THE NEW PERCEPTION THAT AGE-RELATED MACULAR DEGENERATION MAY BE A VASCULAR DISEASE OPENS UP THERAPEUTICAL/PREVENTIVE THERAPEUTICAL VISTAS FULL OF PROMISE: Part II

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ABSTRACT

Regarding the treatment, preventiv therapy of AMD, the foregoing performed human studies in the AMD field reflect a "local/ophthalmic" and non-systematic/holistic view: one should make an alteration in this usual/habitual orthodox approach/attitude(!):

(I) Non-medicinal therapy: (1) Lifestyle modifications: smoking cessation; reduction of body weight; physical activity; diet (appropriate dose of flavonoids, polyphenols, respectively, curcumin; omega-3 long-chain polyunsaturated fatty acids: docosahexaenoic acid, eicosapentaenoic acid; carotenoids (lutein and zeaxanthin); management of dietary glycemic index; caloric restriction; elimination of stressful lifestyle; elimination of chronic stress. We have to prefer non-pharmacological actions (against the disadvantageous lifestyle/habits).

(II) Medicinal prevention/preventive treatment of AMD: Medicines described below - RAAS-inhibiting angiotensin converting enzyme inhibitors and angiotensinreceptor blockers; direct renin inhibitors; statins; acetylsalicylic acid; trimetazidin; third generation beta blockers; PPARgamma agonist; folate; vitamin D; melatonin; AGE crosslink breakers alagebrum; ET receptor antagonist bosantan; coenzyme Q10; "causal" antioxidant vitamins; N-acetyl-cysteine; resveratrol; L-arginine; 5-HT(1A) receptor agonists 8-OH DPAT; tumor necrosis factor alfa blockers; specific inhibitor of AP of complement; adiponectin peptide I; EPA/AHA; doxycyclin - all have beneficial effects in ED. Restoration of ED can restabilize the condition of chronic vascular disease including age-related macular degeneration as well.

(III) Completely to eliminate risk factors of CV/AMD disease.- The human vascular system is consubstantial, non-medicinal methods should be applied, and the mentioned medicines should be given to patients: who have no macular degeneration, but have risk factors of AMD.
inducing ED, and are older than 50 years; patients who have been diagnosed with unilateral AMD, in order to prevent the damage of the contralateral eye; and finally patients with bilateral AMD, in order to avert deterioration and in the hope of a potential improvement.- (IV) Performance of randomised, prospective, clinical trials is necessary.

KEYWORDS: age-related macular degeneration, endothelial dysfunction, oxidative stress, risk factors, primary and secondary prevention.

INTERODUCTION

ACE I = angiotensin converting enzyme inhibiton; ADMA = asymmetrical dimethyl arginine; AGE = advanced glycation end-products; AMD = age-related macular degeneration; AMDRFs = AMD risk factors; Ang-1 = angiopoetin-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 = glycative 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; immunglobulin 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; PGII = 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 glycate 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-a = tumor necrosis factor-alpha; tPA = tissue plasminogen activator; Th-1 = proinflammatory T-helper; Th-2 = antinflammatory 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-systhematic/holistic view": one should make an alteration in this usual/habitual orthodox approach/attitude(!).

(I) Non-medicinal therapy, preventive treatment of 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 (33). 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. 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/lifestyle

(1) Lifestyle modifications of patient with AMD

Preventive medicine for AMD which have lifestyle-related diseases as a systemic background, has attracted growing attention (138). 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 (139) 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 reduces 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 (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 (140).

(a) **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 (123, 64). 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 (141).

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 (142).

(b) **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 .(143). Higher body mass index (BMI) significantly increased the progression the risk for advanced forms of AMD.

(c) It is most desirable making the patients to perform regular, appropriate physical activity (increased shear-stress by physical exercise→improvement of ED!). Although pharmacoeutical 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). (144). 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 mainstains 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. Herculian efforts are not required: great benefit is achieved with modest activity, e.g. 30 minutes of brisk walking on most day (145) 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 TNFα, and thereby may offer protection against TNFα-induced vascular impairment (regular exercise reduces CRP, IL-6, and TNF-α levels and also increases anti-inflammatory 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 (146). Finally, there is evidence that exercise exerts a positive influence on the number and/or function of EPCs (147): physical exercise attenuates age-associated reduction in endothelium-reparative capacity of EPCs by increasing CXCR4/JAK-2 signaling (119) 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, heart-healthy lifestyle prevents the earliest manifestation of AMD.

(d) Prescribing a **diet** which assures the intake of an appropriate dose of the most important **polyunsaturated fatty acid** (PUFA) is of primary significance (the ethyl ester of **eicosapentaenoic acid** (EPA) inhibits/prevents the development of choroidal neovascularisation [CNV] (148, 149). and contains flavonoids (**polyphenols**), **natural antioxidants** in abundance, is rich in vegetables and fruits, cacao and green tea has beneficial effects on endothelial function (150).

**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-sensitive 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.(150). 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 (150/b).

Dietary supplementation with micronutrient inorganic nitrit (with dietary nitrate supplementation (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, respectively (150/a) (Rammos 2014).

Curcumin is a low-molecular-weight phenolic compound originating from turmeric (Curcuma longa): curcumin possesses a wide variety of biological activities, including anti-oxidant, 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 laser-induced 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 RPE-choroid 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-κB, infiltration of macrophages and granulocytes, and up-regulation of inflammatory and angiogenic molecules. Therefore, the curcumin may serve as a therapeutic approach to the treatment of CNV in AMD (151).
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 (152). Eicosapentaenoic acid- (EPA-) rich diet results in significant suppression of CNV and CNV-related inflammatory molecules (intercellellular 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(!) (153, 154)

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 (155). 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 (156). 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) (157).

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 are as endogeneous anti-inflammatory 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 outweights 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) (158). 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 (139) 123. 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) (159).

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(138), and zinc may play a protective role by interrupting the complement cascade (160).

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 disease, 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 (161). 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 glycative stress (SyGS) that is etiologic for these lesions (162).

(f) 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 (163). 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 lifespan 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 (164).
(g) Elimination/discontinuance of the stressful lifestyle (139) 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 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 (165).

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 (166).

Concerning the favourable medicinal influencing of endothelial dysfunction the following statement can 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 continuum 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 (renin-angiotensin system hyperactivation) can induce/cause chronic inflammation (and oxidative stress) which are established 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 (167). In fact, increasing evidence suggests that RAS inhibition may actually prevent progression of AMD: therefore, RAS inhibition may be a promising therapeutic approach to prevent or treat AMD.

The modern RAAS-inhibiting (1) angiotensin converting enzyme inhibitors (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 (168-176). 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 (115).

Ad (1) Angiotensin converting enzyme inhibitors (ACEIs)
ACE inhibition attenuated the superoxide-generating effects of angiotensin II, impaired the breakdown of bradykinin, and increased the production of endothelium-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 (170), and counteracts endothelial cell senescence via facilitating nitrogen monoxide (NO) production (177), and plays a key role to maintain the vascular wall, healthly 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 (178). Telmisartan is an angiotensinreceptor 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 TNFalpha-induced EPC apoptosis and reduces oxidative stress: i.e., re-endothelization is significantly enhanced by telmisartan (179, 180).
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 OS 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) (173, 180, 181, 182). Most probably, concomitant therapeutic administration of ACEI and ARB may be the most expedient (183): 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 (184).- RAS is becoming widely recognized as a proinflammatory mediator: RAS 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 (185). 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 it is given in
combination with aliskiren, the PRA will decrease, i.e. the inhibition of RAAS becomes more complete.

Receptor for prorenin [(pro)renin receptor - PRR] is expressed in the eye, in the microvascular 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 modulates tissue and intracellular RAS), PRR activates renin's enzymatic activity inherent in prorenin leading to the generation of angiotensin II (AngII) by a traditional RAS pathway at the cell/tissue level, and by (pro)renin binding to PRR initiates a cascade of signaling events that are associated with profibrotic and proliferative actions, independent of AngII - this pathogenic mechanism is termed receptor-associated prorenin system [RAPS] -. It was demonstrated the contribution of RAPS to the pathogenesis of CNV and dual regulation of VEGF by signal transduction via (pro)renin receptor (PRR) and AT1-R. RAPS contributes to the 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 improvement 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 gained significant interest as a PRR antagonist: in the eye, HRP has been shown to be beneficial 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 pressure-lowering and cardioprotective effects of the renin inhibitor aliskiren (186).

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 (187).
(4) Statins (HMGCoA)

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-lipaemic products, the up-to-date hydroxy-methylglutaryl-coenzyme A (HMGCoA) reductase inhibitor statins (simvastatin, lovastatin, atorvastatin, resuvasatin, fluvastatin, etc.) exert their multifaceted favourable effects due to their pleiotropic properties including anti-inflammatory, anti-endothelial dysfunction, anti-angiogenic, and antioxidant activities - independently of the reduction of total and LDL cholesterol levels (188-196). 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. Edothelium-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") (197). 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 (198).

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-κB and KLF2. These antithrombotic activities of statins likely contribute to the ability of statins to reduce the incidence of cardiovascular death (199).

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 (194). 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 (195). Statins reduces endothelial cell apoptosis by confining inflammation, by increasing the bioavailability of nitric oxide, and through their anti-oxidative effects (192). Statins lower accumulation of lipids in Bruch medmembrane: 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 (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 (201) 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-\(\alpha\) (TNF-\(\alpha\)) level was also decreased, statin may 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 (202).

Another retrospective study suggest 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; \(P=0.137\)) (203).

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 (189)\(^{165}\). 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 (204, 205). Many have recently advocated the use of statins, in retinal eye disease, based on their anti-apoptotic, 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 (206). 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 (207).

(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 anti-inflammatory and anti-oxidant effects as well as the lipid-lowering actions of the drugs (208).

(6) Fenofibrat

Non-lipid-related mechanisms are currently regarded as the most plausible explanation for the beneficial effect of fibrate 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. Fibric 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 (209).

(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) acts not only by inhibiting platelet aggregation, but just by *restoring the balance of endothelium* (regarding its vasodilating, antiadhesive, antithrombotic, and anti-inflammatory 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* (210, 211): 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 (212). Aspirin is associated with decreased rates of CNV among AMD patients (205).

Several studies were conducted to evaluate the association between aspirin use and incidence of AMD, while no accordant conclusions were drawn. (213).

(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 (214). 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 (215), (216). 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 (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 (219). Trimetazidine *protects the retina against ischemic damage* (219): TMZ has a beneficial effect on retinal lipid peroxidation and changes due to ischemic injury (220).

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* (221) and the *peroxisome proliferator-activated receptor-gamma (PPARgamma) agonist: pioglitazone and rosiglitazone* (222) exert their vascular protective effects exactly *via their mitochondrial antioxidant activity*.

Third generation beta blocker directly effects on the endothelial L-arginine/NO pathway (223). 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 AMD (224). They directly inhibit the activation of vascular endothelial growth factor (VEGF), the main promoter of the development of choroidal neovascularisation (CNV). PPARγ 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 PPARγ agonists may directly alter vascular endothelial function, to advantage (178).

AMD involves the abnormal retinal pigment epithelium (RPE), drusen formation, photoreceptor atrophy, and choroidal neovascularization. Peroxisome proliferator-activated 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 (225).

(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 (225).

(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 (226).

(13) 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 FP15 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 (180) 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. Anti-inflammatory 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 hydroxyradicals 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 (227, 228). 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 glycacion 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 (229), 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 (224) 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.

(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 (230). 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 peroxide-dependent peroxidation of membrane lipids. RV has anti-inflammatory effects, and is a non-specific COX-1 and COX-2 inhibitor (231).

RSV exerts various bioactivities in addition to its classical antioxidant property: the molecular mechanism of reveratrol-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 (230). 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-vitreal 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/diseasedchoroidal 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 (231).
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 (232).

(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 (233). L-arginine supplementation was able to restore endothelial-dependent vasodilation by augmenting cGMP production (234).

(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 (235). 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 (236). 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 (237): 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 (238). 5-HT(1A) 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 (238/a).
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 refractory neovascular age-related macular degeneration (239): Tumor necrosis factor-α inhibition improves endothelial function and decreases arterial stiffness (240).

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 AP of complement significantly reduces CNV and the physiological consequences of CNV on retina function (241).

A potent antioxidant N-acetyl-cysteine (NAC) inhibits indicators of oxidative stress and the activation of NF-κB, and, consequently, suppresses macrophage and neutrophil infiltration and the development of CNV: this suggests novel preventative and interventional therapeutic strategies for age-related macular degeneration (242). 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.

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 (243).
(27) Adiponectin (APN), adiponectin peptide I (APNpI), respectively 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 vitreous 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 (244).

(28) Ivabradin

Increased resting heart rate multiplies risk and interferes at all stages of the vascular disease continuum initiating from endothelial dysfunction to end-stage (cardio)vascular disease: effects can appear directly on myocardium or on a systemic level improving endothelial function and modulating immune cell migration. Selective heart rate reduction by the I(f) current inhibitor ivabradine provides an option to intervene effectively along the chain of events (245).

(29) EPA/DHA

Regular consumption of docosahexaenoic acid (DHA) and EPA and fish significantly reduced the risk of incident AMD (155).

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) (157).

(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) (246)

(31) **Luteolin**

*Luteolin* is capable of inhibiting endothelial dysfunction induced by Ang II by *suppressing the upregulation of Nox4, p-Akt and VEGF* (247), 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 (247/a).

(33) **miRNA (miRNA)-based therapy** , **miRNA (miRNA)-based therapy**, respectively provides the rationale basis for an effective antiangiogenic treatment: activity of specific miRNAs is important for blood vessel formation have potential implications in ocular neovascular diseases to maintain either vascular function or dysfunction, and miRNAs have been shown to contribute to the pathogenesis of numerous disease processes, such as pathological angiogenesis, oxidative stress and inflammation. Improvement of our knowledge in not only miRNA specificity, but also how miRNA sequences and functions can be altered will enhance the therapeutic utility of such molecules (246/a): several miRNAs have been shown to be directly associated with processes potentially involved in AMD by *vitro* studies, miR-based therapies for AMD are still on the horizon. miRNAs plays critical roles in pathological angiogenesis, the oxidative stress response, immune response and inflammation, all of which have important and interdependent roles in the pathogenesis and progression of AMD: miRNAs show promise as AMD therapeutic targets due to their direct involvement in choroidal neovascularization or retinal pigment epithelium atrophy.
(III) Elimination of chronic stress due to civilized lifestyle (248)

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 (249). 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 (156).

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. 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. 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 (250).

(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.

CONCLUSION

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 anti-inflammatory 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, non-medicinal preventive treatment of AMD, respectively: smoking cessation; reduction of body weight (slimming); regular, appropriate physical activity; prescribing a diet 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); elimination/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, change 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 produced by crowding may lead to alterations in nitric oxide (NO) production and NO-dependent relaxation in the course of stress, resulting in endothelial dysfunction and hypertension].

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

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

ACKNOWLEDGMENTS

I offer this study to memory of the innocent martyrs of the Holocaust (Shoa).

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