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Review

Is the age-related macular degeneration (AMD) vascular disease, part of vasculopathy, respectively? Novel considerations on AMD arising from the newest pathophysiological, clinical and clinical-pharmacological observations (Preliminary Communication)

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In the genesis and later development of age-related macular degeneration (AMD), endothelial dysfunction (ED) has a crucial role. AMD-risk factors, which play a decisive role in AMD, are in a close connection, correlate with, and often are identical wih the risk factors (RFs) of cardiovascular diseases (CVDs), so that it can reasonably be presumed that the two conditions have a similar pathogenesis. These risk factors, which seem essentially different, lead to chronic vascular injury based on the same mechanism of action: by inducing oxidative stress (OS). ED itself is a consequential-consecutive phenomenon (OS→ED!), and is a clinico-pathophysiologically important connecting link between harm(s)/noxa and vascular injury (harm [noxa] → oxidative stress (OS) → endothelial activation (EA), endothelial 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. Changes in blood vessels including those in choroids may be triggered by several repeated and/or prolonged mechanical, physical, chemical, microbiological, immunologic, and genetic influences/impacts/noxa (in fact, the risk factors!), against which protracted response[1]) (increased ROS formation → oxidative stress → endothelial activation/dysfunction → aftermath of EA/ED) may develop, and in consequence of this, (chronic) vascular damage (functional and then structural alteration [remodelling] of the blood vessel), pathological consecutive changes ending in AMD, ultimately, may develop (choriocapillaris degenerates in exudative AMD, choriocapillaris degeneration precedes retinal pigment epithelial atrophy in wet AMD). All this goes to show that AMD may be a local manifestation of systemic (vascular) disease, undoubtedly. 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 as can be understood from the fact that aging individuals often demonstrate dysfunctional blood vessel repair after vascular injury and 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 (primary abnormalities in ocular perfusion worsen with age, 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**

1 **) The so-called host defense response: any kind of noxa endangering steadiness of homeostasis → increased ROS formation → oxidative stress → endothelial activation, endothelial dsfunction, respectively, in order to eliminate, avert, clear disturbing noxa

of AMD. Regarding therapy/preventive treatment/prevention of AMD: (I) Non-medicinal (preventive) treatment such as lifestyle modifications of AMD patients (modifying lifestyles behavours of diet, smoking and physical activity) is of indispensable importance; they influence strongly and very beneficially the established vascular risk factors and also advantageously affect novel pathways of risk such as inflammation/oxidative stress, endothelial function, thrombosis/coagulation. Modest alterations of these lifestyle risk factors are achievable and have substantial effects on (vascular) risk. (II) Various medicaments: (1) ACE inhibitors, (2) AR blockers [including telmisartan with its peroxisome proliferator-activated receptor-gamma |PPARgamma| agonist effect], (3) statins, (4) acetylsalicylic acid, (5) trimetazidine, (6) third generation beta blockers, and (7) PPARgamma agonists, exert a beneficial effect on endothelial dysfunction and its consequential functional, structural and metabolic disorders. The advantageous/beneficial effect of a favourable influence on the successful treatment of ED in patients with chronic vascular and cardiovascular diseases has become evidence now, as the human vascular system is uniform, consubstantial thus medicines beneficial in ED may exert a favourable effect also on the vessels of the eye, in the retina/choroid (per analogiam of cardiovascular disease). The antioxidant vitamins (AOVs) used for preventing OS, conventionally, 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: the inhibition of the reaction pathway peroxynitrite → DNA damage → PARP by rapid catalytic breakdown of peroxynitrite with the help of the so-called "causal" antioxidants with mitochondrial effects (FP15 metalloporphyrin compound), showing great promise, or by the inhibition of PARP with INO-100 may open a new possibility in the treatment of OS induced vascular dysfunction in several pathologic conditions including AMD.- Nevertheless, we have excellent therapeutic possibilities/options also, until then: the statins, the ACEIs, ARBs, ASA, the trimetazidin, third generation beta-blockers, PPARgamma agonists. As the human vascular system is uniform and consubstantial, thus medicines and non-medicinal methods/treatments beneficial in ED may exert a favourable effect also on the vessels of the eye, in the choroid/retina. Consequently, based on the aforementioned, it seems logical to presume that, as a part of our primary and secondary preventive activity, that such medicines should be given to: (1) patients who have no macular degeneration, but have risk factors of AMD (and of cardiovascular (CV) disease, respectively) inducing ED, and are older than 50 years; (2) patients who have been diagnosed with unilateral AMD, in order to prevent the damage of the contralateral eye due to macular degeneration; (3) 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 (III) completely eliminate/treat the risk factors of macular degeneration (and ones of the CV disease) which induce OS and consequential ED, in addition.

Key words: Age-related macular degeneration, endothelial dysfunction, oxidative stress, risk factors, primary and secondary prevention.

INTRODUCTION

The importance of age-related macular degeneration (AMD) and 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 be compared with that of Alzheimer's disease plus multiple sclerosis. 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.

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NOVEL CONSIDERATIONS ABOUT THE ETIOPATHOGENESIS AND PATHOPHYSIOLOGY OF AMD

In the genesis and later development of age-related macular degeneration (AMD), endothelial dysfunction (ED) has a crucial role (Fischer, 2004; Lip et al., 2001; Fischer, 2009). Vascular endothelium regulates retinal arteriolar tone, circulation in the ophthalmic and ciliary arteries, that is, the eye including ophthalmic micro-circulation. The disordered function of endothelium, in the

vessels supplying the affected ocular structures with blood, endothelial dysfunction (ED), plays key role in the genesis and development of AMD. 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, it is almost impossible (or at least it seems to be forced, artificial) for the vascular events to be discussed and clinically separated as sharply discerned entities (Fischer, 2009).

AMD-risk factors (AMDRFs), which play a decisive role in AMD, are in a close connection, correlate with, and often are identical wih the risk factors of cardiovascular (CVDRFs) diseases (Table 1) (Jonas et al., 2010; Fischer, 2009; Machalinska et al., 2011; Katherin et al., 2002; Evereklioglu et al., 2003; Christe et al., 2009; Millen et al., 2011; Seddon et al., 2004; Desoriet et al., 2006; Machalinska et al., 2009; Lip and Blann, 1997; Chakravarthy et al., 2010; Poston, 2006; Yu et al., 2009; Seddon et al., 2008; Chong et al., 2008; Choi et al., 2011; Mulder et al., 2010; Kaushic et al., 2008; Raoul et al., 2010; Kijlstra et al., 2005; Liew et al., 2008; Klein et al., 2004; Csiszar et al., 2008; Vingerling et al., 1995; Duan et al., 2006; Williams, 2009; Mozaffarian et al., 2008; Mares et al., 2011), so that it can reasonaly be presumed that the two conditions have a similar pathogenesis. Some examples of this: (a) In 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 as well as the incidence of vascular diseases including coronary artery disease and peripheral arterial disease and stroke is increased. (b) In endothelial dysfunction of the coronaries there is a significantly increased chance of developing cerebrovascular events. (c) In patients with type 2 diabetes mellitus, age-related macular degeneration has proven to be an independent risk factor of cardiovascular mortality. (d) Plaques in the carotid bifurcation were associated with a 4.7 times increased prevalence odds of macular degeneration; those with plaques in the common carotid artery showed an increased prevalence odds of 2.5; lower extremity arterial disease was associated with a 2.5 times increased prevalence odds of AMD, respectively. (e) Age-related macular degeneration (AMD) developed in 22% of patients with coronary artery disease (CAD) who require coronary intervention or underwent it. (f) The presence of AMD also signals an increased risk of CVD, independent of the effect of age and shared risk factors, and persons with early AMD had double the risk of incident stroke over 10 years, where those with late AMD had triple the risk of incident coronary heart disease (CHD). (g) Presence of AMD, especially neovascular AMD, is prospectively associated with a higher risk of incident myocardial infarction (MI). (h) Disorders of the retinal microvascular system are good predictors of severe cardiovascular and cerebral events. Narrower retinal arterioles is a marker of systemic microvascular damage, it may serve as a marker of coronary microvascular disease. (i) The significantly lower FMD in patients with glaucomatocyclitic crisis (GCC) implies (peripheral) vascular endothelial dysfunction: the impairment of endothelial function of the brachial artery in patients with GCC observed indicated a systemic rather than a local vascular effect (Fischer, 2009a; 2009b).

All this goes to show, in the author's opinion that AMD may be local manifestation of systemic disease, undoubtedly.

The aforementioned risk factors, which seem essentially different leading to chronic vascular injury are based, after all, on the same mechanism of action: by inducing oxidative stress (OS). ED itself is a consequential-consecutive phenomenon (OS→ED!), and it is a clinically/pathophysiologically important connecting link between harm (noxa) and vascular injury.

AMD is the disease of the aging body (Fischer, 2009; Jonas et al., 2010), and the normal aging processes can lead to structural and blood flow changes that can predispose patients to AMD. Advancing age is a privotal and independent RF 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 (neo)angiogenesis. 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 (primary abnormalities in ocular perfusion worsen with age) secondarily causing dysfunction of the retinal pigment epithelial cells, predisposing eyes to AMD (choriocapillaris degenerates in exudative AMD, and the choriocapillaris degeneration may precede retinal pigment epithelial atrophy in wet AMD!); these changes together with individual's (environmental) risk factors set the stage for the subsequent development of AMD.

ED has a key role in the genesis and development of age-related macular degeneration: changes in blood vessels of the human organism including those in the choroids may be triggered by several repeated and prolonged mechanical, physical, chemical, microbiological, immunologic, and genetic influences-impacts (Spaide and Amstrong, 2003), against which protracted responses [increased ROS formation → oxidative stress → endothlial dysfuunction → its consequential pathological-clinical disorders (Fischer, 2011) may develop, and in consequence of this, chronic vascular damage (functional and then structural alterations of the vessel [remodlling]), pathological consecutive changes ending in AMD, ultimately, may develop. All this goes to show, in author's opinion, that AMD may be local manifestation of systemic disease, undoubtedly.

Table 1. Cardiovascular and AMD risk factors (RFs).

Cardiovascular RFs	AMD RFs
"Classical" risk factors:	
Smoking	
Hypertension	+
Increased LDL-C	+
Decreased HDL-C	
Aging	+
Diabetes mellitus	+
Early AS in the family	+ (familial accumulation of AMD)
Overweight	+
Physical inactivity	
Atherogenic nutrition	
Concomitant cardiovascular disease (CVD)	+
Lower extremity arterial disease	+
"More recent" risk factors:	
High fibrinogen level	+
High ox-LDL-C level	+
Elevated serum Lp(a)	
High serum ICAM level	+
Elevated serum homocysteine	+
pp hyperglycaemia	+ (high GI: early AMD!)
pp hypertriglyceridaemia	
Diabetic dysmetabolism	
Metabolic syndrome	+
Insulin resistance	
Left ventricular hypertrophy	
Chronic renal disease	+
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	+
Oestrogen deficiency	
Alcohol abuse	+

Modified, after Fischer, 2009

THERAPEUTIC STRATEGIES FOUNDED ON THE PATHOPHYSIOLOGICAL/PHARMACOLOGICAL EVIDENCES

The beneficial effect of a favourable influence on ED in its successful medicinal therapy is an established fact in CVD, and the treatment of ED is an inherent part of the therapy of "underlying disease". As the human vascular system is an uniform entity, all – central and peripheral – parts of it are consubstantial physiologically and pathophysiologically as well as with regard to their ability to react, to avert) (that is, 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.

MEDICINAL PREVENTIVE TREATMENT OF AMD

Various medicines, such as ACE inhibitors , AR blockers [including telmisartan with its peroxisome proliferator-activated receptor-gamma (PPARgamma) agonist effect], AR blockers, statins, acetylsalicylic acid, trimetazidine, third generation beta blockers, and PPARgamma agonists, may exert a beneficial effect on endothelial dysfunction or its consequential functional, structural and metabolic disorders (Lonn et al., 2003; Task Force of ACE-Is of European Society of Cardiology, 2004; Heagerty, 2004; Kwang et al., 2003; López-Sendón et al. 2004; Task Force on ACE-inhibitors of the European Society of Cardiology, Pershadsingh and Moore, 2008; Muenzel and Gori, 2009; Almutti et al., 2006; Liao and Laufs, 2005; Wilson et al., 2004; Wu et al., 2002; Coyas, 1990; Wilkinson-Berka et al., 2010; Vitalem et al., 2004). The beneficial effect of a favourable influence on and successful treatment of ED in patients with chronic vascular and cardiovascular diseases has become evidence now, thus medicines beneficial in ED may, as the human vascular system is consubstantial (Fischer, 2008; Wilkinson-Berka et al., 2010; Mares et al., 2011; Ian and Simon, 2011), induce a favourable effect also on the vessels of the eye, in the choroid/retina.

In ED induced by oxidative stress (OS) ACE inhibitors, AR blockers and statins regenerate the lost balance between vasoconstrictors and vasodilators, growth factors and their inhibitors, proinflammatory and anti-inflammatory factors, as well as pro-thrombotic and fibrinolytic factors: (1) RAAS-inhibiting angiotensin converting enzyme ihibitors (ACE-inhibitors – ACEIs) and/or (2) angiotensin II receptor blockers (AR-blockers - ARBs) improve endothelial function; they substantially reduce ED, they act against the oxidative stress (OS), inhibit the development of OS and the evolution of its harmful effects; they significantly relieve inflammation, and inhibit thrombogenesis. ACE inhibition also improves the life and death cycle of the endothelium; in addition, the T1-receptor blocker telmisartan with its peroxisome proliferator-activated receptor-gamma (PPARgamma) agonist effect, also inhibits the development of choroidal neovascularisation (CNV), improves it, and exert the protective vascular effects exactly by means of their mitochondrial antioxidant effects. (3) Hydroxy-methylglutaryl-coenzyme (HMGCoA) reductase inhibitor statins improve endothelial function (EF) and substantially reduce ED, promote the process of restoring endothelial injuries and actively participate in it, they inhibit thrombus formation, they significantly mitigate OS and inflammation, statins reduces endothelial cell apoptosis, also. (4) Aspirin, besides its antiplatelet activity, effectively contributes to the restoration of the balance of endothelium, exerts potent antioxidant (that is, anti-ED) properties. (5) Trimetazidine helps in normalising, restoring the pathological metabolic status of organ tissues with impaired function: partially inhibits the fatty acid oxidation and substantial mitigates/reduces the damage due to free radicals. (6) The peroxisome proliferator-activated receptor gamma (PPARgamma) agonist pioglitazone and rosiglitazone as well as the (Katherin et al., 2002) third generation beta blocker carvedilol, nebivolol exert their protective vascular effects by means of their mitochondrial antioxidant effects. (7) We can reasonably presume that the inhibition of renin (Wilkinson-Berka et al., 2010) 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. 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 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, that is, the inhibition of RAAS becomes more completed.

NON-MEDICINAL PREVENTIVE THRAPY OF AMD

Lifestyle modifications of AMD patients (modifying lifestyles behavours of diet, smoking and physical activity) is of indispensable importance (Mares et al., 2011; Ian and Simon, 2011): lifestyle risk factors modifications including bad dietary habits, physical inactivity, smoking, and adiposity, strongly and very beneficially influence the established vascular risk factors and also advantageously affect novel pathways of risk such as inflammation/oxidative stress, endothelial function, thrombosis/coagulation; modest alterations of these

lifestyle risk factors are achievable and have substantial beneficial effects on vascular risk. Our health also depends on our lifestyle choice; it is very important to identify modifiable risk factors (lifestyle risk factors) that may reduce disease occurrence or prevent progression to advanced stages. Modifying lifestyles behavours of diet, smoking and physical activity 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. Diet 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). The PPAR-dependent effect of 3-PUFAs on NV formation is large and comparable to anti-VEGF treatment (!); dietary supplementation with omega-3 fish oils also improves endothelial function and reduces oxidative stress and may therefore confer vascular, choroid-vascular benefits (Mares et al., 2011; Ian and Simon, 2011; Augood et al., 2008).

CONCLUSION

As the human vascular system is uniform and consubstantial, the aforementioned medicines 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, (I) such medicines 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, (II) lifestyle modifications of AMD patients (modifying lifestyles behavours of diet, smoking and physical activity) is of indispensable importance. We should strive to completely (III) eliminate the risk factors of macular degeneration (and ones of the CV disease) which induce OS and consequential ED, in addition.

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I offer this work to my parents of blessed memory whose death occured in the time of the Holocaust.

Abbreviations: ACE I, Angiotensin converting enzyme inhibiton; **ADMA,** asymmetrical dimethyl arginine; **AGE,** advanced glycation end-products; **AMD,** age-related macular degeneration; **Ang-II,** angiotensin II; **AO,** antioxidant; **AOVs,** antioxidant vitamins; **ARB,** angiotensin II receptor blocker; **ASA,** acetylsalicylic acid; **AS,** atherosclerosis; **ATP,** adenosine triphosphate; **AT1R,** AT1 receptor of angiotensin II; **CAD,** coronary artery disease; **CD40,** cluster of differentiation 40; **CFH,** complement factor H; **CI,** confidence interval; **CNV,** choroidal neovascularisation; **COX-2,** cyclooxygenase-2; **CR,** caloric restriction; **CRP,** C-reactive protein; **CV,** cardiovascular; **CVD,** cardiovascular disease; **EA,** endothelial activation; **ED,** endothelial dysfunction; **EF,** endothelial function; **EPCs,** endothelial progenitor cells; **ET-1,** endothelin 1; **eNOS,** endothelial nitric oxide synthetase; **FMD,** flow-mediated dilatation; **GI,** glycaemic index; **HDL-C,** high density lipoprotein cholesterol; **HMGCoA,** hydroxy-methylglutaryl-coenzyme A; **hsCRP,** high sensitivity C-reactive protein; **ICAM,** intracellular adhesion molecule; **IgSF,** immunglobulin superfamily; **IL-6,** interleukin 6; **LDL-C,** low density lipoprotein cholesterol; **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; **ox,** oxidized; **PAI-1,** plasminogen activator inhibitor 1; **PARP,** poly (ADP-ribose) polymerase; **pp,** postprandial; **PPAR,** peroxisome proliferator-activated receptor; **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; **SIRT1,** silent information regulator 1; **SOD,** superoxide dismutase; **TF,** tissue factor; **TM,** thrombomodulin; **TNF-a,** tumor necrosis factor-alpha; **tPA,** tissue plasminogen activator; **Th-1,** proinflammatory T-helper; **Th-2,** anti-inflammatory T-helper; **TXA2,** thromboxane-A2; **VCAM-1,** vascular cell adhesion molecule 1; **VEGF,** vascular endothelial growth factor; **vWF,** von Willebrand factor; **+,** overlap between CV and AMD risk factors.

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