REVIEWS

Adv Clin Exp Med 2015, **24**, 6, 1099–1104
DOI: 10.17219/acem/27093

ISSN 1899–5276

Hanna M. Zając-Pytrus[1, A–D], Agnieszka Pilecka[2, A–C], Anna Turno-Kręcicka[1, E], Joanna Adamiec-Mroczek[1, E], Marta Misiuk-Hojło[1, F]

The Dry Form of Age-Related Macular Degeneration (AMD): The Current Concepts of Pathogenesis and Prospects for Treatment

[1] Department of Ophthalmology, Wroclaw Medical University, Poland
[2] The Higher School of Humanities, Leszno, Poland

A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article

Abstract

Age-related macular degeneration (AMD) is a disease that causes varying degrees of blindness, which afflicts millions of adults in their later years. Preliminary changes occur during normal aging, but in some individuals the pathology leads to the development of AMD. The pathology seems to be a mixture of biochemical, cellular, and molecular events. Lipofuscinogenesis and early drusen genesis are in the early stages of AMD and their inhibition or reversal would dramatically increase the quality of vision in elderly people. The disease is characterized by abnormal extracellular deposits, known as drusen, which accumulate along the basal surface of the retinal pigmented epithelium RPE. Widespread drusen deposition is associated with retinal pigmented epithelial cell dysfunction and degeneration of the photoreceptors. Recent studies have shown that drusen contain a variety of immunomodulatory molecules, suggesting that the process of drusen formation involves local inflammatory events, including activation of the complement cascade. Molecular pathways involved in the etiology of this disease and the potential prospects of its treatment will be presented on the basis of the results of the current studies (**Adv Clin Exp Med 2015, 24, 6, 1099–1104**).

Key words: dry AMD pathogenesis, dry AMD treatment, dry AMD prophylaxis.

The Current Concepts of Pathogenesis

AMD is the main cause of vision loss in developed countries. Typical symptoms in the late stages of the disease include decreased night vision and progressive loss of central vision. Due to prolonged life expectancy in modern societies AMD constitutes a severe medical and socio-economic problem. There are two AMD forms: dry (in 90% of patients) and wet (in 10% of patients).

In the wet form the cause of potential central vision drop is a subchoroidal neovascularization. An inflammatory reaction initiates a pathological angiogenesis. Pathological neovascularization penetrates through the defects in the Bruch membrane and the RPE layer to the subretinal space, where exudation and bleeding destroy photoreceptors. Commonly used anti-VEGF factors given in repeated intravitreal injections inhibit neovascularization and can stabilize vision acuity in some patients.

In the dry form of AMD the slow apoptosis of RPE, neuroretina and choriocapillaris develops and causes permanent central vision loss. At present, there is no effective treatment of the latter form. The etiology of the disease is also unknown.

The development of the disease is connected with the coexistence of a combination of environmental and genetic factors as well as numerous metabolic and functional anomalies typical of the anatomic-functional complex involving photoreceptors, RPE-cells, Bruch membrane and choriocapilaries.

Smoking is associated with a twofold increased risk of developing AMD [1, 2].

The Bruch's membrane exhibits increased deposition of cholesterol and calcium with age. In the course of the disease the alternative complement path is activated (which might be due to genetic factors) by lipofuscin constituents as a response to the inflammatory process connected with drusen genesis [3].

Lipofuscin collects in RPE cells in the form of insoluble deposits called old age spots.

Lipofuscin is made up of membrane phospholipids, membrane proteins, visual cycle proteins, lipid-protein complexes and retinoids resulting from incomplete enzymatic degradation in phagolizosoms. Phospholipids of plasmatic membranes contain a lot of docosahexaenoic acid DHA, multisaturated Omega-3 type lipid acid. When eyes are exposed to sunlight, in an environment rich in oxygen, DHA combines with phosphatydyloetanoloamine PE (DHA-PA) and phosphatydylocholine PC (DHA-PC) and by peroxidation splits into 7 carbonic fragments called HOHA, which when combined with protein make up carboxyethylpyrrole-protein adducts (CEPs). The role of CEP in the inflammatory process connected with AMD has been confirmed. It is also suggested that CEP may initiate neovascularization in the wet form of the disease [4, 5].

Malondialdehyde (MDA) is another molecule which plays a role in AMD progression. Complement factor H binds MDA and can block MDA-induced proinflammatory effects [6].

Due to the impaired autophagy (an essential lysosomal pathway that degrades cytoplasmic proteins and damaged organelles) the stressed RPE releases exosomes that are coated with complement and can bind CFH. This may be a mechanism for sub-RPE deposit formation [7–9].

Drusen genesis is a sign of AMD progression. Drusen are amorphic extracellular deposits in the space between RPE and Bruch membrane. Drusen may be of various sizes (30–50 μm or larger when confluent) and of various compositions. Their occurrence signals the degree of advancement of the disease. The chemical analysis of drusen has indicated traces of RPE cells.

Other materials can be trapped in the drusen as they pass through them in transit between the RPE and choriocapllaris.

Drusen consists of 2 completely different focal types: The first consists of a focal thickening of the RPE basement membrane and the drusen are nodular meaning 'hard' or 'discrete. In fluorescein angiography FA, they cause early hyperfluorescence and late staining. It is unclear if they represent a high risk factor for the development of dry AMD. Histologically nodular drusen have an eosinophilic, PAS-positive appearance and are located externally or contiguously or replace the thin basement membrane of the RPE. Nodular drusen may become calcified, lipidized, cholesterolized or rarely vascularized (Fig. 1 – reprinted from Ocular Pathology, Elsevier, 2009). The second is a limited separation of the normal basement membrane of the RPE from its attachment to Bruch's membrane at the inner collagenous zone by a wide variety of materials, whose consistency differs from bone to fluid. In FA they show staining; sometimes they are hypofluorescent due to lipid accumulation (Fig. 2– reprinted from Ocular Pathology, Elsevier, 2009).

In the dry form of AMD, geographic atrophy (GA) develops after the progression of the disease going from a stage of large, confluent drusen to hyperpigmentation and finally drusen regression. In 25% of cases highly refractile deposits precede GA.

In the course of the disease the neural retina can show microcystoid or macrocystoid (retinoschisis) degeneration. Eventually, hole formation may occur in the inner wall of the macrocyst. A total hole rarely develops with rounded, smooth edges.

Sometimes large, coalescent drusen form pigment epithelial detachments (PEDs). It can be stable over time with an associated slight decrease of visual acuity or progress quicker in volume and area before CNV develops.

Deposits located above the RPE are called reticular pseudodrusen or drusenoid subretinal deposits.

They do not fluoresce with fluorescein or indocyanine green in angiography.

Pseudodrusen can also precede GA as a result of the derangement of the retinal pigment epithelium by the underlying atrophy and fibrosis of the choroid.

In AREDS1 Study GA development led to visual acuity (VA) loss from 3.7 letters at first GA documentation and to 22 letters after 5 years.

Gene Testing Rationale in AMD

AMD is a complex genetic disorder. Gene CFH localized in chromosome 1 in a human being, which encodes Factor H participates in the complement system regulation. The mutation changing tyrosine into histydine in locus 402 of the gene coding this factor (Y 402H) causes chronic inflammatory reaction due to hyperactivity of the alternative complement pathway. Mutations of CFB, C2, and C3 also contribute to this hyperactivity

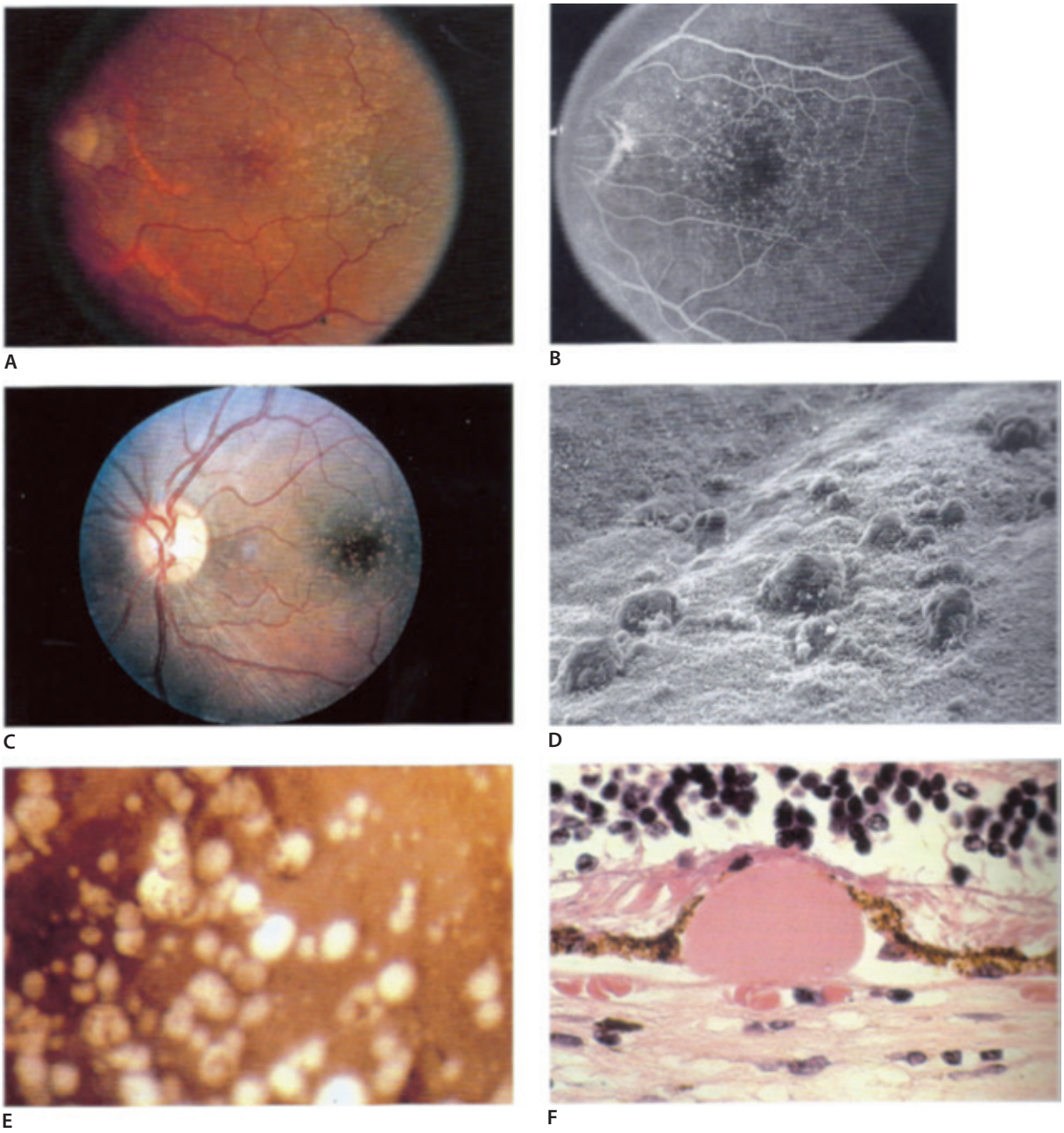


Fig. 1. Nodular ("hard") drusen. Clinical (A) and fluorescein (B) appearance of nodular drusen, which have a random distribution scattered in the posterior pole. C) Basal laminar drusen appear in clusters in the posterior pole. Scanning electron microscopic (D) and gross (E) appearance of nodular drusen. F) Histologic section shows an eosinophilic nodular druse external and contiguous to the original thin basement membrane of the retinal pigment epithelium (RPE; i.e., between RPE basement membrane and Bruch's membrane) (D and E, Courtesy of Dr. RC Eagle, Jr.)

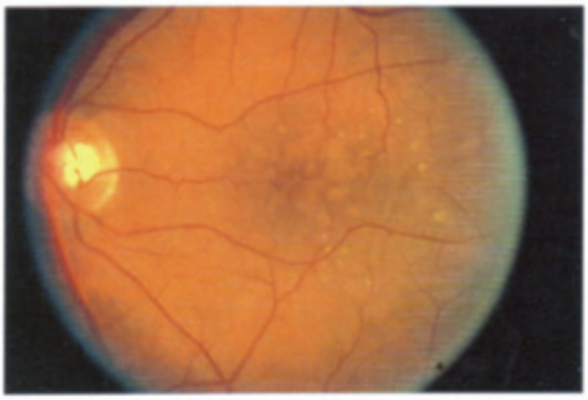
or to membrane attack complexes. Genes ARMS2, HTRA1 and PLEKHA1 are localized in chromosome 10q26. This location is directly connected with the disease. The above genes code proteins whose expression takes place in the RPE cells. The presence of these proteins in drusen is also suggested.

Other genes could intervene in the high-density lipoprotein (HDL) cholesterol pathway (LIPC, A ABCA1 and CETP); in the extracellular matrix pathway (TIMP3, COL10A1 and COL8A1) and angiogenesis pathway (VEGFA).

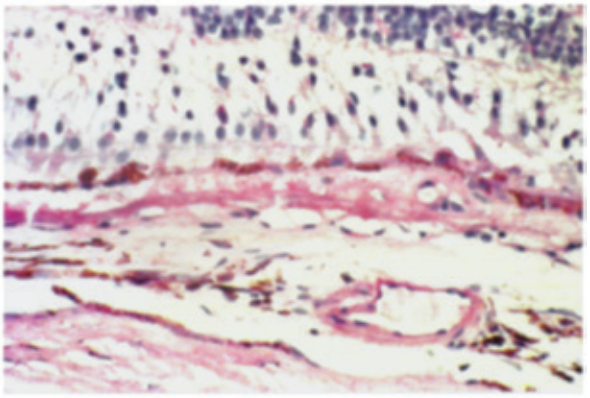
Genetic studies should be an integral part of clinical studies of AMD, but due to the lack of specific efficacious preventive treatments, routine genotyping of AMD patients is not needed yet [10].

The combination of metabolic data, e.g. carboxymethyllysine (CML), pentosidine and carboxyethylpyrrole (CEP) and genotype data may help to improve the identification of clinically-relevant biomarkers for AMD.

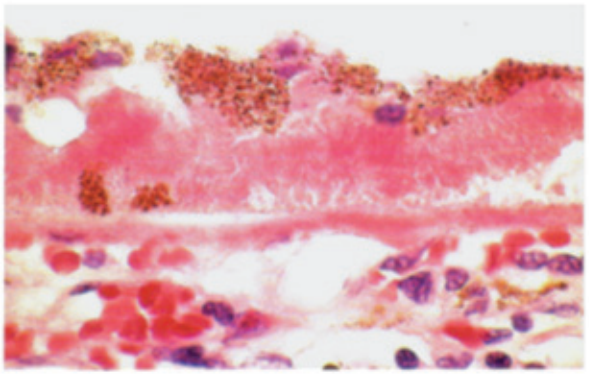
The correlations between genotype and its response to anti-VEGF treatment are inconsistent on the base of present scientific studies results.



A



B



C

Fig. 2. Large ("soft") drusen. A) Clinical appearance of large drusen scattered in the posterior pole. B) An amorphous material is present between retinal pigment epithelium and Bruch's membrane. Note presence of tiny blood vessels in material. C) Brushlike appearance helps identify the basal laminar deposit (C, Courtesy of Dr. RC Eagle, Jr.)

The Prospects for Treatments of AMD

At present, management of AMD involves mainly prophylactic supplementation and potential inhibition of the disease progression.

The Age Related Eye Disease Study (AREDS), a multicenter, randomized, controlled clinical trial showed that oral supplementation of a combination of vitamin C (500 mg), vitamin E (400 UI), beta-carotene (15 mg), zinc oxide (80 mg) and cupric oxide (2 mg) in patients with intermediate or advanced AMD in one eye had a 25% less chance of developing advanced AMD in the other eye over the next 5 years [11].

Long chain omega-3 fatty acids supplementation may also help to prevent oxidative, inflammatory AMD retinal damage. In the ALIENOR Study an inverse relation between late stages of AMD and plasma omega-3PUFA was observed [12–16].

Statins do not reduce the risk of AMD. Zeaxanthin and lutein, two macular carotenoid pigments, are believed to prevent lipofuscin photooxidation and thus they may play a protective and preventive role in AMD [17–19].

The results of the present published scientific data are not sufficient to recommend routine nutritional supplementation for primary prevention of AMD, but patients with intermediate or advanced risk in one eye are recommended to take AREDS type supplements for slowing the progression of AMD in the other eye.

Hyperhomocysteinemia is responsible for vascular damage and is also an AMD risk factor.

Vitamin B12 and folate reduce blood homocysteine concentration and according to the WAFACS Study can reduce the risk of developing AMD by 35–40%.

In some epidemiologic studies the protection role of vitamin D is suggested due to its rejuvenating action in aging eyes by reducing inflammation and clearing amyloid β. Therefore, hypovitaminosis D in the elderly should be taken into account as being a potential AMD risk factor [20–23].

Current research suggests that the analysis of lipid profile in Bruch membrane is indispensable with regards to identifying the pathology progressing with age and then establishing early diagnostic and treatment procedures [24, 25].

RPE secretes apolipoprotein B-lipoprotein, which cumulates in drusen and eventually forms a lipid wall, a precursor of basal laminar deposit. Constituents of these eye lesions react with reactive oxygen species and form pro-inflammatory peroxidised lipids which elicit neovascularization.

On the other hand, the transport across human Bruch's membrane is due to protein carriers which diminishes with age, but could be enhanced by ginseng compounds [26].

During the process of aging, amyloid β accumulates in different tissues: in senile plaques of the Alzheimer's disease brain and in drusen of AMD patients [27–29].

T helpers 2 reveal activity against amyloid – the potential vaccine could reduce amyloid β accumulation.

Synthetic apolipoprotein mimetics can regulate lipid transport within the bloodstream and can even remove lipid accumulation in vessel walls. Intravitreal apolipoprotein A-I mimetic peptide D-4F injection in an animal model of AMD reduced the lipid deposition and the thickness of Bruch membrane. This strongly points towards the possibility of the future prophylactic AMD treatment in the human eye [30].

There is a hope of an effective neuroprotective therapy in dry AMD treatment by the use of a drug which could block cell death signals and enhance cell survival signaling.

Currently, different drugs are being tested in patients with dry AMD:

1) ciliary neurotrophic factor CNTF,
2) brimonidine Brimo PS DDS,
3) fluocinolone acetonide ILUVIEN,
4) 4-hydroxy (phenyl) retinamide FENRETINIDE,
5) Compstatin derivate PDT-4 (targets reversibly C3-a point of convergence for all three pathways of complement activation),
6) Eculizumab – humanized monoclonal antibody specifically C5 binding.

Modulation of the recruitment of microglia (resident immune cells in the central nervous system CNS and retina) and macrophages to the site of injuried RPEs is also a potential target for AMD treatment.

Polymorphisms in the CX3CR1 chemokine receptor found on microglia and macrophages have been associated with increased risk of AMD [31, 32].

Another way to preserve vision in AMD could be embryonic cell transplantation. We still await the results of studies being carried out on human eyes with RPE cells injected to rescue photoreceptors and stop the progression of macular degeneration.

The immunogenicity, stability of the cells and the propensity to form tumors still limit the practical use of RPE replacement therapy [33].

References

[1] **Thornton J, Edwards R, Mitchell P, Harrison RA, Buchan I, Kelly SP:** Smoking and age-related macular degeneration: a review of association. Eye 2005, 19, 935–944.

[2] **DeBlack SS:** Cigarette smoking as a risk factor for cataract and age related macular degeneration: a review of the literature. Optometry 2003, 74, 99–110.

[3] **HagemanGS, Luthert PJ, Chong NHV, Johnson LV, Anderson DH, Mullins RF:** An Integrated Hypothesis That Considers Drusen as Biomarkers of Immune-Mediated Processes at the RPE-Bruch's Membrane Interface in Aging and Age-Related Macular Degeneration. Prog Retin Eye Res 2001, 20, 705–732.

[4] **Bergmann M, Schutt F, Holz FG, Kopitz J:** Inhibition of the ATP-driven proton pump in RPE lysosomes by the major lipofuscin fluorophore A2-E may contribute to the pathogenesis of age-related macular degeneration. FASEB J 2004, 18, 562–564.

[5] **Finnemann SC, Leung LW, Rodriguez-Boulan E:** The lipofuscin component A2E selectively inhibits phagolysosomal degradation of photoreceptor phospholipid by the retinal pigment epithelium. Proc Natl Acad Sci USA 2002, 99, 3842–3847.

[6] **Weismann D, Hartvigsen K, Lauer N:** Complement factor H binds malondialdehyde epitopes and protects from oxidative stress. Nature 2011, 478, 76–81.

[7] **Eskelinen EL:** New insights into the mechanisms of macroautophagy in mammalian cells. Int Rev Cell Mol Biol 2008, 266, 207–247.

[8] **Wang AL, Lukas TJ, Yuan M, Du N, Tso MO, Neufeld AH:** Autophagy, exosomes and drusen formation in age-related macular degeneration. Autophagy 2009, 5, 563–564.

[9] **Wang AL, Lukas TJ, Yuan M, Du N, Tso MO, Neufeld AH:** Autophagy and exosomes in the aged retinal pigment epithelium: possible relevance to drusen formation and age-related macular degeneration. PLoS One 2009, 4, 4160.

[10] **Deangelis MM, Silveira AC, Carr EA, Kim IK:** Genetics of age-related macular degeneration: current concepts, future directions. Semin Ophthalmol 2011, 26, 77–93.

[11] Age-Related Eye Disease Study Research Group: A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss AREDS report no. 8. Arch Ophthalmol 2001, 119, 1417–1436.

[12] **Merle B, Delyfer MN, Korobelnik JF:** Dietary omega-3 FA and the risk for ARM: the ALIENOR Study. IOVS 2011, 52, 6004–6011.

[13] **Merle B, Delyfer MN, Korobelnik JF:** Plasma omega 3-fatty acids and the risk for age-relatedmacular degeneration: the ALIENOR Study ARVO 2012:370; Program number 3813-A427.

[14] **Delyfer MN, Buaud B, Korobelnik JF:** Association of macular pigment density with plasma omega-3 fatty acids: the PIMAVOSA study. Invest Ophthalmol Vis Sci 2012, 53, 1204–1210.

[15] **Stahl A, Krrhone TU, Sapieha P:** Lipid metabolites in the pathogenesis and treatment of neovascular eye disease. Br J Ophthalmol 2011, 95, 1496–1501.
[16] **Shalev V, Sror M, Goldstein I:** Statin use and the risk of age-related macular degeneration in a large health organization in Israel. Opthalmic Epidemiol 2011, 18, 83–90.
[17] **Seddon JM, Ajani UA, Sperduto RD:** Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. Eye Disease Case-Control Study Group. JAMA 1994, 272, 1413–1420.
[18] **Moeller SM, Parekh N, Tinker L:** Associations between intermediate age-related macular degeneration and lutein and zeaxanthin in the Carotenoids in Age-related Eye Disease Study (CAREDS): ancillary study of the Women's Health Initiative. Arch Ophthalmol 2006, 124, 1151–1162.
[19] **Tan JS, Wang JJ, Flood V, Rochtchina E, Smith W, Mitchell P:** Dietary antioxidants and the long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. Ophthalmology 2008, 115, 334–341.
[20] **Parekh N, ChappellRJ, Millen AE:** Association between vitamin D and age-related macular degeneration in the national health and nutrition examination survey. Arch Ophthalmol 2007, 125, 661–669.
[21] **Millen AE, Voland E, Sondel SA:** Vitamn D status and early age-related macular degeneration in postmenopausal women. Arch Ophthalmol 2011, 129, 481–493.
[22] **Morrison MA, Silveira AC, Huynh N:** Systems biology-based analysis implicates a novel role for vitamin D metabolism in the pathogenesis of AMD. Hum Genomics 2011, 5, 538–568.
[23] **Lee V, Hoh Kam JH, Jeffery G:** Vitamin D rejuvenates aging eyes by reducing inflammation, clearing amyloid beta and improving visual function. Neurobiol Aging 2012, PMID 22217419.
[24] **Curcio CA, Johnson M, Rudolf M, Huang JD:** The oil spill in ageing Bruch membrane. Br J Ophthalmol 2011, 95, 1638–1645.
[25] **Curcio CA:** Pathophysiology of Non-Neovascular Age-Related Macular Degeneration: The Oil Spill in Bruch's Membrane and beyond. Ophthalmologica 2012, 228, Suppl 1, 23–25.
[26] **Kang MY, Sim CM, Seok JH:** Albumin diffusion across human Bruch's membrane: modulation by ginseng compounds. ARVO 2012, 215: Program number 1595-A548.
[27] **Ohno-Matsui K:** Parallel findings in age-related macular degeneration and Alzheimer's disease. Prog Retin Eye Res 2011, 30, 217–238.
[28] **Armstrong RA:** The molecular biology of senile plaques and neurofibrillary tangles in Alzheimer's disease. Folia Neuropathol 2009, 47, 289–299.
[29] **Isas JM, Luibl V, Johnson LV:** Soluble and mature amyloid fibrils in drusen deposits. Invest Ophthalmol Vis Sci 2010, 51, 1304–1310.
[30] **Curcio CA, Johnson M, Huang JD, Rudolfd M:** Aging, age-related macular degeneration, and the response-to-retention of apolipoprotein B-containing lipoproteins. Prog Retin Eye Res 2009, 28, 393–422.
[31] **Tuo J, Smith BC, Bojanowski CM:** The involvement of sequence variation and expression of CX3CR1 in the pathogenesis of age-related macular degeneration. Faseb J 2004, 18, 1297–1299.
[32] **Combadiere C, Feumi C, Raoul W:** CX3CR1-dependent subretinal microglia cell accumulation is associated with cardinal features of age-related macular degeneration. J Clin Invest 2007, 117, 2920–2928.
[33] **Rickman B, Farsiu C, Toth C, Cynthia A:** Dry age-related macular degeneration: mechanisms, therapeutic targets, and imaging. IOVS 2013, 54, 14, 68–80.

Address for correspondence:

Hanna M. Zając-Pytrus
Ophthalmological Department
Wroclaw Medical University
Borowska 213
50-556 Wrocław
Poland
Tel.: +48 501 477 764
E-mail: hzp@spektrum.wroc.pl

Conflict of interest: None declared

Received: 27.05.2014
Revised: 30.06.2015
Accepted: 16.07.2014