Author's response to reviews

Title: Matrix metalloproteinases and tissue inhibitors of metalloproteinases in the aqueous humour of patients with primary angle closure glaucoma - a quantitative study

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Author's response to reviews: see over
Dear Editor,

Thank you for the most insightful comments. We have prepared responses to each of them below and hope that the article is now much improved and up to the standards of your esteemed journal. Thank you.

Amir Samsudin (on behalf of all authors)

Reviewer 1:

Major Compulsory Revisions
Abstract. The authors should enclose mean ± SD values of MMPs and TIMPs in abstract as well
We have now revised the abstract to include most of the values. We are unable to include some MMP and TIMP values due to the constraints of the 350-word limit. We hope that this is not detrimental to the quality of the article.

Text:
Methods: the authors should include a reference of glaucoma diagnosis criteria used and more data concerning perimetry used and patient examination (for example, was the examination conducted by the same doctor-glaucoma specialist for both study and control groups?)
Reference added (European Glaucoma Society guidelines). Text has been added to explain that glaucoma diagnoses (including perimetry findings) were made by ophthalmologists of varying levels/ experience but confirmed by fellowship-trained glaucoma specialists prior to enrolment.

Results:
1. the authors should include ±SD and p values for MMP/TIMP ratios comparison
These have now been added and discussed.

2. the authors mention a sub analysis -comparison of patients with and without prostaglandin analogues treatment. Please provide more information of these subgroups (number of samples, statistical data) in the participants' and results' section
These have now been added to the Introduction, Results (including Table 3) and Discussion sections.

Table 2. The authors should include ±SD and p values for each ratio
These have now been added.

Minor Essential Revisions
Discussion- paragraph 4 (limitations of the study). As already mentioned, some of the patients enrolled for the study, are under topical antiglaucoma treatment. If the authors have more information about the type and number of medication used, they should report it and make a comment in this section about the possible influence of antiglaucoma medication on aqueous humor protein and MMP concentrations.
The types and numbers of meds have now been added. Additional discussion about the possible effect of prostaglandin analogue use and multi-drug therapy has also been added to the discussion.
Discretionary Revisions

Figure 2 and 3. Although mentioned in the legends, I think it is advisable to report detection sensitivity of assay kits in a different table (including min and max concentrations detected according to manufacturer's information).

The sensitivity levels of each test kit have now been added to the text in the Methods section.

Quality of written English: Needs some language corrections before being published

This has now been rechecked by a native English speaking colleague and improved upon.

Reviewer 2:

The authors analyzed the level of MMP-2,3 and TIMP-2,3 in the aqueous humor of patients with PACG, POAG, and non-glaucomatous control eyes. They found altered amount of MMPs and TIMPs as well as imbalance of MMP/TIMP ratios in PACG eyes compared to POAG and non-glaucomatous eyes. A few minor concerns were addressed below:

1. In the demographic of the subject, systemic conditions (such as diabetes, systemic hypertension, etc) were not described in the text and in the table. As there have been reports on the altered plasma level of MMP and TIMP in diabetes and systemic hypertension (as shown in the references below), it needs to be clarified among the subjects.

   Diabetics were excluded from this study. This has now been clarified in the text.

   Hypertensives were not excluded from this study. This has now been discussed as a limitation of this study.

2. The number of IOP medication may be provided in the Table 1.
   This has now been added.

3. In MMP/TIMP ratio table (Table2), the p values among the groups should be provided.
   This has now been added.

Quality of written English: Needs some language corrections before being published

This has now been rechecked by a native English speaking colleague and improved upon.

Editor's comments:

1) Make sure statistical significance is shown for all comparisons made. There are several comparisons made in the results without a p-value shown.
   These have now been added.
2) Please provide much greater detail about the types of meds used by patients preoperatively, and which comparisons were made in subgroup analyses. Is it possible that some differences may reflect the type of preop medical treatment?

   The types and numbers of meds have now been added. Additional discussion about the possible effect of prostaglandin analogue use and multi-drug therapy has also been added to the Discussion section.

3) Several MMPs and TIMPs are discussed, though even after reading the paper it is not clear to me why of these form a pair. Please discuss this research, and use it to justify the specific ratios of MMP/TIMP provided. As stated above, please provide statistics to determine if these ratios are statistically significant across groups.

   The pairings were investigated to look at imbalances between MMPs and TIMPs, and to enable comparison with the work of Schlotzer-Schrehardt et al. and Fountoulakis et al. This has now been clarified in the Discussion section.

4) Please put Acknowledgment before Competing Interest.

   This has now been done.

5. We recommend that you ask a native English speaking colleague to help you copyedit the paper.

   This has now been rechecked by a native English speaking colleague and improved upon.