Review Article

Insights into COVID-19 in age-related macular degeneration

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Abstract

Studies have shown that age-related macular degeneration (AMD) patients present a poor prognosis in coronavirus disease 2019 (COVID-19). These diseases have completely different etiologies and clinical courses. COVID-19 is a systemic, fast-evolving, and lethal infectious disease. AMD, in turn, is a chronic disease triggered by oxidative stress and is considered the main cause of irreversible blindness in old age. Both COVID-19 and AMD have in common the participation of immunological and inflammatory components arising from the imbalance of the redox state, responsible for the most severe phases of these diseases. Therefore, this study aims to present the triggering pathways of these diseases, as well as analyze the possible molecular mechanisms that increase the severity of COVID-19 in patients with AMD.

Keywords: Age-related macular degeneration, chemokines, coronavirus disease 2019, cytokines, inflammation, oxidative stress

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Received: 23 December 2022, **Revised:** 19 March 2023, **Accepted:** 17 April 2023, **Published Online:** 11 May 2023

INTRODUCTION

A retrospective study that analyzed 6,393 patients with COVID-19 found that 88 patients presented macular degeneration, and among these, the mortality rate was 25%. This mortality rate in patients with AMD was higher than in those with other comorbidities, such as type 2 diabetes mellitus (21%) and obesity (13.8%).[1] Corroborating these findings, a population-based nationwide cohort study in Korea (total n = 135,435) reported that patients with wet AMD (wAMD) were more susceptible to COVID-19, presenting a considerably higher risk of serious clinical outcomes.[2] Coronavirus disease 2019 is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[3,4] It is an infectious disease with high morbidity,[5] and estimated fatality rate between 4% and 7%.[6] Preexisting conditions, such as old age, obesity, smoking, diabetes mellitus, cardiovascular disease, a change in coagulation status, and an impaired complement system, contribute to the development of severe COVID-19.[1,7-9] These preexisting conditions that are related to the poor prognosis of COVID-19 are also related to the pathogenesis of AMD, the leading cause of irreversible blindness in old age.[10-13]

The imbalance of the redox state, a determining factor for the advancement of COVID-19, activates important molecular pathways such as nuclear factor kappa B (NF-κB), receptor for advanced glycation end products (RAGE), and nucleotide-binding oligomerization domain-like receptor containing pyrin domain 3 (NLRP3) inflammasome, in the main effector cells of the innate and adaptive immune system, such as macrophages, monocytes, neutrophils, dendritic cells, natural killer (NK) cells, epithelial and endothelial cells.[14] The activation of these

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Quick Response Code:	Website: www.thepajo.org
	DOI: 10.4103/pajo.pajo_71_22

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How to cite this article: Torres RJ. Insights into COVID-19 in age-related macular degeneration. Pan Am J Ophthalmol 0;0:0.

molecular pathways triggers the release of large amounts of pro-inflammatory cytokines and chemokines, such as interleukin (IL)-1 β, IL-2, IL-6, IL-7, IL-10, tumor necrosis alpha (TNF-α), interferon (IFN)-γ, C-C Motif Chemokine Ligand 2 (CCL2), CCL5, chemokine interferon-γ inducible protein 10 kDa (CXCL10), named cytokine storm. It is an acute, rapid and potentially lethal process responsible for acute respiratory distress syndrome.[14-19]

In aging eyes, the imbalance of the redox state also activates the same molecular pathways (NF-κB, RAGE, and NLRP3 inflammasome)[20-24] inducing the slow and gradual release of the same cytokines. The release of pro-inflammatory cytokines causes chronic low-grade inflammation, leading AMD to its most advanced stages of geographic choroidal atrophy and/ or subretinal neovascularization.[25-30] In this context, it is worth noting that the inflammatory mechanisms that facilitate the development of AMD, such as the aberrant innate immunity, also contribute to the development of severe COVID-19.[27,30-38] Studies show that aging, a poor prognostic factor in COVID-19 and the main factor linked to AMD, causes an increase in plasma levels of inflammatory mediators, which may represent the critical point for the increased risk of multimorbidity and mortality in patients with AMD, who have been infected by SARS-CoV-2.[38] The same evolution has been observed in another serious viral disease, the human immunodeficiency virus (HIV), whose plasma levels of the inflammatory biomarkers C-reactive protein (CRP), IL-6, and CXCL10 were elevated in AMD patients and were associated with high mortality. This poor prognosis of HIV in AMD patients was attributed, at least in part, to systemic inflammation.[39]

Considering the worse prognosis of COVID-19 in patients with AMD relative to other serious comorbidities,[1,2] this study aims to present the triggering pathways of these diseases, as well as analyze the possible molecular mechanisms that increase the severity of COVID-19 in patients with AMD.

CORONAVIRUS DISEASE 2019, "THE CYTOKINE STORM"

SARS-CoV-2 is a single-stranded, enveloped RNA virus with the spike glycoprotein that can bind to serine protease, transmembrane serine protease 2 (TMPRSS2), and mainly to the angiotensin-converting enzyme 2 (ACE2) receptor, a master regulator of the renin-angiotensin system, to enter host cells.[40,41] ACE2 is abundantly found in the type II pneumocytes of the lung alveolar epithelium, gastrointestinal tract, vascular endothelium, and other tissues.[42] This fact may explain the dysfunction of multiple organs and systems observed in its most severe clinical forms.[43,44] After SARS-CoV-2 infection, reactive oxygen species (ROS) are overproduced as initiators of the toxic innate immune response against viruses.[45] The intense imbalance of the redox state triggers the activation of NF-κB, responsible for the release of IL-6, IL-1 β, TNF-α, and chemokines from immune and nonimmune cells.[14,15,46] The oxidative stress, as well as the activation of NF-κB, increases the expression of the NLRP3 inflammasome.[47-49] NLRP3 inflammasome activation leads to the production of IL-1 β/18, facilitating and perpetuating the formation of cytokine storm (IL-6/8/10/1RA, TNF-α, and CXCL10).[47] Oxidative stress also contributes to the exacerbation of cell hypoxia and can damage mitochondria in overwhelming amounts.[48,50]

Among the main comorbidities that determine the poor prognosis of COVID-19, age, diabetes, obesity, and cardiovascular diseases play a central role. These comorbidities can accelerate the formation of advanced glycation end products (AGEs).[51] The interaction of AGEs with their RAGE receptor, expressed mainly on the surface of type one and type two alveolar epithelial cells, as well as alveolar macrophages, induces the NF-κB-mediated inflammatory cascade. Activation of NF-κB leads to the production of inflammatory cytokines and chemokines, causing acute lung injury, increasing severity and mortality from COVID-19.[52-54] Besides, pro-inflammatory cytokines and the production of reactive oxygen and nitrogen intermediates, respectively, may lead to endothelial dysfunction and hypercoagulation, worsening the patient's clinical condition.[55,56]

In short, the resolution of the infection is directly linked to ROS overproduction and immune response; however, it can also result in immunopathogenesis and consequent worsening of the inflammatory condition. This condition is clinically expressed as a reduction in viral load that coincides with an increase in disease severity.[57,58]

AGE-RELATED MACULAR DEGENERATION, "THE CYTOKINE DRIZZLE"

As in COVID-19, the imbalance of the redox state imbalance has been considered the main factor that triggers and perpetuates AMD.[59] Such imbalance results in the oxidation of important biomolecules (lipids, proteins, carbohydrates, and deoxyribonucleic acid) that promote increased expression of toxic molecules such as malondialdehyde (MDA), carboxyethylpyrrole, AGEs, 4-hydroxynonenal, and 8-Hydroxy-2'-deoxyguanosine.[60] This excessive production of ROS, responsible for the increased expression of toxic molecules, induces mitochondrial dysfunction and ends up

resulting in the accumulation of lipofuscin in RPE cells.[61,62] This lipofuscin accumulation induces the dysfunction of RPE cells and causes a defective degradation of products derived from the phagocytosis of the outer segments of photoreceptor cells, inducing pathological accumulation of lipids in Bruch membrane (BM), giving rise to the drusen and other extracellular deposits.[63,64] The drusen contain immunological and inflammatory markers such as serum amyloid P component, apolipoprotein E, immunoglobulin light chains, Factor X, prothrombin, and complement proteins (C3a, C5a, and C5b-9 complex), CRP, vitronectin, ubiquitin, integrins, and AGEs,[65-69] closely related to the activation of NLRP3 inflammasome and NF-κB.[70-73] Besides the choriocapillaris, the RPE cells and photoreceptors also present inflammatory and immunological markers such as renin-angiotensin system (including ACE2/Ang1-7), Factor X, fibrinogen, immunoglobulin, human leukocyte antigen-DR isotype (HLA-DR), amyloid A component, apolipoprotein B/E, CRP, CCL5, CCL2, complement C3, C5, prothrombin, ubiquitin, AGEs, and vascular endothelial growth factor (VEGF).[60,74-81] It is important to point out that RPE cells also express a series of necessary cytokine receptors such as IL-1R,-4R,-6R,-8RA,-10RB, and IFN-AR1, indicating the sensitivity to systemic and retinal inflammatory signals.[31] In addition, the sensory retina has microglial cells, immune cells that, in response to the inflammatory stimuli, secrete molecules such as proteinases, nitric oxide, reactive oxygen intermediates, and pro-inflammatory cytokines, including IL-1 β, IL-6, and TNF-α.[82-84] In the AMD process, complement factor H is overexpressed in RPE cells,[85] being upregulated by IFNs.[86] Elevated levels of inflammation-related chemokines, including CXCL10, CCL14, CXCL16, CXCL7, and CCL22, were also found in the aqueous humor of AMD patients. CXC-chemokine ligand 10 and CCL22 were more elevated in eyes with recurrent wet AMD than in treatment-naive eyes. CXC-chemokine ligand 16 was positively correlated with lesion size. The increase in CCL22 was correlated with the OCT images that showed intraretinal fluid or hyperreflective foci.[87] Other studies have reported increased levels of CXCL10 as well as concentrations of CCL2, soluble intercellular adhesion molecule 1, soluble vascular cell adhesion molecule 1, and VEGF in the aqueous humor of patients with wet AMD.[88,89] Studies have shown that the pro-inflammatory cytokine IL-1 β is responsible for the damage of the outer segments and the death of rods as well as for the increased expression in the patients' vitreous affected by polypoidal choroidal vasculopathy.[90-92]

These findings support the current understanding that inflammation plays a critical regulatory role in AMD. It often exacerbates oxidative stress, creating a self-perpetuating, vicious cycle of oxidation and inflammation, aggravating AMD.[93-96] One of the means to perpetuate this cycle is the activation of the NF-κβ, involved in the regulation of gene expression associated with the immune and inflammatory responses.[25,97]

AGE-RELATED MACULAR DEGENERATION, "A SYSTEMIC INFLAMMATION"

Immune and inflammatory markers are not just upregulated within the eyeball. Genetic studies have mapped genes in the complement pathway that are involved in the regulation of innate immunity with AMD susceptibility.[31] Similarly, the association of RAGE gene polymorphisms with AMD has already been observed.[98] In addition, the frequencies of IFN-γ-and IL-17-expressing CD4+ T cells, as well as the levels of IFN-γ and IL-17 expression by CD4+ T cells, were shown to be significantly up-regulated in patients with AMD.[27] The same occurs with the serum levels of IFN beta.[99] Studies analyzing the serum of AMD patients reported elevated levels of proinflammatory cytokines IL-1α, IL-1 β, IL-4, IL-5, IL-10, IL-13, and IL-17, as well as altered expression levels of other inflammatory factors such as CRP, IL-6, and other cardiovascular biomarkers.[32,34,36,100,101] In parallel, altered phenotype and immune cell functions were observed in peripheral blood leukocytes in patients with AMD.[33] Corroborating this study, CCR1 and CCR2 were found to be upregulated in CD14 + CD16 + monocytes in patients with neovascular AMD.[30] Similarly, plasma levels of CCL5 were found to be upregulated in participants with GA.[102] It is important to note that CCL5/CCR5 could attract T-cells to release inflammatory factors and worsen the inflammatory damage.[103] Another study reported that serum eotaxin and CXCL10 levels were significantly elevated in all stages of AMD, except for eotaxin levels in neovascular AMD.[36] While eotaxin (a Th2-associated chemokine that participates in innate immunity) is a potent chemoattractant for eosinophils, CXCL10 has a high affinity for C-X-C Motif Chemokine Receptor 3 (CXCR3) found in activated T cells and NK cells.[104,105] Both eotaxin and CXCL10 could serve as biomarkers to predict the early onset of AMD.[36] Multivariate logistic regression analyses demonstrated significant associations of urinary transforming growth factor-beta 1 levels and CCL2 levels in early AMD, as well as CCL2 levels with GA.[106]

DISCUSSION

"Inflammaging" versus coronavirus disease 2019 versus age-related macular degeneration

A relevant question may be raised: what mostly influenced the increase in COVID-19 mortality among AMD

patients, old age, or AMD per se? This is a difficult question to answer. Initially, studies that demonstrated elevated systemic levels of inflammatory cytokines and chemokines in patients with AMD were compared with participants aged 60 years and older without AMD (control group).[27,32,34,35,99-102,106] This fact indicates that AMD can be related to the increase of systemic inflammatory markers. In Ramlall's study, patients with macular degeneration had a greater risk of severe COVID-19 clinical outcomes. This study attributed failures of the complement system to adverse outcomes.[1] It is important to note that dysregulation of complement cascades is a common feature of both AMD and COVID-19.[31,107] However, this study involved a relatively small number of total patients and macular degeneration patients and did not adjust for confounders, including the known systemic risk factors for AMD. On the other hand, Yang's study, which involved a larger number of participants than Ramllal' 's, performed meticulous matches and adjustments to minimize the confounding effect for known COVID-19 risk factors such as age, sex, history of diabetes, and cardiovascular diseases. Yang *et al.* found an increased risk of susceptibility to severe clinical outcomes of COVID-19 in patients with wet AMD.[2]

Successful aging in adults is associated with low levels of inflammation. On the other hand, inflammation is a marker of biological aging, multimorbidity, and mortality risk.[38] Aging, and the consequent accumulation of senescent cells, is related to the progressive increase of a sterile, low-grade chronic inflammation, called inflammaging.[108,109] Senescent cells activate NF-kB and RAGE signaling, stimulating the secretion of inflammatory cytokines, chemokines, and growth factors that contribute to inflammation.[110-112] Molecular changes related to the aging process, particularly pre-existing inflammatory conditions such as AMD, can exacerbate the morbidity and mortality associated with COVID-19.[113-115] On the other hand, systemic viral infections such as COVID-19 may be a trigger of cellular senescence, responsible for accelerating age-related diseases,[116-118] and can potentially trigger or worsen AMD. This possibility should be considered, as the ACE2 receptor can be found on retinal vascular endothelial, photoreceptor and RPE cells, as well as in the choroid. As such, SARS-CoV-2 can enter these cells, increase oxidative stress, and induce some degree of inflammation, basic conditions for triggering AMD.[40,41,74,75] In addition, COVID-19 promotes an increase in the plasma levels of eotaxin-1, which is closely linked to neuroinflammation and neurodegenerative disorders, also likely to trigger or worsen AMD.[36,119] Figure 1 illustrates the interactions between age, inflammaging, severe COVID-19, and AMD.

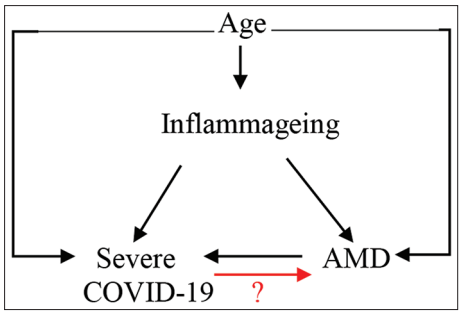


Figure 1: Interactions between age, inflammaging, severe COVID-19, and AMD. AMD: Age-related macular degeneration, COVID-19: Coronavirus disease 2019

CONCLUSION

COVID-19 is still a little understood condition, and different molecular mechanisms that are part of its pathogenesis are likely to be disclosed. Similarly, AMD's pathogenesis is not widely known. Nevertheless, several studies consistently report that COVID-19 and AMD are diseases characterized by an imbalance in the redox state that triggers immune and inflammatory changes. In both diseases, there is the activation of important and interconnected molecular pathways, such as NF-κB and NLRP3- inflammasome, and the interaction between AGE-RAGE. In COVID-19, the activation of these molecular pathways causes extreme systemic oxidative and inflammatory phenomena, leading to loss of life. In AMD, in turn, activation of these molecular pathways causes low-grade inflammation in the RPE/BM complex leading to vision loss. Several inflammatory mediators, including complement components, chemokines, and cytokines, are elevated at systemic levels in AMD and can significantly contribute to a poor prognosis in COVID-19 patients. Additional studies are expected and recommended to confirm the association of severe COVID-19 outcomes in patients with AMD. On the other hand, the possibility of premature triggering or worsening of AMD in patients who contracted COVID-19 are doubt that future epidemiological studies will clarify.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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