 121(5): 422-30.
67. Barbosa DT1, Mendes TS1, Cíntron-Colon HR1, Wang SY1, Bhisitkul RB1, Singh K2, Lin SC1.: Age-related macular degeneration and protective effect of HMG Co-A reductase inhibitors (statins): results from the National Health and Nutrition Examination Survey 2005-2008. *Eye (Lond)*. 2014 Feb 7. doi: 10.1038/eye.2014.8.
68. Gaynes BI.: Statin and aspirin therapy are associated with decreased rates of choroidal neovascularization among age-related macular degeneration patients. *Am J Ophthalmol.*, 2004 Dec; 138(6): 1089.
69. Wilson, H. K., Schwrtz, D. M., Bhatt, H. R.: Statin and aspirin therapy are associated with decreased rates of choroidal neovascularization among patients with age-related macular degeneration. *J. Ophthalmol.*, 2004; 137(4): 615-624.
70. Tan, J. S., Mitchell, P., Rochtchina, E.: Statins and the long-term risk of incident age-related macular degeneration: the Blue Mountains Eye Study. *Am. J. Ophthalmol.*, 2007; 143(4): 685-687.
71. Nakamura T, Hirano M, Kitta Y.: A comparison of the efficacy of combined ezetimibe and statin therapy with doubling of statin dose in patients with remnant lipoproteinemia on previous statin therapy. *J Cardiol.*, 2012; 60(1): 12-7.
72. Morgan, CL, Owens DR, Aubonnet P, Carr ES, Jenkins-Jones S, Poole CD, Currie CJ.: Primary prevention of diabetic retinopathy with fibrates: a retrospective, matched cohort study. *BMJ Open.*, 2013 Dec 3; 3(12): e004025. doi: 10.1136/bmjopen-2013-004025. 209
73. Lu et al.: Therapeutic Potential of Topical Fenofibrate Eyedrops in Diabetic Retinopathy and AMD Rat Models, *J Clin Exp Ophthalmol* 2014, 5:4 <http://dx.doi.org/10.4172/2155-9570.1000347>Clinical & Experimental
74. Wu, R., Lamontagne, D., Champlain, J.: Anti-oxidative properties of acetylsalicylic acid on vascular tissues from rats. *Circulation*, 2002; 105: 387–392.
75. 211. Wu, R., Laplante, M., Champlain, J.: Prevention of angiotensin-II-induced oxidative stress, hypertension and cardiovascular hypertrophy by acetylsalicylic acid. *J. Hypertens.*, 2004; 22: 797–801.

76. Ou, H. C., Lee, W. J., Wu, C. M., Chen, W. H.: Aspirin prevents resistin-induced endothelial dysfunction by modulating AMPK, ROS, and Akt/eNOS signaling. *J. Vasc. Surg.*, 2012; 55(4): 1104-15.
77. Zhu, W., Wu, Y., Xu, D., Li. Y. H.: Aspirin use and risk of age-related macular degeneration: a meta-analysis. *PLoS One*, 2013, 8(3),e58821. doi:10.1371/journal.pone.0058821.
78. Coyas, A.: The efficacy of trimetazidine in cochleovestibular disorders of ischemic origin. A crossover control versus placebo trial. *Annales d'Oto-Laryngologie et de Chirurgie Cervico-Faciale*, 1990; 1(107 Suppl): 81–87.
79. Yoon, J. W., Cho, B. J., Park, H. S.: Differential effects of trimetazidine on vascular smooth muscle cell and endothelial cell in response to carotid artery balloon injury in diabetic rats. 2012 Jan 10.
80. Belardinelli, R., Solenghi, M., Volpe, L.: Trimetazidine improves endothelial dysfunction: an antioxidant effect. *Eur. Heart J.*, 2007; 28: 1102– 1108.
81. Vitale, C., Wajngaten, M., Sposato, B.: Trimetazidine improves left ventricular function and quality of life in elderly patients with coronary artery disease. *Eur. Heart J.*, 2004; 25: 1814–1821.
82. Kaszuba-Bartkowiak, K., Nowak, M.S., Jurowsky, P. The role of trimetazidine on the protection of the retina. *Arch. Med. Sci.*, 2007; 3: S65-S66.
83. Kaszuba-Bartkowiak, K., Nowak, M.S., Jurowsky, P. The role of trimetazidine on the protection of the retina. *Arch. Med. Sci.*, 2007; 3: S65-S66.
84. 220. Demir, T., Torgut, B., Ozercan, I. Trimetazidine for prevention of induced ischemia and reperfusion of guinea pig retina. *Clin. Ophthalmol.*, 2010; 2(4): 21-6.
85. Wu, T.C., Chen, Y.H., Leu, H.: Carvedilol, a pharmacological antioxidant. *Free Rad. Biol. Med.*, 2007; 43: 1508–1522.
86. Cockcroft, J.: A review of the safety and efficacy of nebivolol in the mildly hypertensive patient. *Vasc. Health Risk Manag.*, 2007; 3(6): 909-917.
87. Herzlich, A. A., Jingsheng Tuo, Chi-Chao Chan: Peroxisome proliferator-activated receptor and age-related macular degeneration. Hindavi Publishing Corporation, PPAR Research, Volume 2008; 2008; doi: 10.1155/2008/389507.
88. Herzlich, A. A., Tuo, J., Chan, C. C.: Peroxisome proliferator-activated receptor and age-related macular degeneration. *PPAR Res.* 2008;2008:389507.
89. Shab-Bidar S, Neyestani, T. R., Djazayeri, A.: Improvement of vitamin D status resulted in amelioration of biomarkers of systemic inflammation in the subjects with type 2

- diabetes. *Diabetes Metabolism Research and Reviews*, 2012; Feb 17 doi: 10.1002/dmrr.2290
90. 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.
91. K., Yu, G. P., Chen, M. Urinary 6-sulfatoxymelatonin level in age-related macular degeneration patients. *Mol. Vis.*, 2009; 15: 1673-9.
92. Ziemann, SD. J., Melenovsky, V., Clattenburg, L.: Advanced glycation endproduct crosslink breaker (Alagebrium) improves endothelial function in patients with isolated systolic hypertension. *J. Hypertens.*, 2007; 25(3): 577-83.
93. Ren Y, Yuan Z, Xu W, Somvanshi S, Nagaoka T, Yoshida A, Kuo L.: Functional and molecular characterization of the endothelin system in retinal arterioles. *Invest Ophthalmol Vis Sci.*, 2009 Jul; 50(7): 3329-36. doi: 10.1167/iovs.08-3129.
94. Mouchiroud, L., Molin, L., Dalli  re, N.: Life span extension by resveratrol, rapamycin, and metformin: The promise of dietary restriction mimetics for an healthy aging., 2010; 36(5): 377-82.
95. Yuen-Shan Ho1#*, David Chun-Hei Poon1#, Tin-Fung Chan1 and Raymond Chuen-Chung Chang: From Small to Big Molecules: How Do We Prevent and Delay the Progression of Age-Related Neurodegeneration? *Current Pharmaceutical Design*, 2012; 18: 15-26.
96. Kubota, S., Kurihara, T., Ebinuma, M.: Resveratrol prevents light-induced retinal degeneration via suppressing activator protein-1 activation. *Am. J. Pathol.*, 2010; 177(4): 1725-1731.
97. Jablecka, A., Bogdanski, P., Balcer, N.: 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.
98. Gao, L., Mao, Q., Cao J.: Effects of coenzyme Q10 on vascular endothelial function in humans: a meta-analysis of randomized controlled trials. 2012 *Atherosclerosis*, 2012; 221(2): 311-6.
99. Nakajima, Y., Inokuchi, Y., Bishi, M.: Coenzyme Q10 protects retinal cells against oxidative stress in vitro and in vivo. *Brain Res.*, 2008; 1226: 226-33.
100. Blasi, M. A., Bovina, C., Carella, G.: Does coenzyme Q10 play a role in opposing oxidative stress in patients with age-related macular degeneration? *Ophthalmologica*, 2001; 215(1): 51-4.

101. Thampi, P., Rao, H. V., Mitter, S. K.: 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.
102. Thampi P1, Rao HV, Mitter SK, Cai J: 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. doi: 10.1371/journal.pone.0034468.
103. Hoehn. R., Lorenz, K.: Anti-tumor necrosis factor alpha for retinal diseases: current knowledge and future concepts. *J. Ophthalmic Vis. Res.*, 2012; 7(1): 39-44.
104. Gonem, N., Yoshida, J., Stolz, D. B., Humar, A.: Treprostinil, a prostacyclin analog, ameliorates ischemia-reperfusion injury in rat orthotopic liver transplantation. *Am. J. Transplant.*, 2011; 11(11): 2508-16.
105. Rohrer, B., Long, Q., Coughlin, B.: 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.
106. Hara, R., Inomata, Y., Kawaji, T.: Suppression of choroidal neovascularization by N-acetyl- cysteine in mice. *Curr. Eye Res.*, 2010; 35(11): 1012-20.
107. Moreau, K. L., Deane, K. D.: Tumor necrosis factor- α inhibition improves endothelial function and decreases arterial stiffness in estrogen-deficient postmenopausal women. *Atherosclerosis.*, 2013; 230(2): 390-6.
108. Lyzogubov VV, Tytarenko RG, Bora NS, Bora PS.: Inhibitory role of adiponectin peptide I on rat choroidal neovascularization. *Biochim. Biophys. Acta*, 2012; 1823(8): 1264-72.
109. Augood C¹, Chakravarthy U, Young I 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 Aug; 88(2): 398-406.
110. Dinicolantonio, J. J.: Effects of habitual coffee consumption on vascular function. *J. Am. Coll. Cardiol.*, 2014, 18; 63(6): 607. doi: 10.1016/j.jacc.2013.10.005. 246/a. Saloni Agrawal and Brahim Chaqour: MicroRNA signature and function in retinal neovascularization *World J Biol Chem.* 2014 February 26; 5(1): 1-11.
111. Ding H, Li D, Zhang Y, Zhang T, Zhu H, Xu T, Luo Y, Wang C.: Luteolin Inhibits Smooth Muscle Cell Migration and Proliferation by Attenuating the Production of Nox4, P-Akt and VEGF in Endothelial Cells. *Curr Pharm Biotechnol.*, 2014 Jan 12.

- 112.Scott IU, 1, Jackson GR2, Quillen DA3: Effect of Doxycycline vs Placebo on Retinal Function and Diabetic Retinopathy Progression in Patients With Severe Nonproliferative or Non-High-Risk Proliferative Diabetic Retinopathy: A Randomized Clinical Trial. JAMA Ophthalmol. 2014 Mar 6. doi: 10.1001/jamaophthalmol.2014.93.
- 113.Peter Slezak , Peter Balis , Iveta Bernatova: Long-term social stress induces nitric oxide independent endothelial dysfunction in normotensive rats., 2013; 16(3): 331 339 (doi:10.3109/10253890.2012.725116)
- 114.Badal, S. S., Danesh, F. R.: Strategies to reverse endothelial dysfunction. Sidney. Int.,. 2012; 82(11): 1151-4.
- 115.Fischer, T.: The age-related macular degeneration as an integral part of systemic vascular disease: pathophysiology, prvention and prventive treatment (Hung.). Orvostovábbképzô Szemle, 2013; 20(7-8): 65-67.
- 116.Fischer, T .:Non-pharmacological therapy of age-related macular degeneration resulting from its etiopathogenesis (Hungarian). *Orv Hetilap*, 2015; 156(28): 1128–1132. DOI: 10.1556/650.2015.30128.
- 117.Fischer, T.:Pharmacological therapy of age-related macular degeneration based on the etiopathogenesis (Hungarian). *Orv Hetil.*, 2015; 156(46): 1740–1751. Supplement DOI: 10.1556/650.2015.30207.
- 118.Fischer, T.: Age-Related Macular Degeneration and Non-Pharmacologic Therapy Hungary, 12/2015. 2016/01/26]; Available from: <http://www.vitasearch.com/get/PC/experts/FischerTAT2015-11-23.pdf>.,