Reviewer #1

This review reports on metformin and its possible benefits in AMD.

**Abstract**

Please add the words “late AMD” into this description

The dry form of late AMD is especially characterized by loss of retinal

neurons (geographic atrophy) and the wet form of late AMD is characterized

by pathological neovascularization.

“late AMD” has been added in the description of dry and wet form

Line 19 . Please delete “Not surprisingly”

Has been deleted

**Introduction**

Line 41 and 42 , AMD will not cause blindness it is legal blindness, please

qualify the statement with legal blindness especially when you quote the

German figures, it cant be 50% of real blindness.

We corrected this and added “legal”

Line 50, aggrevate is not the correct word, please change to say, can

rapidly progress

has been changed

Line 53, antagonize is not the best word here, maybe reduce or block the

neovascular signal thus reducing….

Has been changed

Line 55. Report on several, would be better English than report about

Has been corrected

**Main text**

Lines 72 .. And is still not full understood, please re word sentence to

reflect this, until today means we have now today understand it, which is

not correct. Something like, we still do not fully understand…

has been corrected

The main text introduction on AMD is a repeat of the introduction. You

don’t need this twice, you should consolidate all this explanation of AMD

into the introduction.

We did substantial reorganization of the introductory part based on your useful comments. We moved and consolidated the paragraph on AMD classification and treatment into the introduction.

Also note AMD is classified into stages not forms, please re word and better

to say the earlier stages are based upon the size of the drusen deposited

and the presence or not of pigmentary changes

78…. “Early and even intermediate AMD may have no or only minimal

symptoms (10). Possible symptoms of early and intermediate AMD are subtle

distortion (metamorphopsia), increased blurring and decreased contrast

sensitivity.”

In this general overview it would be better just to leave it with early and

iAMD usually have no to minimal symptoms. ( it would be usually to complain

of what you describe, it is more common they have difficulty in dark

adaptation and driving at night not what you describe, so I would just leave

out the example and make the point that they are usually without symptoms

Same comment on “aggrevate”, as above

This is supposed to be a review on metformin in AMD so you don’t need a

whole repeat paragraph on treatment for AMD, all this should be covered in

the introduction then move into the point of the review in the main text.

Surely the point on treatment is we don’t have any except of one form of

late AMD. Hence finding a way to modify the disease is required hence your

review on metformin.

Again, we still cant treat dry so not until today means we now have a

treatment today.

All these comments have been taken into account during the reorganization of the introductory part.

You have defined the Beckman classifcation of AMD, so where in it is the

term dry intermediate?? There si no dry intermediate, it is either iAMD or

dry ( ie GA) Do not use the term dry for anything other than GA. That was

the whole point of the Beckman to stop people using dry when they mean early

or iAMD. You mean iAMD.

This part was changed during the reorganization as mentioned above. There should be no part where we talk about a “dry intermediate” stage.

It is not appropriate to single out one possible treatment for iAMD nor to

go into such detail as to their results, For your review you just need in

the introduction to say we have treatments for wet but nothing else but

there is intense research looking at possible interventions that target…

The part on treatment has been shortened and moved to the introduction.

Start the main text at the section on the current understanding of the

pathophysiology of AMD

In the re-structured manuscript we know start the main part with the pathophysiology as you suggested.

line 124, ref 11 will not be the appropriate ref for changes in the RPE and

BM with age. Please cite other important references.

Ref 11 was removed and a better citation was added

Line 129

“Altogether, age-related changes negatively influence the integrity of the

RPE/Bruch’s membrane interface leading to accumulation of debris that

ultimately leads to the formation of drusen (11)”

It is not clear what cases AMD, we do not know that your statement is

correct, it could be damaged photoreceptor outer segments or choriocapillary

loss as the initiating factor so your statement is one hypothesis not a

fact. Please re word.

Has been reworded.

 Line 140, Ref 11 is not a good ref to diet and AMD. Find a mor

appropriate reference.

We added appropriate references.

Line 145 The latter leads “to a kind of” systemic low-grade

inflammation. “ to a kind of” isn’t very scientific way to describe

the findings of this research. Re phrase…” results in?”

has been reworded

Line 156.. You do not need a review on the complement pathway in this

review on metformin in AMD. Just refer the reader to a review on the topic,

Delete this paragraph explaining the complement system. The complement

system is part of the innate immune system. Its main functions are the

recognition and removal of pathogens, debris and dead cells. These functions

are tightly regulated by about 50 proteins that are part of the complement

cascade (11,26). Activation of the complement cascade can occur via three

pathways: the lectin pathway, the classical pathway and the alternative

pathway. Both the lectin and the classical pathway require recognition of

counterparts on pathogen surfaces. On the contrary, the alternative pathway

is continuously active and its overactivation has to be prevented constantly

to maintain tissue homeostasis and to avoid unnecessary inflammation and

tissue damage (11).

You are right. We have deleted this paragraph on the complement system.

Line 165 “The crucial anatomic site where AMD pathophysiology begins is

the complex of RPE cells, Bruch's membrane, and the choroid.” How do you

know it isn’t the photoreceptors. This is an unproven statement. Modify

this to reflect it is an hypothesis. Also cell senescence might lead to

inflammation not the other way around, these are all still hypothesis, not

proven facts.

We made clear, that it his an hypothesis.

Line 174 “Eventually, the blood-retina-barrier breaks down and

degeneration of the RPE occurs. Ultimately, irreversible damage to the

macular photoreceptors occurs, whether it is the non-neovascular or

neovascular form of AMD (11,26,27).” This implies the photoreceptors are

last to go but that is definitely not a statement that is proven or likely

to be true. Please make sure you are outlining a possible hypothesis, much

better to say that we don’t know the change of events but there are

certain things that likely contribute. Also the RPE is dysfunctional long

before the BRB is disrupted so again you imply the RPE goes after the BRB

fails. Unlikely to be true.

We have rewritten these sentences.

Line 200 GLP-1 needs to be in full first time

Has been corrected

Line 217

217. Before moving on to the experiments in AMD it would be good to

understand the underlying thinking as to why metformin might help AMD. What

was the initial hypothesis that got the first people to even think to do

some work on this, what triggered the interest? Why would there be an

experiment in laser induced CNV what was the underlying hypothesis being

tested? There needs to be a section on what are the actions of metformin

that might be useful in AMD. Then it would be a better flow to then answer

each potential action with a particular experiment that aimed to address

that action.

We moved the paragraph about “proposed actions of metformin” to this place, as you suggested in one of your later comments, see below your comment on line 280.

219, it is not induced exudative AMD, it is laser induced CNV, they don’t

get AMD. Please fix.

Has been fixed.

229. NO needs to be in full.

Has been corrected.

235. more detail on the in vivo work, what were the 2 animal models of

retinal degeneration? Were they good models of AMD? How was retinal damage

measured?

We substantially revised the part about the in-vivo studies of Xu et al.

240 , put all the experiments about anti angiogenic together. Group the

mechanism of action together to get some logic into the list of experiments

written about.

We moved the paragraph about the experiments of Han et al., so that anti-angiogenic experiments are together.

253…261 So this is what your review should be concentrating on, we need

to see much more data on these studies> How do we know it is not Diabetes

that protects from AMD not the metformin. This is where the review needs to

spend more time on detail, how large a cohort? Were they age matched and

matched for smoking, ie how good is the evidence. What were the Odds ratio,

what was the confidence intervals? You need to critic the experiments not

just list them.

We have made substantial changes to the section of the retrospective trials by adding a paragraph with a short description of design and outcome of all eight studies followed by comments on the trials. We hope that this added more value to our manuscript.

262: What does this have to do with nAMD? The review is on AMD not

diabetes, might be different mechanisms at play, really irrelevant to this

review unless you were just supporting a similar finding in AMD. Or put it

in possible modes of action section. Although you have no idea if the effect

seen was through anti VEGF enhancement, might have been anti inflammatory.

We agree that this part is not relevant for the main text part of this review. Please see our comment to your comment to line 315 below.

271. This is irrelevant, the only place a sentence could belong is in the

introduction when talking about the actions of metformin in diseases other

than diabetes.

We agree that this paragraph is irrelevant for the main text part of a review about metformin and AMD association. We deleted it.

280 Proposed mechanisms of action, this discussion should come before all

the AMD experiments, the logic would be these are all the things metformin

can do, now lets se if there was any impact on AMD.

We moved this paragraph before the experiments part. We agree that this is much better for the logic of the manuscript.

315 delete sentences: In addition, it has been shown that metformin is able

to enhance the effect of anti-VEGF agents in the treatment of diabetic

macular edema. The latter is especially interesting for patients with

reduced anti-VEGF responses. Further investigations should elucidate the

underlying mechanism of action and if this effect can also be observed in

patients with neovascular AMD.

We agree that the paragraph of anti-VEGF enhancement in DME is irrelevant for our main text part. But we think it is an interesting finding that we like to mention in the discussion part, because it could be possible, that metformin also enhances anti-VEGF treatment of wet AMD. We changed the respective part in the discussion section.

324 delete “On top of that” and use in addition.

Has been deleted.

325 delete “by gradually increasing the dose, for example”.

Has been deleted.

The limitations need to be written about before the conclusion

We added a subsection in the main part about “Limitations of metformin use” and moved the parts from the conclusion to this new section.

334 . the 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 should have been included in the list of

studies discussed in the main body of the work, what is it, how many people,

 what dose, what endpoints?

We have relocated this paragraph to the main part and added more information about this ongoing trial.