Journal of Pharmaceutical and Scientific Innovation

www.jpsionline.com

Review Article

AGE-RELATED MACULAR DEGENERATION IS A VASCULAR DISEASE, PART OF VASCULOPATHY: HOLISTIC APPROACH OF THE AMD'S PATHOPHYSIOLOGY, PREVENTION AND PREVENTIVE TREATMENT

Tamás Fischer*
Körvasút str. 75/B, H-1158 Budapest, Hungary
*E-mail: t.fischer.med@gmail.com

Received on: 19/10/12 Revised on: 25/11/12 Accepted on: 08/12/12

ABSTRACT

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 key role. AMD-risk factors often are identical wih 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], endothlial dysfunction [ED], respectively → vacular 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 thoose 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. As the human vascular system is uniform and consubstantial, the medicines/non-medicinal methods desribed below [the RAAS-inhibiting (1) angiotensin converting enzyme ihibitors and (2) angiotensinreceptor blockers |AT1 receptor blocker telmisartan included|; (3) direct renin inhibitors;(4) statins;(5) acetylsalicylic acid; (6) trimetazidin; (7) third generation beta blockers; (8) PPARgamma agonist; (9) folate; (10) vitamin D; (11) "causal" AOVs; (12) melatonin; (13) AGE crosslink breakers alagebrium; (14) ET receptor antagonist Bosentan; (15) coenzyme Q10;]; (16) the antioxidant N-acetyl-cysteine], beneficial in ED also exert a favourable effect on the vessels of the eye, in the choroid/retina.- Consequently, based on the preceding discussion, as the human vascular system is uniform and consubstantial, it seems logical to presume that, as a part of our primary and secondary preventive activity: (A) Such medicines - 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 [and ones of cardiovascular (CV) disease] inducing 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) 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 (modifying lifestyles behavours of diet, smoking and physical activity) is of indispensable importance. (C) 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.- Of course, the performance of randomised, prospective, multicentric clinical trials is necessary. Nevertheless, also until then we can begin – while taking the contraindications into consideration – the above outlined medication/methods that bear(s) the burden of few side effects.

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

INTRODUCTION

The role of ED on AMD

The importance of age-related macular degeneration (AMD), its significance for general health is reflected by the observation showing that the impairment in patients' quality of life and the magnitude of direct and indirect costs expended on it can compare with that of Alzheimer's disease plus multiple sclerosis**:** estimates gathered from the most recent World Health Organization (WHO) global eye disease survey conservatively indicate that 14 million persons are blind or severely visually impaired because of AMD.

AMD is a disorder of unknown cause and pathogenesis and no established treatment, causing decrease/loss of the ability to read in the elderly age-group and affecting about 180 million people all over the world.

An observation of great clinical importance indicates that vascular endothelium regulates retinal arteriolar tone[1], circulation in the ophthalmic and ciliary arteries, i.e. the eye[2,3] including ophthalmic microcirculation. The endothelium has emerged as a key regulator of vascular homeostasis. The endothelium not only functions as a barrier but also acts as an active signal transducer for metabolic, hemodynamic and inflammatory factors that modify the function and morphology of the vessel wall. Alterations in endothelial-cell function can precede the development of vascular/atherosclerotic changes and the progression of vascular lesions[4]. It has been recognition of great therapeutic and preventive therapeutic significance that demonstrated the key role of disordered function of endothelium in the vessels supplying the affected ocular structures with blood, endothelial dysfunction (ED) in the genesis and development of age-related macular degeneration[5,6] (changes in AMD may fairly well be associated with endothelium disturbances, becose vascular endothelial growth factor, which is one of the most important mediators of this disease, is mainly produced in the endothelium and has been found elevated in wet AMD):

(1) Attention was called to this implicitly by the fact that serum levels of von Willebrand factor (vWF) are significantly higher in AMD[7,8]; on the other hand, the increase of vWF is a surrogate of endothelial dysfunction (ED): the pathophysiological, pathogenetic and preventive importance of it has been recognized only later[9, 10, 11], and several studies have documented an elevated plasma level of von Willebrand factor, fibrinogen and/or plasminogen activator, inhibitor type 1 (PAI-1) in patients with AMD[12], as is also seen in AS[13].

(2) Several clinical trials have shown evidence linking soluble markers of endothelial dysfunction to drusen

formation or neovascularization, the two hallmarks of AMD[14].

(3) Endothelial progenitor cells (EPCs) enumeration could serve as a novel method for the assessment of AMD-related CNV and demonstrated significantly elevated EPC counts in the peripheral blood of patients with the exudative form of AMD[11]: circulating EPCs not only contribute to endothelial renewal, but may also play an important role in the process of new vessel formation at sites of local retinal ischaemia.

(4) Increased circulating endothelial cells (CECs) was found in the AMD patients compared with the counts in healthy individuals: circulating endothelial cells (ECs) may serve as marker of endothelial activation (EA)/dysfunction: TNF-, other inflammatory cytokines and also bacterial lipopolysaccharides, reactive oxygen species, plasminogen activator C-reactive protein, are able to induce in EMP generation. Circulating endothelial cells (CECs) are desquamated mature cells that have detached from the intimal monolayer in response to endothelial injury: increased numbers of CECs AMD patients reflect a severe vascular disturbance and may contribute to the disease process, like in AS: the measurement of circulating endothelial cells (CECs) in the peripheral blood is gaining ground as an important and novel method for assessing endothelial impairment. and their high number seems to reflect severe endothelial damage. Increased numbers of CECs in the peripheral blood of patients with AMD reflects a severe vascular disturbance and clearly indicates that there is an endothelial alteration accompanying AMD[11]. Any pathological process that causes damage to the endothelium might also cause endothelial cell detachment, resulting in increased numbers of mature CECs in blood[15].

(5) The concentration of monocyte chemoattractant protein-1 (MCP-1), soluble intracellular adhesion molecule 1 (sICAM-1), and soluble vascular cell adhesion molecule 1 (sVCAM-1) are significantly associated/enhanced with/in exudative AMD, this cellular adhesion molecule-regulated process of leukocyte recruitment results in endothelial cell dysfunction which can be manifested as impaired endothelium-dependent vasorelaxtion in arterioles[16] (in choroidal arterioles, also).

(6) In patients with moderate to advanced AMD, serum levels of C-reactive protein (CRP) are significantly higher (CRP is a marker of chronic subclinical inflammation, namely chronic inflammation is associated with ED: CRP level is a surrogate of ED)[17].

(7) Endothelial microparticles (EMPs) are circulating submicron-sized membranous vesicles released by endothelium that acts as primary and secondary messengers of vascular inflammation, thrombosis, in other words, microparticles are submicron vesicles shed from plasma membranes in response to cell activation, injury, and/or apoptosis: these vesicles are emerging as potentially useful indicators of dysfunctioning endothelium, and EMPs are enhanced/increased in cardiopulmonary, renal, cerebral, and metabolic disorders , and in AMD, also[18]. EMP emerge as a new surrogate marker of endothelial health and EMP levels may be used as a biomarker for stratification of patients and identification of subjects with a high risk of developing (cardio)vascular complication/disease, but endothelial microparticles (EMP) not only constitute an emerging marker of endothelial dysfunction, but are also considered to play a major biological role in inflammation, vascular injury, angiogenesis, and thrombosis[19].

(8) AMD is accompanied by enhanced systemic advanced glycacion endproducs (AGE) accumulation: increased serum concentrations of AGE is associated with ED[20].

(9) Lipid peroxidation is increased in patients with AMD: free radical mediated lipid peroxidation products can induce endothhelial cell injury/dysfunction[21, 22].

(10) Evidence for choroidal microvascular dysfunction in AMD includes the following: localization of terminal complement complexes with the choriocapillaris in aging eyes suggesting a possible mechanism for vascular injury in AMD; the clinical association of vascular changes in both the choroidal, and peripheral vasculature that implicate endothelial dysfunction as a contributing factor to the disease[23].

(11) Endothelin (ET)-1 is a potent vasoconstrictor peptide and increased ET-1 levels have been described in diseases associated with vascular dysregulation. The increase of ET-1 in patients is related to vascular dysfunction (p=0.001) and vascular dysfunction is related to sub-clinical intraocular inflammation (p=0.001). The hemodynamics of neovascular age-related macular degeneration (AMD) may involve choroidal vascular dysregulation and vasoconstriction: the increase of ET-1 in patients is related to vascular dysfunction (p=0.001) and vascular dysfunction is related to sub-clinical intraocular inflammation (p=0.001)[24]. The mean plasma ET-1 level in the neovascular AMD patients was significantly higher than the mean level in the controls (the increase of ET-1 is related to vascular dysfunction), elevated plasma ET-1 may be an important risk factor in the development of neovascular AMD: high ET-1 content, may contribute to the development of AMD. All this suggests that an ET receptor antagonist (bosentan) might offer a new therapeutic approach[25].

All this does to show that AMD may be local manifestation of systemic vascular disease, undoubtedly. The starting event of chronic vascular disease (including AMD) begins in the endothelium. This „organ" which has a mass of approximately 1 kg, consists of several trillions of cells, has a surface of almost 5000 m², produces/secretes several dozens of endocrine/paracrine/apocrine substances, hormone-like compounds, and takes care scrupulously of the integrity, stability, homeostasis of internal milieu[26, 27].

The endothelial system assures unhindered functioning and stability of the internal milieu (NO plays a pivotal role in maintaining vascular health and protecting against vascular injury, noxa endangering-imperiling steadiness and inviolability/invulnerability of homeostasis) by producing, synthesising and excreting various substances: vasodilators and vasoconstrictors [manufacturing the vasodilator nitric oxide |NO|, the prostacyclin |PGI2|, the endothelium-derived hyperpolarizing factor |EDHF| and the vasoconstrictor endothelin-1 |ET-1|, the platelet-activation factor |PAF|], 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, either in the basal state or after stimulation, that is inappropriate with regard to the preservation of organ function)**.**

The intimal layer of blood vessels (including those in the choroids, naturelly) may be affected by several repeated and prolonged mechanical, physical, chemical, microbiological, immunologic, and genetic injuries (so-called risk factors

[RFs]), against which protracted responses may develop (host-defense reponse°!) (increased ROS formation"→oxidative stress°°°→endothelial dysfunction): in consequence of this, chronic vascular injury (functional and then structural alteration of the vessel, pathological change [remodelling]) (including choriocapillares in AMD) may originate. As endothelial dysfunction is of general nature, and human vascular system is an uniform entity, all (central and peripheral) parts of it are consubstantial physiologically and pathophysiologically as well as regarding its ability to react (i.e. also from a therapeutic aspect), it is evident that the phenomena described above apply also to the retinal vessels[28]. Author is of the opinion that what is generally referred to as endothelial dysfunction should more appropriately be considered as endothelial activation (EA), which may eventually contribute to vascular disease: endothelial activation represents a switch from a quiescent phenotype toward one that involves the host defense response: any kind of noxa endangering steadiness of homeostasis→increased ROS formation→oxidative stress→endothelial activation, endothelial dysfunction,respectively. Indeed, most vascular risk factors activate molecular machinery in the endothelium that results in expression of chemokines, cytokines, and adhesion molecules designed to target inflammation to specific tissues to eliminate/avert/clear disturbing noxa: initiation and progression of disease, and its later activation to increase the risk of morbid (vascular) events, depends on profound dynamic changes in vascular biology.

In the vascular system, reactive oxygen species (ROS) are produced by different cell types, such as endothelial cells, vascular smooth muscle cells, and inflammatory cells infiltrating the perivascular tissue. **T**he enzyme endothelial NO synthase (eNOS), which normally is "coupled" and produces NO, under some conditions, such as in the presence of excess oxidative stress is "uncoupled" and generates superoxide ($\cdot O_2^-$): this leads to the production of reactive nitrogen species, such as peroxynitrite, as a result of the action of $\cdot O_2^-$ on NO. Thus, oxidative stress decreases NO bioavailability, promoting endothelial dysfunction, vasoconstriction, remodeling, and enhanced systemic vascular resistance [29].

The so-called host defense response - any kind of noxa endangering steadiness of homeostasis → increased ROS formation → oxidative stress → endothelial activation, endothelial dysfunction, respectively, in order to eliminate, avert, clear disturbing noxa: most vascular risk factors activate molecular machinery in the endothelium to eliminate/avert/clear disturbing noxa. In author's view, we can draw a parallel between host defense response and stress-responses (the acute stress-response, explicitly and the chronic stress-one, implicitly).- (I refer to brilliant study about chronic stress/on the principles of Selye's stress theory of K. Simon[30]).

Increased intracellular reactive oxygen species (ROS) is crucial for vascular endothelial dysfunction, a key step in the initiating of vascular injury[31] .

Role of inflammation in AMD

Inflammation and immune-mediated processes (complement activation) play an important role in age-related macular degeneration (AMD) pathogenesis**.** Pathology of AMD lesions demonstrates signs of persistent chronic inflammatory damage, including not only mild infiltration of macrophages and accumulation of microglia, but also presence of inflammatory components such as complement factors and pro-inflammatory cytokines/chemokines in the drusen and AMD lesions[32]. Although AMD is not a classic inflammatory disease, inflammatory cells have an important role in AMD pathogenesis and progression[33]. One of the pathological hallmarks of AMD is the focal deposition of the extracellular material between the retinal pigmented epithelium (RPE) and Bruch's membrane called drusen:

The material, referred to as drusen is composed of several cellular and humoural constituents of systemic inflammatory and immune mediated processes[34]. Macrophages and giant cells localizes near drusen, at the breakdown of Bruch's membrane, and in the CNV membrane: macrophage-derived cytokines, such as tumour necrosis factor-α (TNF-α) and IL-1, have been shown to promote the expression of intercellular adhesion molecule-1 (ICAM-1) in the RPE and vascular endothelial cells, inducing additional inflammatory cellular infiltration. Macrophages can also induce proliferation and migration of vascular endothelial cells by cytokines, which accelerates angiogenesis and CNV formation[350:]: angiotensin II type receptor-mediated inflammation is required for choroidal neovascularisation[36]. Chronic inflammatory cells have been observed on the outer surface of the Bruch membrane in eyes with neovascular macular degeneration: these cells may cause vascular macro- and microvascular injury by direct release of long-acting oxidants, toxic oxygen compounds that may also damage the Bruch membrane[37].

Elevated levels of inflammation-related cytokines in the aqueous humor in various stages of AMD may suggest a crucial pathogenic role of inflammation[38]. Higher values of the inflammatory markers [CRP>3 mg/L, IL>4.9 pg/mL, fibrinogen >3.8 g/L] and lower values of the antioxidative parameters [superoxide dismutase (SOD)<900 U/gHb, glutathione reductase (GR) <55 U/L and total antioxidant status (TAS) <1.15 mmol/L] were significantly associated with AMD: the antioxidant defense system was significantly reduced in patients with AMD and the probability to develop AMD was higher in older individuals with lower values of the antioxidant parameters and higher values of the inflammatory markers[39].

(1) **Autoimmunity** has a role in drusen formation and AMD pathogenesis: the presence of a number of antiretinal autoantibodies has been suggested as early features of AMD pathogenesis: 94% of patients with early-stage AMD and 83% of patients with late-stage AMD had elevated levels of serum retinal autoantibodies, compared with only 9% of normal controls[40]. Regulating ROS in the RPE by modulating antioxidant systems or neutralizing oxidatively damaged molecules termed oxidation specific epitopes (OSEs), through an appropriate innate immune response are potential modalities to treat or prevent early AMD[41].

(2) Some **infectious agents** are associated with AMD: (a) C. pneumoniae infection is related to the increased risk of AMD. (b) Cytomegalovirus (CMV) infection is highly associated with the progression from non-neovascular to neovascular AMD: CMV could infect monocytes, neutrophils, and choriocapillaris endothelium, which could contribute to the initiation of CNV. There is a significant association of high cytomegalovirus IgG titer with neovascular AMD compared with dry AMD and control patients: chronic infection with cytomegalovirus may be a novel risk factor for the progression from dry to neovascular AMD[42]. (c) Oral status

may be a potential source of infection in AMD patients: most of the patients with AMD had inflammatory (infectious) lesions in the oral cavity, the overwhelming majority of the lesions were located in the periodontium (periapical lesions)[43].

(3) One of the most recent indirect evidence of the inflammatory process includes clinical observations showing that individuals possessing **complement factor H polymorphism** (CFH Y402H polymorphism) associated with a disposition to infection and inflammation - complement factor H has a key role in warding off inflammation -, have become ill with AMD significantly more frequently[44]. CFH polymorphisms have been linked to a pro-inflammatory state, including increased CRP and decreased complement inhibitory effect[45]. An association between advanced AMD and complement factor H, an integral component of the alternative pathway of complement activation, factor B and complement components C2 and C3 are also associated with systemic complement activation and AMD[46]. Elevated plasma levels of C3a complement compound (i.e. systemic complement activation) in the exudative form of AMD suggest that chronic inflammatory processes play a crucial role in the evolution and progression of AMD: systemic complement activation is demonstrable in AMD patients[47]. Data provide evidence for an association of systemic activation of the alternative complement pathway with genetic variants of CFH that were previously linked to AMD susceptibility.

Morever there was an unquestionable association of systemic complement activation with atherosclerosis[48,49], so that it can reasonably be presumed that the two conditions have a similar pathogenesixs: both AMD and AS are not only related to local stimulation of the complement system (CS) but also result in systemic CS activation, and these findings show that AMD is accompanied by a general inflammatory response, in the form of CS activation, similar to that observed in degenerative vascular diseases such as atherosclerosis.

(4) In patients with moderate to advanced AMD, serum levels of C-reactive protein (CRP) are significantly higher in comparison to those of control subjects with no maculopathy, and the higher CRP level is a single, independent risk factor of AMD (the same applies to interleukin 6 [IL-6])[50]. This establishment of recent origin implies essential messages:

The elevated level of CRP is a marker of chronic subclinical inflammation**,** while inflammation itself is a very substantial, decisive momentum in the pathological process of macular degeneration (chronic inflammation could influence the risk of AMD through various pathways, including endothelial dysfunction in choroidal vessels): inflammatory stimuli are also known to increase the production of reactive oxygen intermediates, which are thought to play a key role in the pathogenesis of AMD, furthermore, inflammation can reduce the bioavailability of antioxidants, setting the stage for a vicious cycle of altered redox status and increased oxidative stress.

Progression of AMD is linked to augmentation of cellular stress, for example, oxidative stress, proteotoxic stress, inflammation and hypoxia: all these conditions can trigger stress in endoplasmic reticulum (ER) (ER maintains protein quality of cells), and ER stress induces the unfolded protein response (UPR), UPR can restore cellular homeostasis, but ultimately may lead to chronic, overwhelming stress that can cause cell death. ER stress is an inducer of angiogenesis, moreover, stress conditions can induce the expression of VEGF, the increased expression of VEGF is fundamental cause of the neovascularizations, in turn[51].

CRP is not only a biomarker of inflammation (including inflammatory AMD!) but it has a role also in the devolvement of disease: namely the elevated CRP, through tumour necrosis factor-alpha (TNF-alfa), causes chronic inflammation that induces lipid peroxidation, and lipid peroxidation in turn plays a key role in the prolongation of vascular wall injury. CRP is pathogenic factor leading to endothelial dysfunction in the cell culture model[33]. Furthermore, the fact that elevated hsCRP level, considered as a marker of chronic subclinical inflammation, is an independent risk factor of AMD, doubtless demonstrates the key role of endothelial dysfunction in the development and course of AMD: namely chronic inflammation is associated with ED and elevated serum CRP level is a surrogate of ED[52, 53, 54]. In AMD elevated CRP levels are in a causal connection with ED: elevated CRP levels hinder, block the expression of endothelial nitric oxide synthetas (eNOS) and increase the production of free radicals which inactivate NO, i.e. in AMD elevated CRP levels are in a causal connection with ED through oxidative stress (OS). Furthermore, the increased CRP stimulates the AT1 receptors of angiotensin II (AT1R) and, in turn, activation of AT1R induces OS and consequential ED. Accordingly, CRP is not only a biomarker (offering also a basis for prognosis) but it takes part actively also in the development, evolution of the pathological vascular process (AMD in the present case). By generating NADPH-oxidase via activation of RhoA/Rho kinase pathway (also in the choroid/retinal arterioles), CRP inhibits the NO-mediated dilatation of retinal vessels (ED!), and significantly contributes to development of the vascular diseases of the retina (including AMD), and CRP can reduce EPCs number and inhibit EPCs function[55]. There is a large body of evidence indicating the association of CRP with endothelial dysfunction (oxidative stress and production of reactive oxygen species, as well as with lipid status disorder in AMD patients, also): CRP is definitely not only the inflammatory marker but also a mediator of development of the vascular disorders in the retinal circulation[39]. Inflammation (CRP!) and immune-mediated processes (complement activation!) play an important role in age-related macular degeneration (AMD) pathogenesis, and a genetic variation in the gene encoding complement factor H (CFH) and plasma levels of C-reactive protein (CRP), a systemic marker of subclinical inflammation, have consistently been shown to be associated with an increased risk for AMD[56]: The connection with CRP as well as other chronic diseases may share a common pathogenetic pathway that is rooted in inflammation and reflected in vascular damage in the choroid and manifested as damage to the outer retina.. Changes in distribution and relative levels of CRP and CFH are evident in early and late AMD eyes, high levels of CRP and insufficient CFH at the retina/choroid interface may lead to uncontrolled complement activation with associated cell and tissue damage: this fact shores up/supports the hypothesis that inflammation and immune-mediated mechanisms are involved in the pathogenesis of AMD. Detrimental effects of CRP could also affect the ocular circulation and might part contribute to development of the retinal vascular disease.

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[57]: 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.*

Elevated CRP levels can be found also in other diseases such as Alzheimer's, type 2 diabetes mellitus, states associated with insulin resistance, metabolic syndrome, obesity, hypertension, CV disease, coronary artery disease (CAD). Thus, it is reasonable to suppose that AMD has a pathogenesis which is similar to that of these conditions. The predictive value of higher CRP in CV diseases is a match for the predictive value of the risk factors of hypertension or smoking; presumably the same applies – with regard to the uniformity, consubstantiality of the vascular system – to the AMD-CRP relation as well.

AMD risk factors (AMDRFs)

If we thoroughly analyse the conditions which are considered as risk factors of AMD (Table I) [familial accumulation of AMD[58]; elderly age/aging[59]; smoking[60]; obesity/abnormally increased body mass index[60]; hypertension[60], higher systolic, diastolic and mean arterial BPs, respectively[61]; pre-eclampsia[62]; incresed fibrinogen level[60], hypercholesterolemia (increased total cholesterol) and postprandial hyperlipemia[63], cholesterol-enriched diets[64], high fat intake in diet[65], consumption of lard and solid fats (solid vegetable oil) and fried foods using solid fat, respectively (independent of serum cholesterol level or BMI)[61]; high LDL-C level[63] (increased concentration of HDL-cholesterol is considered to be cardioprotective, to be associated with a reduced risk of AMD[62]); decreased HDL-C[66] and; increase of triglycerides (TG)[66]; increased concentration of apolipoprotein B (Apo B) and decreased Apo A[66]; high ox-LDL-C level[67]; increased apolipoprotein A1[68]; higher serum fibrinogen level[60]; elevated CRP[69,52]; high IL-6[52]; high serum ICAM level[52]; elevated vWF[8]; high antiphospholipid antibody levels[70], alcohol abuse[71]; diabetes mellitus[72]; postprandial hyperglycemia, high glycemic index (GI)[73], respestively; enhanced (systemic) advanced glycation endproducts (AGE) (accumulation of AG)[74]; increased leptin[75] and decreased adiponectin levels[75]; hypomagnesemy[76]; low serum zink level[76/a]; metabolic syndrome, inflammatory[77], infectious disease (cytomegalovirus |CMV|[78], periapical infective imflammatory lesions[43] and immune diseases[79]; systemic complement activation[46]; increased systemic arterial stiffness/vessel wall rigidity[80]; concomitant cardiovascular disease (CVD)[53]; lower extremity arterial disease; chronic renal disease[80, 8, 77], pathological serum cystatin C level, respectively[81]; obstructive emphysema[82], bronchial asthma[83], high serum uric acid level, gout[82];vitamin

˚Complement factor H Y402H (1277TC) genotype status to both agerelated AMD and kidney disease (KD) (membranoproliferative glomerulonephritis type II and hemolytic uremic syndrome) has led to deduction that (KD) might be associated with AMD[81]. Furthermore, many factors associated with CKD (OS, inflammation, ED) has have been hypothesized to have a crucial role in the pathogenesis of AMD.

Asthma may affect the development of CNV, by increasing the protein levels of C3 and VEGF in the RPE/choroid layers the same cellular and molecular components, including lipids, proteins and lipoproteins (LPs), are common constituents widely found in ocular drusen and atherosclerotic plaques[84], namely, the same biochemical and immunerelated processes may be involved in both events[85].

ED deficiency[86, 87]; hyperhomocysteinaemia[88], it attracts notice that all of these risk factors which seem essentially different lead to (chronic) vascular injury based, after all, on the same mechanism of action: by inducing oxidative stress and consequential endothelial dysfunction[89-92]. ED itself is a consequential phenomenon, and it is a clinically-pathophysiologically important connecting link between harm (noxa) and vascular injury.

If we compare the factors of AMD (AMDRFs) with the cardiovascular (CV) risk factors (CVRFs) including the "classical" ones (described in the original Framingham Study) and the "more recent" ones (identified thereafter), we can immediately notice the considerable overlap between the two. Risk factors which play a decisive role in AMD are in a close connection, correlate with, and – as we can see – often are identical with the risk factors of cardiovascular (CV) diseases (Table I), several clinical studies have illuminated established atherosclerotic risk factors in the pathogenesis of AMD[85], neovascular age-related macular degeneration (NV-AMD) population is associated with a significant cardiovascular risk[93]. The epidemiological data collected so far indicate unquestionably that, AMD is associated with the occurrence of diffuse arterial atherogenesis at various stages (systemic arterial stiffness is a clear indicator of vascular disease: and pulse wave velocity was significantly higher in the patients with AMD compared with controls (p=0.0025), indicating increased arterial stiffness[80]. So that - according to authors opinion, also - it can reasonably presumed that the two conditions have a similar pathogenesis. The same cellular and molecular components, including lipids, proteins and lipoproteins (LPs), are common constituents widely found in ocular drusen and atherosclerotic plaques[84], namely, the same biochemical and immunerelated processes may be involved in both events[85].

Therefore, I consider it extremely important from preventive and therapeutic aspects and I recommend that – as long as its opposite cannot be demonstrated – we declare the risk factors of CV diseases also to risk factors of AMD, and also treat them on the same way: elimination, therapy of OS and of the the consequential ED.

The role of OS on AMD

Due to its high content of polyunsaturated fats and its extensive oxygen consumption, the retina is particularly susceptible to oxidative stress (OS)[94]. Aging per se, in the absence of other risk factors is associated with oxidative/nitrosative stress and inflammatory changes in the phenotype of blood vessels (of choroidal vasculature, also), and the cosecutive age-associated induction of NF-kappaB activation is especially important, since it contributes significantly to endothelial activation, endothelial dysfunction, respectively, in aged vessels, which is critical step in the development and progression of chronic vascular injury/disease[95].

Under physiological conditions in the human body free radicals are generated during mitochondrial oxidative metabolism: the walls of the mitochondria are curiously leaky to oxygen radicals produced during metabolism, and large amounts of superoxide leak from the mitochondrial walls, such that 1% of oxygen used in respiration actually leaks from the mitochondria in the form of superoxide but in older subjects, the proportion is greater.

In general, ROS are essential to the normal-undisrurbed functions of cells, and to performing the defensive-averting activity of human organism against many noxa (the endothelium takes care scrupulously of the integrity, stability, homeostasis of internal milieu), but adequate levels of antioxidant defenses are required in order to avoid the harmful effects of excessive ROS production.

In order to maintain cellular homeostasis against endogenous and exogenous aggressions, different cellular mechanisms of defence, maintenance and repair are continuously activated throughout life. Hormesis, a concept based on the fact that mild stresses protect cells against subsequent stresses, amplifies the efficacy of the cellular mechanisms of defence and repair: aging, senescence and ultimately death, result from the exhaustion of these mechanisms maintaining cellular functions. One of the major sources of vascular endothelial damage is oxidative stress˚. The age-dependent shift in the redox environment towards pro-oxidation contributes to a progressive compensatory remodelling of the endothelium, an accumulation of damages, and its dysfunction, the premises for vascular injury[91].

During ageing, the balance between the generation of reactive oxygen species (ROS) and ROS clearance can be disturbed resulting-via ROS- in oxidative damage to macromolecules: within the eye. In conditions of increased oxidative stress, excess superoxide radical decreasing NO bioavailability through peroxynitrite formation may inhibit the regulatory effects of NO on systemic and ocular blood flow: lower choroidal perfusion is a risk factor for the development of CNV in the fellow eye of patients with unilateral CNV.

Thanks to the enzymes [superoxide dismutases (SOD), catalase, peroxidase, glutathione-transferase and various reductases] which prevent the pathological accumulation of free oxygen radicals. These processes including physiological free radicals take place without any damage of cellular structures. If the free radicals are not eliminated by preventive mechanisms because of defective state of the protective system or its exhaustion due to overload; they may – as deliberated from the physiological mechanisms – accumulate pathologically, and this state is called oxidative stress[96, 97]. The antioxidant defense system is significantly reduced in patients with AMD (significantly lower glutathione reductase [GR] and total antioxidant status [TAS] values in the group of AMD patients compared to the controls). and the probability to develop AMD was higher in older individuals with lower values of the antioxidant parameters and higher values of the inflammatory markers: logistic regression analysis showed that higher values of the inflammatory markers [CRP, IL fibrinogen] and lower values of the antioxidative parameters [SOD, GR and TAS] were significantly associated with AMD [P=0.032)[39].

Increased intracellular reactive oxygen species (ROS) is crucial for vascular endothelial dysfunction, a key step in the initiating of vascular injury .

In general, ROS are essential to the normal-undisturbed functions of cells, and to performing the defensive-averting activity of human organism against many noxa (the endothelium takes care scrupulously of the integrity, stability, homeostasis of internal milieu). but adequate levels of antioxidant defenses are required in order to avoid the harmful effects of excessive ROS production.

Role of aging as the major AMD risk factor.

Age related macular degeneration is a multifactorial disease of ageing. Cumulative damage to mitochondria and mitochondrial DNA (mtDNA) caused by reactive oxygen species (ROS) is one of the causes of aging: the unbalance between production of free radicals and the ability to neutralize them by antioxidant systems causes a condition of "oxidative stress"). Oxidative damage affects replication and transcription of mtDNA and results in a decline in mitochondrial function which in turn leads to enhanced ROS production and further damage to mtDNA. During ageing, the balance between the generation of reactive oxygen species (ROS) and ROS clearance can be disturbed resulting - via OS - in oxidative damage to macromolecules: within the eye. These damaging reactions are involved in the pathogenesis of AMD: significantly higher malonaldehyde |MDA| and lower NO levels were detected in plasma of patients with AMD[98]. In conditions of increased oxidative stress, excess superoxide radical decreasing NO bioavailability through peroxynitrite formation may inhibit the regulatory effects of NO on systemic and ocular blood flow[99, 100]: lower choroidal perfusion is a risk factor for the development of CNV in the fellow eye of patients with unilateral CNV.

AMD is the disease of the aging body, normal aging processes can lead to structural and blood flow changes that can predispose patients to AMD. Advancing age is a privotal and independent risk factor for vascular disease, and aging individuals often demonstrate dysfunctional blood vessel repair after vascular injury, leading to increased endothelial and smooth muscle proliferation, abnormal repair of the extracellular matrix, excessive fibrosis, and even angiogenesis[101]. Aging is characterized by the development of an endothelial dysfunction, which affects both the nitric oxide (NO)- and the endothelium-derived hyperpolarizing factor (EDHF)-mediated relaxations, associated with vascular oxidative stress and the activation of the angiotensin system: both an angiotensin-converting enzyme inhibitor and an AT1 receptor antagonist have been shown to prevent the aging-related endothelial dysfunction[102] . Aging per se, in the absence of other risk factors is associated with oxidative/nitrosative stress and inflammatory changes in the phenotype of blood vessels: the age-dependent endothelial dysfunction in human vessels is due to the combined effect of oxidative stress and vascular wall inflammation[103]. Primary abnormalities in ocular perfusion worsen with age (decreases in choroidal circulatory parameters may be involved in the development of AMD[104]), secondarily causing dysfunction of the retinal pigment epithelial cells, predisposing eyes to AMD: these changes together with individual's environmental risk factors set the stage for the development of AMD.

Loss in the endothelial homeostasis with aging is clearly a contributor to the initiation and development of CVD. Endothelial progenitor cells (EPCs) contribute substantially to the preservation of a structurally and functionally intact

endothelium (EPCs play an important role in repairing endothelial injury)[105]. Aging is associated with EPC dysfunction: physical exercise has a beneficial impact on EPC activity, as a lifestyle intervention strategy to promote vascular health in aging population[106].

Recently, many (of the common so-called degenerative) diseases of older peaple also have been reported to have significant macrovascular and/ or microvascular component (for instance Alzheimer' disease: microvascular changes in brain; osteoporosis: age-associated changes in the microcirculation of porotic bone; sarcopenia: age-elated changes in muscle microcirculation).

The elderly organism is exposed to a continuous oxidative attack as in the mitochondria of its cells free oxygen-containing radicals and other oxidants, primarily superoxide anions (O2-) and hydrogen peroxide (H2O2) are generated in an increased amount during the imperfectly proceeding terminal oxidation. The overproduction of reactive oxygen- and nitrogen-containing radicals and other oxidants [superoxide, hydrogen peroxide, peroxynitrite (ONOO-) or hydroxyl radical (OH-)]: one of the most potent oxidants, which is produced in the reaction of superoxide anions and nitrogen monoxide, enters the cells where it aggressively attacks the most different cellular structures. It starts the chain reaction of lipid peroxidation and elicits DNA damage, chain breaks[107, 108]. DNA chain breaks activate the poly(ADP-ribose)polymerase (PARP) enzyme in the cellular nucleus, and DNA damage causes excessive activation of PARP which, due to the induced metabolic cycle with enormous energy requirement, depletes the complete reserve of NAD+ and ATP of the cell in a short time, it slows down mitochondrial respiration, it creates energetic crisis in the endothelial cells what reduces NO synthesis occurring upon the effect of endothelium-dependent vasorelaxant agents in the endothelial cells.

Along with aging, oxidative stress and physical stress, such as mechanical stretch, continuously and directly insult vascular cells: such stress induces apoptosis by intracellular signaling through stress kinases in cultured retinal vascular cells (inhibition of such stress kinases could be an effective treatment to protect the vascular cells against age-related damage): angiopoietin 1 (Ang 1) secreted by pericytes suppresses oxidative stress-induced intracellular signaling through stress kinases linked to cell apoptosis and normalizes such retinal pathology. This suggests that the paracrine action of Ang 1 in the pericytes is necessary to sustain normal retinal vasculature, and that Ang 1-triggered intracellular signaling is useful for the treatment of vascular cell pathology associated with pericyte loss[109].

Uniformity and consubstantiality of the human vascular system

As human vascular system is uniform, and consubstantial representing an entity, all of its parts (central and peripheral vessels, of course including the ophthalmic vessels which originate from the internal carotid artery and belong to the eye) are consubstantial[110], it is almost impossible (or at least it seems to be forced, artificial) the vascular events to be discussed clinically separated as sharply discerned entities. Some examples of this:

(a) In patients with vascular type erectile dysfunction (atherosclerosis/ED of the internal iliac arteries and/or the smaller vessels supplying the penis), flow-mediated dilatation (FMD) in the brachial artery is decreased to a significant extent, as well as the incidence of vascular diseases including coronary artery disease and peripheral arterial disease and stroke is increased in patients with erectile dysfunction[111].

(b) In endothelial dysfunction of the coronaries – also without an occlusive CAD – there is a significantly increased chance of developing cerebrovascular events[112].

(c) In patients with type 2 diabetes mellitus age-related macular degeneration has proven to be an independent risk factor of cardiovascular mortality[113].

(d) Plaques in the carotid bifurcation were associated with a 4.7 times increased prevalence odds of macular degeneration (95% confidence interval |CI| 1.8-12.2); those with plaques in the common carotid artery showed an increased prevalence odds of 2.5 (95% CI 1.4-4.5); lower extremity arterial disease (ankle-arm index less than 0.90 on at least one side) was associated with a 2.5 times increased prevalence odds of AMD (95% CI 1.4-4.5), respectively[114].

(e) Age-related macular degeneration (AMD) developed in 22% of patients with coronary artery disease (CAD) who require coronary intervention or underwent it: this percentage of incidence is strongly significantly higher than the percentage occurring in the general population.

(f) The presence of AMD also signals an increased risk of CVD, independent of the effect of age and shared risk factors; where those with late AMD had triple the risk of incident coronary heart disease (CHD): prevalence of early AMD is significantly higher in patients with MI than in a random sample of the population[115].

(g) Presence of AMD, especially neovascular AMD, is prospectively associated with a higher risk of incident myocardial infarction (MI), and this finding suggests the possibility of shared common antecedents between MI and AMD[115].

(h) Several prospective studies have demonstrated that both early and advanced AMD-related retinal changes are important independent risk factors for the incidence of myocardial infarction[116, 117].

(i) Disorders of the retinal microvascular system are good predictors of severe cardiovascular and cerebral events. Narrower retinal arterioles (retinal arteriolar narrowing is a marker of systemic microvascular damage) are associated with lower hyperemic myocardial blood flow and perfusion reserve (perfusion reserve reflects microvascular processes in the organ) in asymptomatic adults with no coronary calcification, which is primary mediated by traditonal cardiovascular risk factors[118]: this finding suggest that retinal arterioral narrowing may serve as a marker of coronary microvascular disease.

(j) The microvascular pathogenic process in different circulatory beds is affected by common risk factors, and theese data are supported, by the studies showing a relationship between coronary flow reserve and microvascular structure in subcutaneous fat tissue[116:] vascular structure in subcutaneous small arteries predicts cardiovascular events[119].

(k) Women who have experienced pre-eclampsia are more likely to develop cardiovascular disease in later life (maternal syndrome of pre-eclampsia arises from a generalised maternal inflammatory systemic response incorporating a substantive component of endothelial cell dysfunction: flow-mediated dilatation (FMD) in the brachial artery is decreased to a significant extent). Pregnant women with pre-eclampsia often demonstrate decreased blood flow in the uterine artery,

and poor utero-placental blood flow (placental underperfusion associates with placental oxidative stress!) sets up a chain of events which culminates in the development of pre-eclmpsia in a woman susceptible of the disease. ED, unlike pre-eclampsia does not resolve post-partum, and persistence of this defect may underpin the increased risk of (cardio)vascular disease in later life: a history of pre-eclampsia increases the risk of future hypertension, ischaemic heart disease, stroke, vascular death, and venous thromboembolism[62].

(l) The significantly lower FMD in patients with glaucomatocyclitic crisis (GCC) implies (peripheral) vascular endothelial dysfunction (several studies have shown impaired vascular endothelial function in glaucoma, also). The impairment of endothelial function of the brachial artery in patients with GCC observed indicated a systemic rather than a local vascular effect: improvement of endothelial dysfunction may inhibit flare-ups of GCC.

(m) Persons with early AMD had double the risk of incident stroke over 10 years. Persons with AMD are at an increased risk of both cerebral infarction and intracerebral hemorrhage, this observation provide further insight into common pathophysiological processes between AMD and stroke subtypes[120].

Not regarding familial accumulation, it cannot be predicted, either, if an individual with coexisting risk factors will suffer myocardial infarction or stroke in the future, if he/she develops AMD or, what is very common, more organ systems will be affected by chronic vascular disease at the same time. From the fact that in the conditions listed in points a, b, c, d, e, f, g, h, i, j, k,l and m, the vascular events presented themselves also at areas of supply (internal iliac artery, arteries of the penis, coronaries, uterine artery, subcutaneous vessels, cerebral vessel. choroidal vessels) far from the brachial artery that showed ED, one can conclude to the **general, systemic nature of endothelial dysfunction, the consubstantiality of vascular system**. The cause of this cognition of essential imiportance may be partly, in the author's opinion, the following:

Until recently, it was believed that the bioactivity of the NO is limited to close temporal and spatial proximity of the endothelium and that NO is mere autocrine/paracrine effector, i.e., that it can only travel short distances in the bloodstream: however, recent studies suggest that free NO is in equilibrium with a pool of various NO-containing compounds in blood (i.e. plasma nitroso compounds - RXNOs) that have bioactivity that in every respect, resembles that of autentic NO. Theese nitroso compounds (RXNOs) are transported and delivered along the complete vascular tree to dilate distal arteries and the microvasculature: ED in pattients with CV RFs is associated with decresed levels of circulating RXNOs, plasma RXNOs (plasma nitroso compounds referred to as the circulating NO pool) may be a surrogate index of ED|!|[121].

For the almost regularly returning, repeated phenomenon, I recommend the use of the term **chain of systemic vascular events**, emphasising the physiological, pathophysiological and therapeutic unity, consubstantiality of the human vascular system also by this way. That is why it seems to be more reasonable, more correct to disregard the terms by organ (system) (stroke prevention, AMD prevention, MI prevention) and simply to say vascular (system) prevention.

(I) Non-medicinal therapy/preventive treatment of AMD

(1) Lifestyle modifications of patient with AMD

Preventive medicine for AMD which have lifestyle-related diseases as a systemic background, has attracted growing attention[122]. 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[123].

The lifestyle modifications of patient with AMD is of indispensable importance, indeed, our health also depends on our lifestyle choice. It i 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 behavours 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[123].

(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[109, 60]. 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.

NT upregulats 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[124].

(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[125.] 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 pharmacoceutical 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 stress induced by an increase in blood flow during exercise|!|). [126]. 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[127]. 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[128]. 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[129]. Finally, there is evidence that exercise exerts a positive influence on the number and/or function of EPCs[130]: physical exercise attenuates age-associated reduction in endothelium-reparative capacity of EPCs by increasing CXCR4/JAK-2 signaling [106]. Physical activity might contribute to greater macular pigment density by reducing inflammation and oxidative stress directly or by reducing obesity[123], exercise training restores the endothelial progenitor cells number and function

(d) Prescribing a **d i e t** which contains polyphenols, natural antioxidants in abundance, is rich in vegetables and fruits; and assuring the intake of an appropriate dose of the most important polyunsaturated fatty acid (PUFA) is primary significance: the ethyl ester of eicosapentaenoic acid (EPA) inhibits/prevents the development of choroidal neovascularisation (CNV)[131, 132].

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[133]. Eicosapentaenoic acid- (EPA-) rich diet results in significant suppression of CNV and CNV-related inflammatory molecules (intercelellular 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(!)[134, 135]. 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-gmma. 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[136]. 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)[137]. 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[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)[138].

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[122], and zinc may play a protective role by interrupting the complement cascade[76/a].

(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[139]. 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 theese lesions[140].

(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. 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 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[141].

(g) Eliminaion/discontinuance of the stressful lifestyle[123]

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/eliminastion/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 significanty associates with myocardial infarct (Ml). 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 pathophysio0logically 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[142].

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[143].

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[1443]. 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 r**esponses, hyperactivation of this** pathway **(**renin-angiotensin system hyperactivation) can **induce**/cause chronic inflammation **(**and oxidative stress) which are establishwd risk factors for age-related macular degeneration**,** and retinal neural dysfunction[145], 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 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[146-154]. They improve endothelial function (EF); they substantially reduce ED; they act against the oxidative stress (OS); they significantly relieve inflammation, and they inhibit thrombogenesis.

Ad (1) Angiotensin converting enzym inhibitors (ACEIs)

ACE inhibition attenuated the superoxide-generating effects of angiotensin II, impaired the breakdown of bradykinin, and increased the production of edothelium-derived nitric oxide (EDNO). Angiotensin converting enzym 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[148], and counteracts endothelial cell senescence via facilitaing nitrogen monoxide (NO) production[155], 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[156]. 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[157-8].

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)[151, 158-160]. Most probably, concomitant therapeutic administration of ACEI and ARB may be the most expedient[57]: 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 mobillisation of endothelial progenitor cells [EPCs] from bone marrow[161].- 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[162]. 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[148]. 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[163].

(4) Statins (HMGCoA)

Of the anti-lipaemic products, the up-to-date hydroxy-methylglutaryl-coenzyme A (HMGCoA) reductase inhibitor **statins** (simvastatin, lovastatin, atorvastatin, resuvastatin, fluvastatin, etc.) exert their multifaceted favourable effects due to their pleiotropic properties independently of the reduction of total and LDL cholesterol levels[164-172]: 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")[173]. 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[174].

They inhibit thrombus formation: by inhibiting RhoA/Rho kinase. They significantly mitigate OS: statins impede the activity of NADPH oxidase enzyme, the main source of vascular OS and by this way they considerably reduce superoxide production. Simvastatin may have some clinical benefits in preventing retinal diseases associated with oxidative stress, such as AMD[175].

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[170]. 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[171]. Statins reduces endothelial cell apoptosis by confining imflammation, by increasing the bioavailibility of nitric oxide, and through their anti-oxidative effects[172]. Statins lower accumulation of lipids in Bruch medmbrane: drusen is a key pathophysiologic pathway for AMD development neovascular membranes associated with AMD include macrophages, which may respond to statins. Neovascularisation is a major complication in AMD, therefore, angiogenesis is potential point of statin modulation[176]: 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 ($P = 0.01$).

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[57]. 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.

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[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[177].- 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[178].

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[179].

(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[180-181].

(6) Acetylsalicylic acid (ASA)

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 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[182-183]. Therapy with aspirin is associated with decreased rates of CNV among AMD patients[177].

(7) 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[184]. 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[185]. 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[186-187]. 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[188]). Trimetazidine protects the retina against ischemic damage[189]**:** TMZ has a beneficial effect on retinal lipid peroxidation and changes due to ischemic injury[190].

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

The third generation beta blockers: carvedilol, nebivolol[191] and the peroxisome proliferator- activated receptor-gamma (PPARgamma) agonist pioglitazone and rosiglitazone[192] exert their vascular protective effects exactly via their mitochondrial antioxidant activity.

Third generation beta blocker nebivolol inhibits the gene expression of adhesion molecules (P and E selectins and VCAM-1) of vascular wall, endothelium and smooth muscle cells, as well as it reduces the number of macrophages migrating into the intimal layer and neointima formation, and increases the NO production, inhibits the free oxigen radicals. Nebivolol a vasodilating beta blocker with antioxidant activity improves OS and endothelial function directly via an effect on the endothelial L-arginine/NO pathway[193].

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[194]. 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[156].

(10) Folate improves endothelial dysfunction by reducing the serum levels of homocysteine (elevated levels of homocysteine (Hcy) 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[195].

(11) 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[87]. 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[196].

(12) The **„symptomatic" antioxidant vitamins (AOVs)** (vitamin C, E) used for preventing, conventionally, OS[152] 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.

(13) 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[158] including AMD. Nevertheless, we have excellent therapeutic possibilities also until then: **statins, ACEIs ARBs, ASA (aspirin), trimetazidin, third generation beta blockers, PPARgamma agonists** .

(14) 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[197-198]. 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.

(15) 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[199]**,** improves overall impedance, AGE-crosslink breakers may reduce central arterial stiffness and vascular remodeling.

(16) 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 receptor antagonist **Bosentan** might offer a new therapeutic approach to this disease [24]. 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.

(17) Resveratrol (RSV) (3,5,4'-trihydroxystilbene), a diet-derived polyphenol (polyphenolic phytoalexin), was reported to mimic many respect of caloric restriction (CR) and to exert vasoprotective effects, attenuating OS, improving endothelial function, inhibiting vascular inflammatiom, and decreasing the rate of endothelial apoptosis. 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[200].

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[201].

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[202].

(18) 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[203]. L-arginine supplementation was able to restore endothelial-dependent vasodilation by augmenting cGMP production[204].

(19) 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[205]. 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[206]. 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[207]: coenzyme Q10 protects retinal cells against oxidative stress.

(20) 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 dysfunctio: **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[208].

(21) 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[209].

(22) 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[210].

(23) 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[211].

(III) 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 consequentual ED[142]: 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 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 key role. AMD-risk factors often are identical wih the risk factors of (cardio)vascular (CV) diseases, so the two conditions have a similar pathogenesis, and 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], endothlial dysfunction [ED], respectively → vacular 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 thoose 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 aforementioned medicines/non-medicinal methods beneficial in ED also exert a favourable effect on the vessels of the eye, in the choroid/retina.

Consequently, based on the preceding discussion, it seems logical to presume that, as a part of our primary and secondary preventive activity,

such medicines - 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 [and ones of cardiovascular (CV) disease] inducing 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.

In addition lifestyle modifications of AMD patients (modifying lifestyles behavours of diet, smoking and physical activity) is of indispensable importance;

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.

Of course, the performance of randomised, prospective, multicentric clinical trials is necessary. Nevertheless, also until then we can begin – while taking the contraindications into consideration – the above outlined medication/methods that bear(s) the burden of few side effects.

ACKNOWLEDGEMENTS I offer this study to memory of martyr victims of the Holocaust**.**

Table 1: Cardiovascular and AMD risk factors

Cardiovascular RFs	AMD RFs
"Classical" risk factors:	
– smoking	+
– hypertension,	+
– higher systolic, diastolic and mean arterial BPs, resp.	+
– increased LDL-C	+
– decreased HDL-C	+
– aging	+
– diabetes mellitus	+
– early AS in the family	+(familial accumulation of AMD)
– overweight	
– physical inactivity	+
– atherogenic nutrition	
– cholesterol-enriched diet	+
– high fat intake in diet	+
– concomitant cardiovascular disease (CVD)	+
– lower extremity arterial disease	+
"More recent" risk factors:	
– high fibrinogen level	+
– high ox-LDL-C level	+
_ high LDL level	+
– low HLD level	+
higher HDL reduces risk of AS	higher HDL tended to reduce risk of AMD
– elevated serum apoLp(a)	+
– high serum ICAM level	+
– elevated serum homocysteine	+
– high aPL = antiphospholipid antibody levels	+
– pp hyperglycaemia	+ (high GI: early AMD!)
– low serum zin k level	+
– pp hypertriglyceridaemia	
– diabetic dysmetabolism	
– metabolic syndrome	+
– insulin resistance	
– left ventricular hypertrophy	
– chronic renal disease,	+
– pathological serum cystatin C level, resp.	+
– bronchial asthma	+
– chronic obstructive pulmonary disease (COPD)	+
– cardiac valve calcification	
– migraine (ophthalmic)	
– high serum uric acid level	+
– elevated hsCRP	+
– higher resting heart rate	
– great amplitude of blood pressure	+
– increased vascular wall rigidity/systemic arterial stiffness	+
– osteoporosis	
– obstructive sleep apnoea	
– increased serum triglyceride level at decreased LDL-C	
– high IL-6	+
– elevated vWF	+
– elevated ADMA	
– accumulation of AGE	+
– high SSAO	
– chronic infections/inflammatory conditions	+
– immune diseases	+
– systemic complement activation	+
– oestrogen deficiency	
– alcohol abuse	+

[Modified, after Fischer T[142] : 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.]

Abbreviations

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; CXCR4JAK-2 = chemokine receptor four/Janus kinase-2; 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; 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 glycative stress; SIRT1 = silent information regulator 1; SOD = superoxide dismutase; 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; unfolded protein response = UPR, VCAM-1 = vascular cell adhesion molecule 1; VD = vascular disease; VEGF = vascular endothelial rowth factor; vWF = von Willebrand factor; += overlap between CV and AMD risk factors.

REFERENCES

1. Donat, G., Pournaras C, Munoz, J. L.: Nitric oxide controls alveolar tone in the retina of the miniature pig. Invest. Ophthalmol. Vis. Sci., 1995, 36, 2228–2237.
2. Meyer, P., Flammer, J.: The vascular endothelium as a regulator of the circulation in the eye: a new concept in ophthalmology. Arch. Ophthalmol., 1994, 39, 123–132.
3. Meyer, P., Flammer, J., Lüschner, T. F.: Endothelium-dependent regulation of the ophtahalmic microcirculation in the perfused porcine eye: role of nitric oxide and endothelin. Invest. Ophthalmol. Vis. Sci., 1993, 34, 3614–21.
4. Rabelink, T. J. Endothelial activation and circulating markers of endothelial activation in kidney disease. Nat. Rev. Nephrol., 2010, 6, 404–414.
5. Fischer, T.: Über die medikamentöse Prävention und die präventive Behandlung der altersbedingten Makuladegeneration (AMD) durch die günstige Beeinflussung der Gefaessendotheldysfunktion (ED). Klin. Monatsbl. Augenheilkd., 2004, , 1062.
6. Machalinska, A., Safranow, K., Dziedziejko, V..: Different populations of endothelial cells in patients with age-related macular degeneration: a novel insight into pathogenesis. Invest. Ophthalmol. Vis. Sci., 2011, 52(1), 93-100.
7. Lip, G. Y. H., Blann, A.: von Willebrand factor: a marker of endothelial dysfunction in vascular disorder? Cardiovasc. Res., 1997, 34, 255–265.
8. Lip, G. Y. H., Blann, A., Hope-Ross, M.: Age-related macular degeneration is associated with incrased vascular endothelial gross factor, hemorrheology and endothelial dysfunction. Ophthalmology, 2001, 108, 705–710.
9. Fischer, T.: Paralipomena zur vorgegangenen Veröffentlichung (Klin. Monatsdbl. Augenheilkd., 2004, 221, 1062). Klin. Monatsbl. Augenkeilkd., 2006, 223, 177-178.
10. Fischer, T.: New possible strategy of the medicinal prevention and preventíve treatment in age-related macular degeneration (Hung.). Orv. Hetil., 2008, 149, 121–127.
11. Machalinska, A.,Kawa, M. P., Marlicz, WS..: Complement system activation and endothelial dysfunction in patients with age-related macular degeneration (AMD): possible relationship between AMD and atherosclerosis. Acta Ophthalmol., 2011, Nov 8. doi: 10.1111/j.1755-3768.2011.02295.x. [Epub ahead of print].
12. Wu, K. H., Tan, A. G., Rochtchina, E..: Circulating inflammatory markers and hemostatic factors in age-related maculopathy: a population-based case–control study. Invest. Ophthalmol. Vis. Sci., 2007, 48, 1983–1988.
13. Vischer, U. M.: Von Willebrand factor, endothelial dysfunction, and cardiovascular disease. J. Thromb. Haemost., 2006,: 4, 1186–1193.
14. Schaumberg, D. A., Christen, W. G., Buring, J. E..: High-sensitivity C-reactive protein, other markers of inflammation, and the incidence of macular degeneration in women. Arch. Ophthalmol. 2007, 125, 300–305.
15. Erdbruegger, U., Haubitz, A., Woywodt, M.: Circulating endothelial cells: a novel marker of endothelial damage. Clin. Chim. Acta, 2006, 373, 17–26.
16.Jonas, J. B., Tao, Y., Neumaier, M: Monocyte chemoattractant protein-1, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 in exudative age-related macular degeneration. Arch. Ophthalmol., 2010, 128(10), 1281-1286.
17. Adali, E., Kurdoglu, M., Adali, F..: The relationship between brachial artery flow-mediated dilatation, high sensitivity C-reactive protein, and uterine artery doppler velocimetry with pre-eclampsia. J. Clin. Ultrasound, 2011, 39(4), 191-197.
18. Yong, P. J., Koh, C . H., Shim, W.: Endothelial Microparticles: Missing Link in Endothelial Dysfunction? Eur. J. Prev. Cardiol., 2012 Apr 10. [Epub ahead of print].
19. Chironi, G. N., Boulanger, C. M., Simon, A..: Endothelial microparticles in diseases. Cell Tissue Res., 2009, 335(1), 143-51.
20. Katherin, C.B., Wing-Sun, C., Victor, H.G..: Advanced glycation end-products and endothelial dysfunction in type 2 diabetes. Diabetes Care, 2002, 25, 1055-1059.
21. Evereklioglu, C, Doganay, S., Cekmen, M.: Nitric oxide and lipid peroxidation are increased and associated with decreased antioxidant anzyme activities in patients with age-related macular degeneration. Doc. Ophthalmol., 2003, 106(2), 129-136.
22. Hennig, B., Ching K. Chow: Lipid peroxidation and endothelial cell injury. Free Radical Biology and Medicine, 1988, 4(2), 99-106.
23. Mullins, R., F., Johnson, M. N., Faidley, E. A.: Choriocappilaris vascular dropout related to density of drusen in human eyes with early age-related macular degeneration. Invest. Ophthalmol. Vis. Sci., 2011, 52, 1606-1612.
24-. Cellini, M., Strobbe, E., Gizzi, C.: Endothelin-1 plasma levels and vascular endothelial dysfunction in primary open angle glaucoma. Life Sci. 2012 Mar 3. [Epub ahead of print]
25. Sakai, T., Mathushima, M Tsuneoka, H.: Endothelin-1 in neovascular AMD. Ophthalmology, 2011, 118(6), 1217.
26. Verma, S., Anderson, T. J.: Fundamentals of endothelial function for the clinical cardiologist. Circulation, 2002, 105, 546–549.
27. Lerman, A., Zeicher, N.: Endothelial function. Cardiac events. Circulation, 2005, 111, 363–368.
28. Fischer, T.: Comment to the human vascular system (Hung.). Orv. Hetil., 2006, 147, 1145.
29. Marchesi, C., Ebrahimian, T., mAngulo, O.: Obesity/Metabolic Syndrome: Endothelial Nitric Oxide Synthase Uncoupling and Perivascular Adipose Oxidative Stress and Inflammation Contribute to Vascular Dysfunction. Hypertension, 2009; 54, 1384-1392.
30. Simon, K.: Chronic stress and epigenetics (Hung.). Orv. Hetil, 2012, 153(14), 525-530. DOI:10.1556/OH.2012.29347.
31. Yi, L., Chen, C. Y., Jin, X.: Differential suppression of intracellular reactive oxygen species-mediated signaling pathway in vascular endothelial cells by several subclasses of flavonoids. Biochimie, 2012, Jun 7. [Epub ahead of print]
32. Xiaoyan Ding, Mrinali Patel, and Chi-Chao Chan: Molecular pathology of age-related macular degeneration. Prog. Retin. Eye Res., 2009, 28(1), 1-18.
33. Coleman H. R., Chan, C. C., Ferris, F. L.: Age-related macular degeneration. Lancet, 2008, 372, 1835–1845.
34. Colak, F., Majkic-Sikngh, N., Zoric,L. et al.: The impact of inflammation to the antioxidant defense parameters in AMD patients. Aging Clin. Exp. Res., 2012, Sep 13. [Epub ahead of print]

35. Apte, R. S.: Regulation of angiogenesis by macrophages. Adv. Exp. Med. Biol., 2010;664:15–1
36. Norihiro Nagai, Yuichi Oike, Kanako Izumi Nagai: Angiotensin II type receptor-mediated inflammation is required for choroidal neovascularisation. Arterioscler. Thromb. Vasc. Biol., 2006, 26, 2252–2259.
37. Penfold. P. L., Killingsworth, M. C., Sarks, S. H.: Senile macular degeneration. Invest. Oph- thalmol. Vis. Sci., 1986, 27, 364-371.
38. Kramer, M., Hasanreisoglu, M.. Feldman, A.: Monocyte chemoattractant protein-1 in the aqueous humor of patients with age-related macular degeneration. Clin. Experiment. Ophthalmol., 2011, doi: 10.1111/j.1442-9071.2011.02747.x.
39. Colak, F., Majkic-Singh, N., Zoric, L.: The role of CRP and inflammation in the pathogenesis of age-related macular degeneration. Biochem. Med. (Zagreb), 2012, 22(1), 39-48.
40. Morohoshi K, Goodwin A. M., Ohbayashi M, Ono S. J.: Autoimmunity in retinal degeneration: autoimmune retinopathy and age-related macular degeneration. J Autoimmun. 2009;33:247–254.
41. Handa, J. T .: How does the macula protect itself from oxidative stress? Mol. Aspects Med., 2012 Apr 5. [Epub ahead of print]
42. Miller, D. M., Espinosa-Heidmann, D. G., Legra, J.: The association of prior cytomegalovirus infection with neovascular age-related macular degeneration. Am. J. Ophthalmol., 2004, 138(3), 323-8.
43. Brzozowska, A., Puchalska-Niedbal, L.: Oral status as a potential source of infection in AMD patients—introduction Klin. Oczna, 2012, 114(1, 29-32.
44. Desoriet, D. D., Klavier, C. C., Witteman, J. C.: Complement factor H polymorphism, complement activators and risk of age-related macular degeneration. JAMA, 2006, 286, 301–309.
45. Klein, R. J.,, Zeiss, C., Chew, E.Y.,: Complement factor H polymorphism in age-related macular degeneration. Science 2005, 308, 385–9.
46. Smaihodzic, D., Klaver, C. C., Klevering, B. J.: Risk alleles in CFH and ARMS2 are independently associated with systemic complement activation in age-related macular degeneration.Ophthalmology. 2012, 119(2),39-46.
47 Scholl, H. P., Charbel,I. P., Walier, M.: Systemic complement activation in age-related macular degeneration. PLoS One, 2008, 3(7), e2593.
48. Machalinska, A., Dziedziejko, V., Mazolewska-Piotrowska, K.: Elevated plasma levels of C3a complement conpound in the exudative form of age-related macular degeneration. Ophthalmic Res., 2009, 42, 54-59.
49. Reynolds, R., Hartnett M. E., Atkinson J. P: Plasma complement components and activation fragments: associations with age-related macular degeneration genotypes and phenotypes. Invest. Ophthalmol. Vis. Sci., 2009, 50, 5818–5827
50. Seddom, J. M., Rifai, N.: Association with C-reactive protein and age-related macular degeneration. JAMA, 2004, 281, 704–710.
51. Salminen, A., Kaupinnen, A., Hyttinen, J. M.: Endoplasmic reticulum stress in age-related macular degeneration: trigger for neovascularization. Mol. Med., 2010, 16(11-12), 535-4
52. Schaumberg, D. A., Christen, W. G., Kazlowski, P.: A prospective assesment of the Y402H variant in complement factor H, genetic variants in C-reactive protein, and risk of age-related macular degeneration. Invest. Ophthalmol. Vis. Sci., 2006, 7(6), 2336-2340.
53. Kern, M. J.: Conditions associated with impaired endothelial function, and surrogate soluble markers of endothelial dysfunction. In: Brauwald's Heart Disease. Ed.: Zipes, D. P., Libby, P., Bonow, R. O., and Brauwald, E. Elsevier-Saunders, Philadelphia, 2005, 1108–1109.
54. Verma, S., Szmitko, P. E., Ridker, P. M.: C-reactive protein comes of age. Nat. Clin. Pract. Cardiovasc. Med., 2005, 2, 29–36.
55. Nagoaka, T., Kuo, L., Ren, Y.: C-reactive protein inhibits endothelium-dependent nitric oxide-mediated dilatation of retinal arterioles via enhanced superoxide production. Invest. Ophthalmol. Vis. Sci., 2008, 49(5), 2053–2060.
56. Bhutto, I. A., Baba, T ., Merges, C..: C-reactive protein and complement factor H in aged human eyes and eyes with age-related macular degeneration. Br. J. Ophthalmol., 2011, 95(9), 1323-30. X
57. 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.
58. Maller, J., George, S., Fagerness, J. Common variation in three genes, including a noncoding variant in CFH, strongly influences risk of age-related macular degeneration.
Nat. Genet., 2006, 38(9), 1055-9.
59. Hussain, A. A., Starita, C., Hodgetts, A.,. Marshall, J.: Macromolecular diffusion characteristics of ageing human Bruch's membrane: implications for age-related macular degeneration (AMD). Exp. Eye Res., 2010, 90(6), 703-10.
60. Chakravarthy, U., Wong, T. Y., Fltscher, A.: Clinical risk factors for age-related macular degeneration: a sístematic overview and meta-anaysis. BMC Ophthalmol., 2010, 10, 31.
61. Ngai, L. Y., Stocks. N., Sparrow, J. M.: The prevalence and analysis of risk factors for age-related macular degeneration: 18-year follow-up data from the Speedwell eye study, United Kingdom. Eye (London), 2011, 25(6), 784-793.
62. Poston, L.: Endothelial dysfunction in pre-eclampsia. Pharmacological Reports, 2006, 57(Suppl), 69-74.
63. Reynolds, R., Rosnar, B., Seddon, J. M.: Serum lipid biomarkers and hepatic lipase gene associations with age-related macular degenertion. Ophthlmol., 2010, 117(10), 1989-1995.0
64. Dasari, B., Prasanthi, J. R., Marwarha, G.: Cholesterol-enriched diet causes age-related macular degeneration-like pathology in rabbit retina. BMC Ophthalmol., 2011, 11, 202. 2011 Aug 18;11:22.
65. Wierzbowska, J., Figurska, M., Stankiewizc, AS. Risk factors in age-related macular degeneration and glaucoma, own observations. Klin. Oczna, 2008, 110(10-12), 370-4.
[Article in Polish]
66. Nowak, M., Swietochowska, E., Marek, B.: Changes in lipid metabolism in women with age-related macular degeneration.Clin. Exp. Med., 2005, 4(4),183-7.
67. Yu, A. L., Lorent, R. L., Harltoglou, C.: Biological effects of native and oxidized low-density lipoproteins in cultured human retinal epithelial cells. Exp. Eye Res., 2009, 88(3), 495-503.
68. Thian, J., Fang, K., Qin, X. Y.: Case-control study of risk factors in age-related macular degeneration. Beijing Da Xue Xue Bao, 2012, 44(4), 588-93.
69. Seddon, J. M., George, S., Rosner, B.: Progression of age-related macular degeneration: prospective assesment of C reactive protein, interleukin 6, and other cardiovascular biomarkers. Arch. Ophthalmol., 2008, 123(6), 774-782.
70. Ozkan, B., Karabas, L. V., Altintas, O.: Plasma antiphospholipid antibody levels in age-related macular degeneration. Can. J. Ophtalmol., 2012, 47(3),264-8.
71. Chong, E. W., Kreis, A. J., Wong, T. Y.: Alcohol consumption and the risk of age-related macular degeneration: systematic review and meta-analysis. Am. J. Ophthalmol., 2008, 145(4), 7007-715.
72. Choi, J. K., Lym, Y. L., Moon, J. W.: Diabetes mellitus and early age-related macular degeneration. Arch. Ophthalmol., 2011, 192(2), 196-199.
73. Kaushic, S., Wang, J.J., Flood, V.: Dietary glycemic index and the risk of age-related macular degeneration. Am. J. Clin. Nutr., 2008, 88(4), 1104–1110.
74. Mulder, D. J., Bieze, M., Graaff, R.: Skin autofluorescence is elevated in neovascular age-relted macular degeneration. Br. J. Ophthalmol., 2010, 94(5), 622-625.
75. Bao, B., Xu, L., Jiang, C. Q.: Relation of serum leptin and adiponectin to cardiovascular risk factors in older adults: a Guangzhou biobank cohort study-CVD. Zhonghua Liu Xing, Bing Xue Za Zhi, 2010, 31(2), 121-125.
76. Reffelmann, T., Dörr, M., Ittermann, T.: Low serum magnesium concentrations predict increase in left ventricular mass over 5 years independently of common cardiovascular risk factors. Atherosclerosis, 2010, 213(2), 563-569.
76/a. Semes, L. P: Recent evidence points to common pathways in AMD, vascular diseas. Research supports dietary modification or supplementation to reduce patients' risk. Primary Care Optometry News, February 2012
77. Raoul, W., Leliévre, E., Auvynet, C.: Role of chemokines in the development of age-related macular degeneration. 2010, 204(4), 311-319.
78. Cousins, S. W., Espinosa-Heidmann, D. G., Miller, D. M. Macrophage activation associated with chronic murine cytomegalovirus infection results in more severe experimental choroidal neovascularization. PLos Pathog., 2010, 8(4), e1 2671.
79. Kijlstra, A., La Hejl, E., Hendrikse, F.:Immunological factors in the pathogenesis and treatment of age-related macular degeneration. Ocul. Immunol. Inflamm., 2005, 13(1), 3-11.
80. Sato, E., Feke, G. T., Appelbaum, E. Y.: Association between systemic artery stifness an age-related macular degeneration. Gaefes Arch. Clin. Exp. Ophthalmol., 2006, 244(8), 963-971.
81. Klein, R. J., Knudtson, M. D., Lee, K. E.: Serum cystatin C level, kidney disease markers, and incidence of age-related m0acular degeneration: the Beaver Dam Eye Study. Arch. Ophthalmol., 2009, 127(2), 193-199.
82. Klein, R. J., Klein, B., Tomany, S. C.: Association of emphysema, gout, and inflammatory markers with long-term inidence of age-related maculopathy. Arch. 0phthalmol., 2004, 121, 674-678
83. Sun, Y., Yu, W., Huang, L. et al.: Is asthma related to choroidal neovascularization? PLoS One, 2012, 7(5), e:35415.
84. Sivaprasad, S., Bailey, T.A. & Chong, V.N.: Bruch's membrane and the vascular intima: is there a common basis for age-related changes and disease? Clin. Experiment. Ophthalmol., 2005, 33,:518–523.
85. Connell, P. P., Keane, P. A., O'Neill, E. C.: Risk factors for age-related maculopathy. J Ophthalmol 2009: 1–39.

86. Morrison M. A., Silveira A. C., Huynh Net al.: Systems biology-based analysis implicates a novel role for vitamin D metabolism in the pathogenesis of age-related macular degeneration. Hum. Genomics. 2011 Oct;5(6):538-68.
87. Millen A.E., Voland, R., Sondel, S. A.: Vitamin D status and early age-related macular degeneration in postmenopausal women. Arch. Ophthalmol., 2011, 129(4), 481-489.
88. Axer-Siegel, R., Bouria, D., Ehrlich, D.: Association of neovascular age-related macular degeneration and hyperhomocysteinemia. Am. J. Ophthalmol., 2004, 137(1), 84-89.
89. Dröge, W.: Free radicals in the physiological control of cell function. Progr. Cardiovasc. Dis., 1995, 378, 129–154.
90. Greene, D. G., Stevens, M. J., Obrosova, I.: Glucose-induced oxidative stress and programmed cell death in diabetes mellitus. Eur. J. Pharmacol., 1999, 375, 217–223.
91. Thorin-Trecases, N., Voghel, G., Farhat, N.: Age-dependent oxidative stress: toward an irreversible failure in endothelial maintenance. Med. Sci. (Paris), 2010, 26(10), 875-80.
92. Fischer, T: Noxa → oxidative stress → vascular endothelial activation, consecutive vascular endothelial dysfunction, respectively → cell/tissue/organ/ demage. RINPAS Journal, 2011, 3(Supplement), 4.
93. Olea J. L., Tuñón, J.: Patients with neovascular age-related macular degeneration in Spain display a high cardioascular risk. Eur. J. Ophthalmol., 2012, 22(3), 404-11. ˚
94. Keaney, J. V., Vita, J. A.: Oxidative stress, and antioxidant protection in endothelium-derived relaxing factor action. Prog. Cardiovasc. Dis., 1995, 378, 129–154.
95. Fischer T: New possible strategy for prevention and preventive treatment of age-related macular degneration resting on recent clinical and pathophysiological observations. CEMED, 2009, 3(3), 415-430.
96. Augustin, A. J., Dick, J., Offermann, J.: Bedeutung oxidativer Mechanismen bei Erkrankungen der Netzhaut. Klin. Monatsbl. Augenheilkd., 2002, 219, 631–643.
97. Yin, J., Thomas, F., Lang, J. C.: Modulation of oxidative stress in the human retinal epithelium following treatment with vitamin C. J. Cell Physiol., 2011, 226(8), 2025-32.
98. Totan, Y., Cekin, Os., Borazan, M.: Plasma malondialdehyde and nitric oxide levels in age related macular degeneration. Br. J. Ophthalmol. 2001, 85, 1426–1428.
99. Violi, F., Marino, R., Mili, M. T.: Nitric oxide and its role in lipid peroxidation. Diabetes Metab. Res. Rev., 1999, 15, 283–88.
100. Goldstein, I. M., Ostwald, P., Roth, S.: Nitric oxide: a review of its role in retinal function and disease. Vis. Res., 1996, 36, 2979–94.
101. Csiszar, A., Wang, M., Lakatta, E. G., and Ungvari, Z.: Inflammation and endothelial dysfunction during aging. J. Appl. Physiol., 2008, 1(5), 1333-1341.
102. Idris, K. N., Chataigneau, T., Auger, C: Grape-derived polyphenols improve aging-related endothelial dysfunction in rat mesenteric artery: role of oxidative stress and the angiotensin system. PLosS One, 2012, 7(2):e32039.
103. Rodrigez-Manas, L., El-Assar, M., Vallejo,. S.: Endothelial dysfunction in aged humans is related with oxidative stress and vascular inflammation. Aging Cell; 2009 Jun;8(3):226-38
104. Xu, W., Grunwald, J. F., Metelitsina, T. I.: Association of risk factors for choroidal neovascularization in age-related macular degeneration with decreased foveolar choroidal circulation. Am. J. Ophthalmol., 2010, 150(1), 40-47.e2.
105. Moreno, P.l R., Sanz, J., Fuster, V.:: Promoting mechanisms of vascular health: circulating progenitor cells, angiogenesis, and reverse cholesterol transport. J. Am. Coll. Cardiol., 2009, 53, 2315–2323.
106. Xia, W. H., Li, J., Su, C.,: Physical exercise attenuates age-associated reduction in endothelium-reparative capacity of endothelial progenitor cells by increasing CXCR4/JAK-2 signaling in healthy men. Aging Cell, 2012, 11(1), 111-119.
107. Espinosa-Heidmann, D. G., Suner, I., Hernandez, E. P.: Age as independent risk fgactor for severity of experimental chorioidal neovascularization. Invest. Ophthalmol. Vis. Sci., 2002, 43(5), 1567-1573.
108. Radovits, T.: New antioxidant strategy in the age associated cardiovascular dysfunction (Hung.). Orv. Hetil., 2008, 149, 2377–2385.
109. Tagaki, H.: Aging and retinal vascular diseases. Nippon Ganka Gakkai Zasshi, 2007, 111(3), 207-230.
110. Fischer, T.: New possible strategy for prevention and preventive treatment of age-related macular degneration resting on recent clinical and pathophysiological observations (Hung.). Orv. Hetil., 2009, 150(11), 503-512.
111. Kaiser, D. R., Billups, K., Mason, C.: Impaired brachial artery endothelium-dependent and –independent vasodilatation in men with erectile dysfunction and no other clinical cardiovascular disease. J. Am. Coll. Cardiol., 2004, 43, 179–184.
112. Cheitlin, M. D.: Erectile dysfunction: Thymoquinone improves aging-related endothelial dysfunction in the rat mesenteric artery the earliest sign of generalized vascular disease? J. Am. Coll. Cardiol., 2004, 43, 185–186.
113. Voutilainen-Kaunisto, T., Uusitupa, M. I., Terasvirta, M. E.: Age-related macular degeneration in newly diagnosed type 2 diabetic patients and control subjects. Diabetes Care, 2000, 23, 1672–1678.
114. Targonski, P. V., Bonetti, P. O., Pumper, G. M.: Coronary endothelial dysunction is associated with an increased risk of cerebrovascular events. Circulation, 2003, 107, 2805–2809.
115. Liutkeviciene, R., Leseauskaite, V., Zaliaduonyte-Peksiene,D. et al.: Early age-related macular degeneration in patients with myocardial infarction. Curr. Eye Res., 2012, 37(2), 94-100.
116. Duan,Y, Mo, J., Scott, I. U.: Age-related macular degeneration is associated with incident myocardial infarction among elderly. Am. Ophthalmology, 2006, 114(4), 732-737.
117. Liao, J. K., Laufs, U.: Pleiotropic effects of statins. Annu. Rev. Pharmacol. Toxicol., 2005, 45, 89–118.
118. Vingerling, J. R., Dielemans, J., Bots, M. L.: Age-related macular degeneration is associated with atherosclerosis. The Rotterdam Study. Am. J. Epidemiol., 1995, 142(4), 404-409.
119. Lu Wang, Tiewn Y Wong, Sharrett, A. R.: Relationship between retinal arteriolar narrowing and myocardial perfusion. Multi-ethnic study of atherosclerosis. Hypertension, 2008, 51, 119-126.
120. Ikram, M. K., Mitchell, P., Klein, R.: Age-related macular degeneration and long-term risk of stroke subtypes. Stroke, 2012, 43(6), 1681-3.
121. Heiss, C., Lauer, T., Dejam, A.: Plasma nitroso compounds are decreased in patients with endothelial dysfunction. J. Am. Coll. Cardiol., 2006, 45, 573-579.
122. Ishida, S.: Lifestyle-related diseases and anti-aging ophthalmology: suppression of retinal and choroidal pathologies by inhibiting renin-angiotensin system and inflammation. Nihon Ganka Gakkai Zasshi, 2009, 113(3), 403-422 (in Japanese)
123. Mares, J. A., Voland, R. P., Sondel, S. A.: Healthy lifestyle related to subsequent prevalence of age-related macular degeneration. Arch. Ophtalmol., 2011, 129(4), 470-480.
124. 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 May 27. [Epub ahead of print]
125. 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.
126. Werner C, Furster T, Widmann T.: Physical exercise prevents cellular senescence in circulating leukocytes and in the vessel wall. Circulation, 2009, 120, 2438–2447.
127. Golbidi, SD., Laher, I.: Exercise and the Cardiovascular System. Cardiol. Res. Pract., 2012, 2012: 210852.
128.. Williams, P. T.: 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), 101-106.
129. 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.
130. 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.
131. 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.
132. 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.
133. 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.
134. 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.
135. SanGiovanni, J. O., Chew, E. J.: The role of omega-3 long-chain polyunsaturted fatty acids in health and disease of the retina. Prog. Retin. Eye Res., 2005, 24(1), 87-138.
136. Wight, S. A., O'Prey, F. M., McHenry, M. T.: A randomized interventional trial of omega-3-polyunsturated fatty acids on endothelial function and disease activity in systemic lupus arythematosus. Ann. Reum. Dis., 2008, 67(6), 841-8.

137. Kijlstra, A., Tian, Y., Kelly, E. R.: Lutein: More than just a filter for blue light. Prog. Retin Eye Res., 2012. [Epub ahead of print.]
138. 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.
139. Chiu, C. J., Taylor, A.: Dietary hyperglycemia, glycemic index and metabolic retinal diseases. Prog. Retin. Eye Res., 2011, 30(1),18-53
140. 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.
141. Anderson, R. M., Weindruck, R.: The caloric restriction paradigm: implications for healthy human aging. Am. J. Hum. Biol., 2012, 24(2), 101-6. doi: 10.1002/ajhb.22243.
142. 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.
143. Muenzel, T., Gori, T.: Nebivolol. the somewhat-different beta-adrenerg receptor blocker. J. Am. Coll. Cardiol., 2009, 54, 1491-1499.
144. Abramov, D., Carson , P. E.: The role of angiotensin receptor blockers in reducing the risk of cardiovascular disease. Journal of Renin-Angiotensin-Aldosterone System; DOI: 10.1177/1470320312443910, published online 18 May 2012.
145. Kurihara, T., Ozawa, Y., Ishida, S.: Renin-Angiotensin system hyperactivation can induce inflammation and retinal neural dysfunction. Intern. J. Inflam., 2012, 2012, 581695, doi:10.1155/2012/581695
146. Heagerty, A. M.: Effect of AT1-receptor blockade on vascular structure and function. Eur. Heart J., 2004, 6 (Suppl. H), H17–H21.
147. 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.
148. 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.
149. 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.
150. Soehnlein, O., Schmeisser, A., Cicho, J..: ACE inhibition lowers angiotensin-II-induces monocyte ahesion to HUVEC by reduction of p65 translocation and ATI expression.J. Vasc. Res., 2005, 42, 399–407.
151. 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, 1454–1470.
152. 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.
153. Wassman, S., Nickenig, G.: The role of AT1-receptor in the cardiovascular continuum. Eur. Heart J., 2004, 6 (Suppl. H), H3-H9.
154. Landmesser, M., Harrison, D. G.: Oxidant stress as a marker for cardiovascular events. Ox marks the spot. Circulation, 2001, 104, 2638–2640.
155. Erusalimsky, J. D.: Vascular endothelial senescence: from mechanism to pathophysiology. J. Appl. Physiol., 2009, 106(1), 326-332.
156. Pershadsingh, H.A., Moore, D.M.: PPAR gamma agonist: Potential therapeutics for neovascular retinopathies. PPAR Res., 2008, 2008, 164–273.
157. 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.
158. Ceriello, A.: New insights on oxidative stress and diabetic complication may lead to a „causal" antioxidant therapy. Diabetes Care, 2003, 25, 1589–1596.
159. 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.
160. Asselberg, F. W., van der Harst, P., Jessurum, G. A. J.: Clinical impact of vasomotor assessment and role of ACE-inhibitors and AR-blockers. Vasc. Pharmacol., 2005, 42, 125–140.
161. 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
162. 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.
163. 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.
164. Almutti, K., Rimawi, R., Spevack, D.: Effects of statins beyond lipid lowering: Potential for clinical benefits. Internat. J. Cardiol., 2006, 109, 7–15
165. Hall, N.F., Gale, C.R., Sudall, H.: Risk of macular degeneration in users of statins: cross-sectional study, BMJ, 2001, 323, 375–376.
166. Minoru, M., Atachi, Y., Yamada, H.: Chorioidal neovascularisation is provided by bone marrow cells. Stem. Cells, 2004, 22, 21–26.
167. 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.
168. Ray, K., Cannon, C. D.: The potential relevance of the multiple lipid-indpendent (pleiotropic) effects of the statins. J. Am. Coll. Cardiol., 2005, 46, 1425–1433.
169. Wydlanski, M. E., Gokce, N., Keanea, J. E.: The clinical implication of endothelial dysfunction. J. Am. Coll. Cardiol., 2003, 42, 1149–1160.
170. 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
171. Palinsky, W., Tsimiskas, S.: Immunomodulatory effects of statins. J. Am. Soc. Nephrol., 2002, 13, 1673–1681.
172. McGwin, G., Owsley, C., Curcio, C. A.: The association between statin use and age related macular degeneration. Br. J. Ophthalmol., 2003, 87, 1121–1125.
173. Asselberg, F. W., van der Harst, P., Jessurum, G. A. J.: Clinical impact of vasomotor assessment and role of ACE-inhibitors and AR-blockers. Vasc. Pharmacol., 2005, 42, 125–140.
174. 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.
175. Kim, K. J., Kim, K. S., Kim, N. R.: Effects of Simvastatin on the Expression of Heme Oxygenase-1 in Human RPE Cells. Invest. Ophthalmol. Vis. Sci., 2012, 53(10), 6456-64.
176. Shahsuvaryan, Marianne: HMG CoA (3-hydroxy-3methylglutaric coenzyme A reductase inhibitors): Evaluation of the role and actions in age-related macular degeneration. J. Physiol. Pathophysiol., 2010, 1(2), 13-17.
177. 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.
178. 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.
179. Morawietz, H: LOX-1 receptor as a novel target in endothelial dysfunction and atherosclerosis. Dtsch Med Wochenschr; 2010 Feb;135(7):308-12.
180. 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, Mar 22. [Epub ahead of print].
181. Marti, C. N., Gheorgiade, M., Kalogeropoulos, A P.: Endothelial Dysfunction, Arterial Stiffness, and Heart FailureJ. Am. Coll. Cardiol., 2012, Sep 8. [Epub ahead of print]
182. Wu, R., Lamontagne, D., Champlain, J.: Anti-oxidative properties of acetylsalicylic acid on vascular tissues from rats. Circulation, 2002, 105, 387–392
183. 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.
184. Coyas, A.: The efficacy of trimetazidine in cochleovestibular disorders of ischemic origin. A crossover control versus placebo trial. Annales d'Oto-Laryngologe et de Chirurge Cervico-Faciale, 1990, 1 (107 Suppl), 81–87.
185. 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. [Epub ahead of print]
186. Belardinelli, R., Solenghi, M., Volpe, L.: Trimetazidine improves endothelial dysfunction: an antioxidant effect. Eur. Heart J., 2007, 28, 1102–1108.
187. Vitalem, 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.

188. National Pharmaceutical Institute: Drug Compendium (Hung.). MediMedia Információs Kft., Budapest, 2002, 75.
189. 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.
190-. Demir, T., Torgut, B., Ozercan, I. Trimetazidine for prevention of induced ischemia and reperfusion of guinea pig 0retina. Clin. Ophthalmol., 2010, 2, 4, 21-6.
191. Wu, T.C., Chen, Y.H., Leu, H.: Carvedilol, a pharmacological antioxidant. Free Rad. Biol. Med., 2007, 43,1508–1522.
192. Hwang, J., Kleinheinz, D. J., Rupnow, H. L. et al.: The PPARgamma ligand, rosiglitazone, reduce vascular oxidative stress and NADPH oxidase expression in diabetic mice. Vascul. Pharmacol., 2007, 46(6), 456-62.
193. 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.
194. 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.
195. Christe, W. G., Glynn, R. J., Chew, E.Y.: Folic acid, pyridoxine, and cyanocobalamin combination treatment and age-related macular degeneration in women: the Women's Antioxidant and Folic Acid Cardiovascular Study. Arch. Intern. Med.. 2009, 169(4), 335-41.
196. Shab-Bidar S, Neyestani, T . R., Djazayery, 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 [Epud ahead of print]
197. 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.
198. Tai, K., Yu, G. P., Chen, M. Urinary 6-sulfatoxymelatonin level in age-related macular degeneration patients. Mol. Vis., 2009, 15, 1673-9.
199. 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.
200. Mouchiroud, L., Molin, L., Dalliére, N.: Life span extension by resveratrol, rapamycin, and metformin: The promise of dietary restriction mimetics for an healthy aging. 2010, 36(5), 377-82.
201. 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.
202. Lassalaletta, A. D., Chu, L. M., Elmadhun, N. Y.: Cardioprotective effects of red wine and vodka in a model of endothelial dysfunction. J. Surg. Res. 2012 Jun 21. [Epub ahead of print]
203. 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.
204. Sharma, A., Bernatchez, P. N.: Targeting Endothelial Dysfunction in Vascular Complications Associated with Diabetes. Int J Vasc Med., 2012, 2012: 750126.
205. 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.
206. 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.
207. 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.
208. 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.
209. Mirshaki, A., 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.
210. 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.
211. Hara, R., Inomata, Y., Kawaji, T.: Suppression of choroidal neovascularization by N-acetyl-cysteine in mice. Curr. Eye Res., 2010, 35(11), 1012-20.

QUICK RESPONSE CODE	ISSN (Online) : 2277 –4572
	Website http://www.jpsionline.com

How to cite this article:
Tamás Fischer. Age-related macular degeneration is a Vascular disease, part of Vasculopathy: holistic approach of the AMD'S pathophysiology, prevention and preventive treatment. *J Pharm Sci Innov*. 2012; 1(6): 15-35.