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RESPONSE TO LETTER

Insights and Considerations for "Higher Intraocular Levels of Inflammatory Factors Are Related to Retinal Vascular and Neurodegeneration in Myopic Retinopathy" [Response to Letter]

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Dear editor

We are honored that our recently published article titled "Higher Intraocular Levels of Inflammatory Factors Are Related to Retinal Vascular and Neurodegeneration in Myopic Retinopathy"[1] has attracted the attention of Cao and Ma.[2] It is encouraging to see that our work has been recognized for its potential contribution to myopic retinopathy research. In response to the specific issues raised in their letter,[2] we provided the following clarifications, addressing each point individually:

1. Regarding the non-myopic control group, we agree that information on intraocular inflammatory cytokine levels in emmetropic controls would add great value to the study. Ideally, the samples should come from age-matched emmetropic eyes without any ocular disorders and be collected in the same way as we did in myopic eyes. Unfortunately, it is impossible to obtain such samples. Aqueous humor collection is a traumatic procedure and it is unethical to ask healthy people to donate aqueous humor for research. The lack of emmetropic controls in our study was an unavoidable limitation and was acknowledged and discussed in our paper.[1] Nonetheless, in our study, we included samples from myopic eyes without any retinal pathologies (simple myopia) and eyes with different degrees of myopic retinopathy (posterior staphyloma with and without chorioretinal atrophy). This study design is appropriate to uncover myopic retinopathy-related intraocular cytokines.
2. Causality between inflammation and retinal degeneration. Our work was an observational study and not designed to determine the causality between intraocular inflammation and retinal degeneration in myopic eyes. Although the initial cause of intraocular inflammation and retinal degeneration in myopic eyes remains elusive, the sustained inflammatory microenvironment would be detrimental to retinal neurons. Therefore, we believe that intraocular inflammation observed in our study may contribute to the progression of myopic retinopathy. We agree with Cao and Ma that additional longitudinal studies and animal experimentation with cytokine modulation could help determine whether inflammation drives degeneration. Since aqueous humour collection can only be conducted when patients are undertaking eyecare-related medical procedures (with institutional approval and patient's consent), a longitudinal study on the dynamic changes of aqueous humour cytokines and retinal degeneration at different stages of myopic retinopathy will be extremely difficult and practically nearly impossible.

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3. Systemic inflammatory factors. A previous study has reported a link between myopia and systemic inflammatory diseases such as type 1 diabetes, uveitis, and systemic lupus erythematosus.[3] To understand if myopic retinopathy was related to abnormal intraocular inflammation, we excluded patients with known inflammatory or autoimmune disorders from our study. We found that elevated levels of intraocular inflammatory factors such as Chi3l1, IL-6Ra, and IL-8 were associated with myopia-related retinal microvascular and neurodegeneration. Unfortunately, we did not measure systemic inflammatory markers, therefore, we do not know whether these inflammatory factors are generated locally from the degenerative retina or recruited from the blood circulation. This will be the focus of our future studies.
4. The impact of ICL surgery on cytokine levels. Cao and Ma suggested that the potential influence of surgical stress on cytokine levels should be addressed, and they proposed including a preoperative validation group and collecting samples at different times post-operation from the myopic patients. Whilst we acknowledge the proposed study is interesting and would provide valuable information on how surgical stress may affect intraocular cytokine levels, this was not the purpose of our research. Furthermore, the impact of lens surgery on intraocular inflammation is well-acknowledged in the clinic, exemplified by the well-known lens surgery-induced cystoid macular oedema.[4] Although a time-course study to evaluate the impact of ICL surgery on intraocular cytokine production in patients, as suggested by Cao and Ma, has never been conducted by any group due to ethical considerations, animal studies have confirmed higher levels of retinal inflammatory gene expression following lens surgery, even in the fellow un-operated self-control eyes.[5] The concern raised by Cao and Ma is whether the elevated cytokines reported in our paper are linked to myopic progression or surgical preparation. In our study, aqueous humour was collected immediately before ICL surgery in all participants. We found that eyes with myopic retinopathy had significantly higher levels of inflammatory cytokines than eyes without myopic retinopathy. Our results suggest that elevated intraocular cytokines are related to retinal degeneration and, therefore, linked to myopia progression rather than surgical preparation.

We believe that the comments raised by Cao and Ma in their "Letter to the Editors" reflect their expert knowledge in this subject matter and feel that the discussions have allowed us to think more critically about how data from clinical observational studies should be interpreted. We appreciate their comprehensive comments on our work but feel that their suggestions to "include emmetropic controls" and "evaluate the impact of ICL surgical stress on cytokine levels in patients" are unrealistic and practically impossible as such studies would likely be against human research ethics detailed in the Declaration of Helsinki set by the World Medical Association.[6]

Disclosure

The authors report no conflicts of interest in this communication.

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