Reviewer #2

In the manuscript authors have described metformin use for AMD. They have

also reviewed mechanism of metformin effects as well as pathophysiology of

AMD.

Abstract

- I think that it is too limited description: ”The dry form is especially

characterized by loss of retinal neurons (geographic atrophy)”

There should mention it more widely. There appear RPE, Bruch`s membrane,

choriocapillaris and photoreceptor degeneration. Of course, when it is

progressed to the more bad disease stage losing of neurons especially

photoreceptors leading vision loos but still there should mention also RPE

and choriocapillaris degeneration from which it start.

We have corrected the sentence and added more details.

Keywords

- modify language

-Why there is AMPK? It is not even mentioned in the abstract. Why is it

keyword? Please, mention AMPK as well in the abstract because it is quite

important area in the main text.

We added some sentences on the AMPK-pathway in the abstract.

Main text

- Sentence in lines 121-123 is confusing and need to clarify.

We rewrote this sentence and hope that it is more clear now.

- line 245, give some example about ”…AMPK-independent pathways…”

We added two sentences about this.

- lines 259-261; “Romdhoniyyah et al. performed a meta-analysis over five

retrospective trials (3). They found a positive odds ratio for the

association of metformin use and the risk to develop AMD but their analysis

did not reach the level of significance.”

Basicly, they did not find anything because it was not statistically

significant. It can not say they found something as positive odds ratio but

it was not significant. Based to no-significant results the positive ratio

could just be coincidence. Please, clraify, modify or do something for that

part. As well the positive ratio stay ambiguous if it was meaning increased

or decreased disease.

This part was rewritten to clarify that their met-analysis was not significant.

-lines 307-309; What mean next sentence and how it belongs to this context?

Is it really necessary in this point? At least need to modify if it is as

discussion related to metformin or just delete.

 ”This corroborates findings that another direct NLRP3 inhibitor

(fluoxetine) is associated with reduced risk to develop AMD.”

We reformulated the sentence to make clear that we see a possible parallel finding between fluoxetine and metformin regarding inhibition of the NLRP3 inflammasome. NLRP3 inhibition has been reported to prevent RPE degeneration.

Conclusion

- lines 332-222, Please when manuscript is named based to title as metformin

and AMD it is not sound good in conclusion to add next text to the sentence

”….and other diseases for which metformin use has been associated with

beneficial outcomes.” It is more like example in main text not conclusion.

This part of the sentence has been deleted

- This is nice and very interesting way to write end of the conclusion as

follow” There is one ongoing prospective, phase II clinical trial that is

investigating the ability of metformin to decrease the progression of

geographic atrophy in non-diabetic patients with AMD (50). Study completion

is expected by the end of 2024.”

But still I missed some bigger context after that e.g. what after that study

or is there something that still should study more with that. It left too

big hole for known nothing about the results of the study and should our now

waiting until 2024 without getting anything know about the possibility of

metformin use to treat AMD so or what after that. Give some positive effect

or what is coming related to this topic in the future in bigger perspective.

Of course, it should based to literature not only promises or single study.

But something that it not end as incomplete after inform of 2024 coming

results and writing process. That is also good to know but manuscript can

not end to that.

We did major re-structuring of the manuscript based on comments of another reviewer. The discussion does not end anymore with this ongoing trial.

General

- There could also be more figures e.g. effects of the metformin through

AMPK and overall consequences of it.

We included a figure about the AMPK pathway and possible mechanisms of metformin.