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

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ABSTRACT OF PART ONE

The endothelial system assures unhindered functioning and stability of the internal milieu maintaining vascular health and protecting against vascular injury, noxa. by 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. It is of great therapeutic significance that demonstrated the key role of disordered function of endothelium in the vessels supplying the affected ocular structures with blood: the recognition is of great preventive therapeutic significance that demonstrated the key role of ED in the vessels supplying the affected ocular structures with blood, i.e., that ED plays major role in the genesis and development of ED. Inflammation/parainflammation and immune-mediated processes (complement activation) play an important role in ED, in consecutive AMD pathogenesis. Chronic inflammation, a feature of AMD, is tightly linked to diseases associated with ED: AMD is accompanied by a general inflammatory response, in the form of complement system activation, similar to that observed in degenerative vascular diseases such as atherosclerosis. All these facts indicate that age-related macular degeneration (AMD) may be a vascular disease, part of systemic vasculopathy(!), in the end, as a matter of fact: this recognition/perception could have therapeutic implications. harm (noxa, i.e., risk factors [RFs]) → oxidative stress [OS] → endothelial activation [EA], endothelial dysfunction [ED], respectively → vascular injury, vascular disease). Wall of blood vessels including those in
choroids also, may be triggered by several repeated and/or prolonged mechanical, physical, chemical, microbiological, immunologic, and genetic influences-impacts-stimuli (noxa, i.e., RFs), against which protracted response, the so-called host defense response may develop, and in consequence of this, vascular damage pathological consecutive changes ending in vascular injury (e.g., atheroscleros/age-related macular degeneration) ultimately, may develop.- AMD-risk factors also act directly on the endothelium through an increase in the production of reactive oxygen species, promoting an endothelial activation, which lead to endothelial dysfunction, the onset of vascular disease. Thus endothelial dysfunction is a connecting link between harm (noxa) and vascular injury: any kind of noxa start/trigger off an defensive chain that results in inflammation to specific tissues to eliminate/clear/avert (AMD-)risk factors, and even early AMD is associated with the occurrence of diffuse arterial vascular injury state at various stages[!]1: patients with early AMD exhibit signs of systemic and retinal vascular alterations. All these facts indicate that age-related macular degeneration (AMD) may be a vascular disease, part of systemic vasculopathy(!), in the end, as a matter of fact: this recognition/perception could have therapeutic implications.

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

**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 = angiopeotin-1; Ang-II = angiotensin II; AO = antioxidant; AOVs = antioxidant vitamins; aPL = antiphospholipid antibody levels; ARB = angiotensin II receptor blocker; ASA = acetylsalicylic acid; AS = atherosclerosis; ATP = adenosine triphosphate; AT1R = AT1 receptor of angiotensin II; BMI = body mass index;; CAD = coronary artery disease; CD 40 = cluster of differentiation 40; CFH = complement factor H; CR = caloric restriction; CI = confidence interval; CNV = choroidal neovascularisation; COX-2 = cyclooxygenase-2; CRP = C-reactive protein; CV = cardiovascular; CVD = cardiovascular disease; hTERT = catalytic subunit of telomerase; DHA = docosahexaenoic acid; DR = diabetic retinopathy; ER = endoplasmic reticulum; EA = endothelial activation; ED = endothelial dysfunction; EDHF = endothelium-derived hyperpolarizing factor; EDNO = endothelial-derived nitric oxide; EF = endothelial function; EMP generation = endothelial microparticle generation; EPCs = endothelial progenitor cells;
ET-1 = endothelin 1; eNOS = endothelial nitric oxide synthetase; Fib = fibrinogen; FMD = flow-mediated dilatation; GCC = glaucomatocyclitic crisis; GLP-1 = glucagon like peptide-1 receptor; GI = glycaemic index; GR = glutathione reductase; GS = glycate stress; HDL-C = high density lipoprotein cholesterol; HMGCoA = hydroxy-methylglutaryl-coenzyme A; hscCRP = 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; STAT-3 = signal transducer and activator of transcription; aMT6s = 6-sulfatoxymelatonin levels; TAS = total antioxidant status; TF = tissue factor; TM = thrombomodulin; TNF-a = tumor necrosis factor-alpha; tPA = tissue plasminogen activator; Th-1 = proinflammatoty T-helper; Th-2 = antiinflammatoty T-helper; TXA2 = thromboxane-A2; TRLs = triglyceride-rich lipoproteins; UPR = unfolded protein response; -VCAM = vascular cell adhesion molecule 1; VD = vascular disease; VEGF = vascular endothelial growth factor; vWF = von Willebrand factor; += overlap between CV and AMD risk factors.

Age-related macular degeneration (AMD) is an ophthalmologic disease which usually affects older adults and results in a loss of vision in the center of the visual field, because of damage to the central retina, called the macula. Early AMD is characterized by drusen (yellow spots) and pigmenary changes in the choroid/retinal pigment epithelium (RPE) layers in the macula. Late AMD has interconvertible ‘dry’ and ‘wet’ forms. The advanced form of dry AMD, also called geographic atrophy (GA), is characterized by extensive loss of the RPE, its overlying photoreceptors (PRs) and, possibly, the underlying choriocapillaris. Choroidal neovascularization (CNV), which involves abnormal growth of blood vessels from the
choroid, is a hallmark of wet (or neovascular) AMD. At this early stage of the disease experts are speaking of age-related maculopathy rather then AMD. If the drusen are becoming more numerous, geographic atrophy or marked pigmentary changes are occurring the term AMD is applied. Especially, the prevalence and incidence of AMD is increasing in individuals older than 50 years old. According to the World Health Organization in 2002, AMD is among the most common causes of blindness, particularly irreversible blindness, in the world. Among the elderly it is regarded as the leading cause of blindness in the world. 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/less of the ability to read in the elderly age-group and affecting about 180 million people all over the world the pathogenesis of AMD is still poorly understood, and treatment options remain limited therefore.

INTRODUCTION
Although the molecular underpinning of AMD remains unclear, it is postulated that oxidative stress, inflammation and angiogenesis play critical roles in AMD pathogenesis. The retina is a highly metabolic tissue and is particularly susceptible to oxidative stress: consistent with a causative role for oxidative stress in AMD, smoking, which is linked to increased oxidative stress in the RPE, has been known to be an established risk factor for AMD. RPE cells are critical to the integrity of the retina, as they are responsible for phagocytizing PR fragments and stabilizing the local extracellular environment: oxidative damage can induce RPE cell death, local autoimmune responses and chronic inflammatory responses, which in turn may result in wide-spread GA and CNV. GA is defined as a sharply circumscribed area of RPE atrophy with exposure of the underlying choroidal vessels. GA is defined as a sharply circumscribed area of RPE atrophy with underlying choroidal vessels, and by histology, GA presents as thinning or absence of the RPE and closure of choriocapillaris and degeneration of the overlying PRs. During CNV, neovessels originate in the choroid and grow under and
through the RPE and Bruch’s membrane (BM), spreading beneath the retina and causing subretinal hemorrhage, RPE detachment and fibrotic scar formation.

The Role of ED on AMD

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/(chronic) vasculopathies and the progression of vascular lesions (4). In parallel, there is considerable evidence implicating endothelial dysfunction (ED) in the pathogenesis of both atherosclerosis and (AS) and AMD (5, 6), and cellular oxidative stress appears to be a common denominator underlying this process. 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) (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 .

(2) Several clinical trials have shown evidence linking soluble markers of endothelial dysfunction to drusen formation or neovascularization, the two hallmarks of AMD.

(3) Endothelial progenitor cell’s (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. Circulating endothelial cells (CECs) are desquamated mature cells that have detached from the intimal monolayer in response to endothelial injury; increased numbers of CECs in AMD patients reflect a severe vascular disturbance and may contribute to the disease process (11), 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): raised circulating levels sICAM-1 are indicative of a state of endothelial dysfunction and increased interaction with leukocytes, with consequent activation of target cells and induction of inflammatory activity. In a study with AMD-patients, serum markers of inflammation (high-sensitivity C-reactive protein, tumor necrosis factor–α receptor 2, interleukin-6, and white blood cell count), oxidative stress (8-isoprostane and total carbonyl content), and endothelial dysfunction (soluble vascular cell adhesion molecule–1 and soluble intercellular adhesion molecule–1) were measured: modest evidence of relationships of serum high-sensitivity C-reactive protein, tumor necrosis factor–α receptor 2, interleukin-6, and soluble vascular cell adhesion molecule–1 to the 20-year cumulative incidence of early AMD independent of age, smoking status, and other factors (16/a).
(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 (11), 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 endproducts (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 endothelial cell injury/dysfunction (21, 22).

(10) Evidence for **choroidal microvascular dysfunction** in AMD suggests a possible mechanism for vascular injury in AMD (decreased choroidal circulatory parameters may be involved in the development of AMD [23]): choroidal microvascular changes are related to the pathogenesis of AMD and suggest that vascular endothelial cell loss occurs in association with sub-RPE deposit-formation. If drusen preferentially develop over regions of capillary lumen-depleted choroid, reduced vascular perfusion may contribute to drusen formation. (24).

(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, vasoconstrictio: (the increase of ET-1 in patients in AMD is related to vascular dysfunction [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, and the 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).

(12) AMD is associated with the occurrence of diffuse arterial atherogenesis at various stages (and whereupon systemic arterial stiffness) (26); correlation was shown between increased arterial stiffness and ED (27): endothelial dysfunction and arterial stiffness are surrogate markers of arterial health.

(13) In wet type age-related macular degeneration comparing with control, a significant increase in LDL-C concentrations (p=0.006), were noticed (28): high levels of LDL-C, a vasoconstrictor, proinflammatory and thrombogenic molecule, inhibits synthesis and release of endothelial nitric oxide synthase (eNOS), hence resulting in endothelial dysfunction (28).

All this goes 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 (29, 30).

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 anti-inflammatory 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, naturally) may be affected by several repeated and prolonged mechanical, physical, chemical, microbiological, immunologic, and genetic noxa/injuries (so-called risk factors [RFs], in author’s opinion), against which protracted responses may develop (i.e., host defense response). In order to eliminate, avert, clear disturbing noxa: most vascular risk factors activate molecular machinery in the endothelium to eliminate/avert/clear disturbing noxa. We can draw a parallel between host defense response and stress-responses [the acute stress-response, explicitly and the chronic stress-one, implicitly] (33). Increased intracellular reactive oxygen species (ROS) is crucial for vascular endothelial dysfunction, a key step in the initiating of vascular injury (34.) → 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 (31). 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 [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. The 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 \(O_2^-\) on NO. Thus, oxidative stress decreases NO bioavailability, promoting endothelial dysfunction, vasoconstriction, remodeling, and enhanced systemic vascular resistance (32) \(\rightarrow\) 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.

Role of inflammation/parainflammation, respectively in AMD

Inflammation/parainflammation and immune-mediated processes (complement activation) play an important role in age-related macular degeneration (AMD) pathogenesis. Inflammation is a two-edged sword. In acute situations, or at low levels, it deals with the abnormality and promotes healing. When chronically sustained at high levels, it can seriously damage viable host tissue (35/a). Chronic inflammation, a feature of AMD, is tightly linked to diseases associated with endothelial dysfunction: Chronic inflammation results in endothelial dysfunction and facilitates the interactions between modified lipoproteins, monocyte-derived macrophages, T-cells and normal cellular elements of the retinal arterial wall.

The endothelium is a common target for all vascular risk factors, and functional impairment of the vascular endothelium in response to injury occurs long before the development of overt AMD disease: the ophthalmic microvasculature is central to a destructive cycle of events where inflammation precedes drusen deposition and drusen in turn promotes release of inflammatory mediators.

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 (35). Although AMD is not a classic inflammatory disease, inflammatory cells have an important role in AMD pathogenesis and progression (36). 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 humoral constituents of systemic inflammatory and immune mediated processes (37). Macrophages and giant cells localizes near drusen, at the breakdown of Bruch’s membrane, and in the CNV membrane: macrophage-derived cytokines, such as tumor 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 (38): angiotensin II type receptor-mediated inflammation is required for choroidal neovascularisation (39). 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 (40).

Elevated levels of inflammation-related cytokines in the aqueous humor in various stages of AMD may suggest a crucial pathogenic role of inflammation (41). 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 (42).

**Parainflammation** is an adaptive response of the innate immune system that occurs in the context of stressors to which we were not exposed during our early evolution, including overfeeding, underactivity, aging, artificial lighting and novel foodstuffs and drugs. Parainflammation is a tissue adaptive response to noxious stress or malfunction and has characteristics that are intermediate between basal and inflammatory states. The physiological purpose of para-inflammation is to restore tissue functionality and homeostasis. Para-inflammation may become chronic or turn into inflammation if tissue stress or malfunction persists for a sustained period. Chronic para-inflammation contributes to the initiation and progression of many human diseases including obesity, type 2 diabetes, atherosclerosis, and age-related neurodegenerative diseases. Evidence from our studies and the studies of some others suggests that para-inflammation also exists in the aging retina in physiological conditions and might contribute to age-related retinal pathologies. In the aging retina, on the other hand, oxidized lipoproteins and free radicals are considered to be major causes of tissue stress and serve as local triggers for retinal para-inflammation. At the retinal/choroidal interface para-inflammation is manifested by complement activation in Bruch's membrane and RPE cells, and microglia accumulation in subretinal space. With age,
para-inflammatory changes have also been observed in the choroidal tissue. An increased knowledge of retinal para-inflammation is essential for the better understanding of the pathogenesis of age-related macular degeneration (42/a).

Although the aging represents the main determinant of AMD, it must be considered a multifaceted disease caused by interactions among environmental risk factors and genetic backgrounds. Mounting evidence and/or arguments document the crucial role of inflammation and immune-mediated processes in the pathogenesis of AMD. Proinflammatory effects secondary to chronic inflammation (e.g., alternative complement activation) and heterogeneous types of oxidative stress (e.g., impaired cholesterol homeostasis) can result in degenerative damages at the level of crucial macular structures, that is photoreceptors, retinal pigment epithelium, and Bruch’s membrane. In the most recent years, the association of AMD with genes, directly or indirectly, involved in immunoinflammatory pathways is increasingly becoming an essential core for AMD knowledge. The risks of degenerative diseases, at least partially related to the pathophysiologic inflammatory response, are especially relevant in those tissues functionally dependent on nonproliferative cells and characterized by very high metabolism and other oxidative stress, such as the macular retina. Inflammation is defined as a condition of tissue adaptive response to noxious stress or malfunction. Although the physiological purposes of normal inflammation are to preserve tissues homeostasis and to restore their functionality, when a tissue is exposed to stress and/or malfunction for a prolonged period, it is implicated in both initiation and progression of many human age-related disorders, such as AMD. Because of cell and tissue damage/malfunction, mainly due to accumulative oxidative and metabolic changes in NR-RPE-BM-CC complex induced by reactive oxygen species (ROS), the vision sensitivity progressively declines during the aging process. In accordance with the “free radical theory of aging,” age-related degeneration is basically caused by an imbalance between ROS-induced tissue damages and repair/remodelling processes: the concept seems to be extremely important for human AMD; in fact, AMD risk factors all augment ROS generation: particularly, the outer photoreceptor/RPE/MB complex, that is, the site of onset of the elementary AMD lesions (drusen), is considered more prone to oxidative stress because of both its proximity with the highly variable choroidal hemodynamics and its continuous exposition to photooxidation due to light stimuli.
In fact, unregulated blood flow may increase the fluctuations of tissue oxygen concentration, leading to elevated ROS generation by the mitochondria: photooxidation in photoreceptors is associated with complement activation increasing membrane attack complex formation, an important trigger of apoptotic processes inducing retinal degeneration, ROS augmentation can also trigger angiogenic severe complication of AMD, that is, choroidal neovascularization (CNV). In other words, several factors, linked to AMD etiopathogenesis, lead to increased ROS generation and can mediate apoptosis and angiogenesis, which are more implicated in the atrophic and neovascular AMD forms, respectively. The critical position of complement must be emphasized: dysregulation of complement pathways leads to damage which, at the macular level, is manifested by the development of drusen, and this earliest hallmarks of AMD may act as foci of chronic inflammation.

(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 (43). 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 (44).

(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 (45).

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) (46).
(3) Complement factor H polymorphism.
Insightful knowledge on the mechanisms of retinal inflammation, as well as of complement dysregulation, is fundamental to comprehensively understand the pathogenesis of AMD and to develop better curative therapeutic strategies for the different forms of this harmful disease. Complement system consists of over 40 proteins and regulators which are detectable in the blood circulation. It plays a key role in host defense against pathogens, adaptive immune responses, removal of the immune complexes and apoptotic cells.

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 (47). CFH polymorphisms have been linked to a pro-inflammatory state, including increased CRP and decreased complement inhibitory effect (48). 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 (49).
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 (50). 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.

Moreover there was an unquestionable association of systemic complement activation with atherosclerosis (51), (52), so that it can reasonably be presumed that the two conditions have a similar pathogenesis: 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.

(5) 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) (53). This establishment of recent origin implies essential messages
(a) 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.

(b) 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 neovascularization is, in turn (54).

(c) 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 (36). 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 (55, 56, 57). In AMD elevated CRP levels hinder, block the expression of endothelial nitric oxide synthetases (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).
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 (58). CRP is definitely not only the inflammatory marker but also a mediator of development of the vascular disorders in the retinal circulation (59), and this fact may help our understanding the pathogenesis of the retinal vascular disease associated with high levels of CRP).

(d) 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 (42). 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 (60): 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. [Estradiol |E2| can interfere with CRP pro-inflammatory effects via activation signals using its rapid, non-genomic pathway that may provide a new mechanism to improve vascular repair (61)].

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.

Role of theAMD risk factors (AMDRFs) in the genesis of AMD
If we thoroughly analyse the conditions which are considered as risk factors of AMD (Table I) - familial accumulation of AMD (62); elderly age/aging (63); one or more complement-related gene polymorphisms predisposing to the AMD-disease (63/a): smoking (64); obesity/abnormally increased body mass index (64); hypertension (64), higher systolic, diastolic and mean arterial BPs, respectively (65); pre-eclampsia (66); increased fibrinogen level (67), hypercholesterolemia (increased total cholesterol) and postprandial hyperlipemia (67), cholesterol-enriched diets (68), high fat intake in diet (69), consumption of lard and solid fats (solid vegetable oil) and fried foods using solid fat, respectively (independent of serum cholesterol level or BMI) (65); high LDL-C level (67) (increased concentration of HDL-cholesterol is considered to be cardioprotective, to be associated with a reduced risk of AMD [66]); decreased HDL-C (70) and; increase of triglycerides (TG) (70); increased concentration of apolipoprotein B (Apo B) and decreased Apo A (70); high ox-LDL-C level (71); increased apolipoprotein A1 (72); higher serum fibrinogen level (64); elevated CRP (73, 55); high IL-6 (55); high serum ICAM level (55); elevated vWF (8); high antiphospholipid antibody levels (74), alcohol abuse (75); diabetes mellitus (76, 77); postprandial hyperglycemia, high glycemic index (GI) (78), respectivelly; enhanced (systemic) advanced glycation endproducts (AGE) (accumulation of AG) (79); increased leptin (80) and decreased adiponectin levels (80); hypomagnesemy (81); low serum zink level (82); metabolic syndrome (83); inflammatory infectious disease (cytomegalovirus |CMV| (84), periapical infective inflammatory lesions (46) and immune diseases (85); systemic complement activation (63/a); increased systemic arterial stiffness/vessel wall rigidity (86); concomitant
cardiovascular disease (CVD) (56); lower extremity arterial disease; chronic renal disease (83, 86), pathological serum cystatin C level, respectively (87); obstructive emphysema (88), bronchial asthma (89); high serum uric acid level, gout (88); vitamin D deficiency (90, 91); hyperhomocysteinaemia (92) - 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 (93 94, 95, 96) 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 risk 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) (97), neovascular age-related macular degeneration (NV-AMD) population is associated with a significant cardiovascular risk (98); patients diagnosed with early AMD exhibit signs of systemic and retinal vascular alterations that correlated with known risk markers for future cardiovascular morbidity: the AMD patients showed significantly greater C-IMT and augmentation index (AIx), higher oxidized glutathione (GSSG), lower redox index, higher LDL-C (99, 100).

These facts provide evidence of links between cardiovascular risk factors and AMD, these findings could have therapeutic implications (99). The classical cardiovascular risk factors (CRFs) act directly on the endothelium through an increase in the production of reactive oxygen species, promoting an endothelial activation mediated by the expression of adhesion and proinflammatory molecules, which lead to endothelial dysfunction, the onset of (cardio)vascular disease, and the progression of the vascular injury/vasculopathy. Thus endothelial dysfunction itself is a consequential phenomenon, and it is a clinically-pathophysiologically important connecting link between harm (noxa) and vascular injury. As a part of the host defense response, any kind of noxa including the well-known and the not yet known risk factors endangering steadiness of homeostasis start/trigger off an defensive chain founded on increased ROS formation (permanently existing/repeating noxa→persistent/lasting 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 interact with leukocytes and platelets and target inflammation to specific tissues to eliminate/clear/avert (101, 102).

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: pulse wave velocity was significantly higher in the patients with AMD compared with controls (p=0.0025), indicating increased arterial stiffness) (86), 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 (103), namely, the same biochemical and immuno-related processes may be involved in both events (104). Patients diagnosed with early AMD exhibit signs of systemic and retinal vascular alterations that correlated with known risk markers for future cardiovascular morbidity (100).

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 consequential ED.

**The role of OS on AMD**

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.

Cells in aerobic condition are constantly exposed to reactive oxygen species (ROS), which may induce damage to biomolecules, including proteins, nucleic acids and lipids. In normal circumstances, the amount of ROS is counterbalanced by cellular antioxidant defence, with its main components— antioxidant enzymes, DNA repair and small molecular weight antioxidants. An imbalance between the production and neutralization of ROS by antioxidant defence is associated with oxidative stress, which plays an important role in the pathogenesis
of many age-related and degenerative diseases, including age-related macular degeneration (AMD), affecting the macula—the central part of the retina. The retina is especially prone to oxidative stress. Proper functioning of antioxidant defense may be crucial for the occurrence and progression of this disease (105).

Due to its high content of polyunsaturated fats and its extensive oxygen consumption, the retina is particularly susceptible to oxidative stress (OS).

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 coexist 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 (106).

In general, ROS are essential to the normal-undisurbed 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 (95).

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. 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 (107, 108).

Oxidative stress plays a causative role in both the initiation and progression of CNV: the use of antioxidant supplementation to counter cellular oxidative stress results in the suppression of experimental CNV, and generation of ROS is responsible for early stages of nephropathy, treatments that reduce the formation of ROS is successful in preventing retinopathy (109).

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) (42): 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-undisurbed 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 increasing of LDL-C in OS, in wet type age-related macular degeneration comparing with control, significant reduction in the duration of lag phase (p<0.004) and a significant increase in LDL-C concentrations (p=0.006), were noticed, a significant negative correlation
between Lag phase and LDL-C levels (p=0.004, r=-0.364) was found in the patient group.

The increased LDL concentration and enhanced susceptibility of LDL to oxidation may play a roll in the wet type AMD process (110).

**Role of aging as the major AMD risk factor in AMD**

Aging deteriorates vascular integrity, characterized by endothelial dysfunction and increasing vascular stiffness. The latter jointly precede and entail incident systolic blood pressure (SBP), with an increase in cardiovascular morbidity and mortality. 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 (111). 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 (112, 113) 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 (114). 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 (115).

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 (116). Primary abnormalities in ocular perfusion worsen with age (decreases in choroidal circulatory parameters may be involved in the development of AMD (116)), 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) (117): 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 (118).

Ocular vascular diseases such as age-related macular degeneration, whose population increases along with aging, have become leading causes of severe visual disturbance. Such ocular vascular diseases are caused by vascular cell aging and vascular damage associated with lifestyle-related diseases including diabetes mellitus, hypertension, hyperlipidemia, and obesity. 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: inhibition of such stress kinases could be an effective treatment to protect the vascular cells against age-related damage (119). Despite the fact that AMD is essentially a choroidal disease, retinal vessels show a functional abnormality, which may suggest that the vascular abnormality in this disease is more generalized (120).-

Recently, many (of the common so-called degenerative) diseases of older people also have been reported to have significant macrovascular and/ or microvascular component (for instance Alzheimer’s 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 (121, 122).

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 (123).

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 (124), 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 (125).

(b) In endothelial dysfunction of the coronaries – also without an occlusive CAD – there is a significantly increased chance of developing cerebrovascular events (126).

c) In patients with type 2 diabetes mellitus age-related macular degeneration has proven to be an independent risk factor of cardiovascular mortality (127).

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 (128).

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.

Early and late AMD are independent predictors of future CVD, and the association is much stronger for late AMD (128/a).

(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 (129).

The relevant study is have provided evidence for a strong association between cardiovascular disease and neovascular AMD:cardiovascular disease is associated with the development of Choriodal neovascularization and they have similar pathogenic pathways. The improvements in survival experienced in recent years through advances in clinical management of
cardiovascular disease may contribute to an increase in the prevalence of AMD as more people live to experience the result of atherosclerotic changes in the choroidal circulation. (129/a).

(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 (130).

(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 (131).

(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 traditional cardiovascular risk factors (132). This finding suggests that retinal arteriolar 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 these data are supported by the studies showing a relationship between coronary flow reserve and microvascular structure in subcutaneous fat tissuevascular structure in subcutaneous small arteries predicts cardiovascular events (133).

(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-eclampsia 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.(66).

(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.(134).

(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 (135).

(n) Diabetes-related changes in the structures and functions of the RPE, Bruch’s membrane and the choroid layer result in an increased risk of developing AMD (136).

**General, systemic nature of endothelial dysfunction, the consubstantiality of vascular system**

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, m and n, 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 importance 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 authentic NO. These nitroso compounds (RXNOs) are transported and delivered along the complete vascular tree to dilate distal arteries and the microvasculature: ED in patients with CV RFs is associated with decreased levels of circulating RXNOs. Plasma RXNOs (plasma nitroso compounds referred to as the circulating NO pool) may be a surrogate index of ED (137).

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.

Legend of Table 1

Between risk factors of AMD (AMDRFs) and cardiovascular risk factors (CVRFs) are considerable overlap: AMDRFs often are identical with CVRFs. (Table 1),

<table>
<thead>
<tr>
<th>Cardiovascular RFs</th>
<th>AMD RFs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>“Classical” risk factors:</strong></td>
<td></td>
</tr>
<tr>
<td>– smoking</td>
<td>+</td>
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<tr>
<td>– hypertension,</td>
<td>+</td>
</tr>
<tr>
<td>– higher systolic, diastolic and mean arterial BPs, resp.</td>
<td>+</td>
</tr>
<tr>
<td>– increased LDL-C</td>
<td>+</td>
</tr>
<tr>
<td>– decreased HDL-C</td>
<td>+</td>
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<tr>
<td>– aging</td>
<td>+</td>
</tr>
<tr>
<td>– diabetes mellitus</td>
<td>+</td>
</tr>
<tr>
<td>– one or more complement-related gene polymorphisms predisposing to the AMD-disease</td>
<td>+(familial accumulation of AMD)</td>
</tr>
<tr>
<td>– early AS in the family</td>
<td></td>
</tr>
<tr>
<td>– overweight</td>
<td>+</td>
</tr>
<tr>
<td>– physical inactivity</td>
<td>+</td>
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<tr>
<td>– atherogenic nutrition</td>
<td></td>
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<tr>
<td>– cholesterol-enriched diet</td>
<td>+</td>
</tr>
<tr>
<td>– high fat intake in diet</td>
<td>+</td>
</tr>
<tr>
<td>– concomitant cardiovascular disease (CVD)</td>
<td>+</td>
</tr>
<tr>
<td>– lower extremity arterial disease</td>
<td>+</td>
</tr>
<tr>
<td><strong>“More recent” risk factors:</strong></td>
<td></td>
</tr>
</tbody>
</table>
- high fibrinogen level  +
- high ox-LDL-C level  +
- high LDL level  +
- low HDL 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  +
- cardio-ankle vascular index (CAVI) elevation (Taniguchi 2013)  +
- 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  +

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

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