Author's response to reviews

Title: Influence of retinopathy in the achromatic and chromatic vision of patients with type 2 diabetes

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Research article
Influence of retinopathy in the achromatic and chromatic vision of patients with type 2 diabetes
BMC Ophthalmology (Section: Neuro-ophthalmology)

Editor's Comments

1) Please use standard English, not American.
   A) Done.

2) Significant correction required.
   A) Done.

Editor's Additional request

3) Requesting for Copy-Edit. We recommend that you ask a native English speaking colleague to help you copyedit the paper. If this is not possible, you may need to use a professional language editing service. For authors who wish to have the language in their manuscript edited by a native-English speaker with scientific expertise, BioMed Central recommends Edanz (www.edanzediting.com/bmc). BioMed Central has negotiated a 10% discount to the fee charged to BioMed Central authors by Edanz. Use of an editing service is neither a requirement nor a guarantee of acceptance for publication. For more information, see our FAQ on language editing services at http://www.biomedcentral.com/authors/authorfaq/editing.
   A) We hope that the manuscript now is acceptable (in terms of language). If not, we are going to get help from Edanz.
Title: Influence of retinopathy in the achromatic and chromatic vision of patients with type 2 diabetes

Version: 2
Date: 5 April 2014
Journal: BMC Ophthalmology
Type of article: Research article


Abstract

1) (See some suggested changes to abstract)
Background: Achromatic contrast sensitivity (CS) and color vision (CV) are considered to have great predictive value in the evaluation of type 2 diabetic retinopathy. However, these two visual dimensions have seldom been investigated in the same group of patients. In the present study we measured CS and CV in a group of patients with type 2 diabetes and correlated the results with estimates of common metabolic markers for the disease. A subgroup of patients had no clinical signs of retinopathy.

Methods: The vision of twenty-seven patients (n = 50 eyes) suffering from type 2 diabetes, with retinopathy (n = 20 eyes) or without retinopathy (n = 30 eyes), were evaluated using two psychophysical tests: Farnsworth-Munsell 100 hue test (FM 100); and measurement of the luminance contrast sensitivity at 11 spatial frequencies. The results were compared with measurements obtained with an age-matched control group (n = 32) and correlated with the level of glycated hemoglobin, glycemic level, and time of disease. Any signs of retinopathy were identified during the ophthalmological examination.

Results: Contrast sensitivity and color vision impairments were present in different degrees in diabetes patients. Eyes with retinopathy yield more severe loss than eyes without retinopathy. FM 100 test was more sensitive to separate patients and controls. Color vision loss had no color axes preference. The contrast sensitivity test appears to have some advantage in differentiating patients with retinopathy from patients without retinopathy.

Conclusions: Both methods can be useful to follow the visual function of diabetic patients and should be used together to discriminate patients and controls as well as to identify early signs of retinal damage.

A) Done. We accepted all the suggestions.

Comments on manuscript

2) The study reports results for contrast sensitivity (CS) and colour vision (CV) tests in a group of patients with type 2 diabetic retinopathy. The selected patients fall into two subgroups: a. those with clear clinical signs of retinopathy, and b. those without. In addition to comparing the relative merits of CS and CV, the authors also examine the correlation with principal metabolic markers in patients with type 2 diabetes. The authors report interesting and useful findings, but the script has grammatical errors and spelling mistakes and would benefit from thorough editing.

A) Done. An English native-speaker corrected the manuscript.
3) Some of the comments are too generalised, e.g., These two procedures should be better studied to determine their specificity and sensitivity to diabetic retinopathy. One must distinguish between chromatic and achromatic mechanism and the ability to use achromatic and colour tests of CS and CV that will differ widely in sensitivity and this in turn may affect specificity in relation to detection of abnormal changes that can be linked to the earliest vision losses in diabetes.

A) Done. We inserted in the Introduction section the following sentences (Page #5, Line#108):

“These two procedures should be better studied to determine their specificity and sensitivity for diabetic retinopathy. The mechanisms that support these results of both tests should be different. For contrast sensitivity measurements, the visual response is mediated by mechanisms working in threshold levels, while for colour vision evaluation estimated using the Farnsworth-Munsell 100 hue test, there are possibly many mechanisms working in suprathreshold levels activated. So, both tests could show different or complementary neural impairment.”

4) The authors employ the Ishihara plates test to exclude congenital deficiency. How specific is the Ishihara plates test at differentiating between acquired and congenital loss of red – green colour vision?

A) Done. We corrected the sentence. We inserted the following sentence (Page #7, Line #142):

“In addition, the Ishihara plates test was applied as screening to identify subjects with some degree of red-green colour vision loss.”

5) State type of LCD monitor / manufacturer / grey levels per gun / and calibration procedure.

A) Done. We inserted in the Methods section the following sentences (Page #7, Line#152):

“All stimuli were displayed in a 21” colour LCD monitor (spatial resolution of 1280 x 1200 pixels, 75 Hz, 8 bits, Ecofit P2270 model, Samsung, Seoul, South Korea) in a dark room. A dithering routine was used to obtain additional grey levels [27]. Luminance linearization was performed by gamma-correction using a colorimeter (CS100-A, Konica Minolta, Osaka, Japan).”

6) The 100 Hue test is also simulated on a visual display. One must be more specific as to what one means by 30% colour saturation. Is the display based 100 Hue simulation equivalent to the Munsell based 100 hue test illuminated with D65? If not, the differences should be discussed briefly in relation to acquired loss.

A) Done. In resume, our computerized FM100 is equivalent to the original set illuminated by standard lightning. We re-wrote this sentence in the Methods section as follows (Page #8, Line #168):

“For the FM 100 test, the subject was positioned at a 1 m distance from the monitor. The stimulus was composed of 85 circles of different hues, saturated colors, 1° of visual angle, and 42 cd/m$^2$ of luminance. The computerized test is equivalent to the original test illuminated by D65 and was previously applied in other clinical investigations [27, 29].”

7) Also, some explanation as to how the log of the 100 hue score captures red-green and yellow-blue losses.
A) Done. We used the log-transformation only to permit the application of parametric statistical tests. We inserted the following sentence (Page# 8, Line #176):
“The log-transformation in both results of contrast sensitivity test and FM 100 hue test were used to meet the assumptions of parametric statistical tests [27].”

8) The loss of contrast sensitivity is surprisingly small when the diabetics and compared to normal subjects. The variability is also very large. This may be because of the large stimulus size employed in the test and differences in criteria when sinusoidal gratings are employed. To add value to the manuscript, it may be worth commenting on the advantages / disadvantages of using gratings and a number of different spatial frequencies (which for the patient is a long and demanding test) or letters / Landolt rings of fixed size and variable contrast (which is a more reliable and rapid test). Such a comparison is likely to be of interest to clinicians / ophthalmologists.
A) Done. We inserted the following sentences (Page#14, Line#308):
“For the investigation of luminance contrast sensitivity, we used sinusoidal gratings at several spatial frequencies as stimuli to detect the contrast threshold. Other studies with diabetic patients applied other stimuli configurations to estimate contrast threshold [25,37-40] However, the use of sinusoidal grating is important because the visual system has different channels for spatial frequency processing. It is still not clear which channels would be impaired in diabetes. Different studies showed deficits in the contrast sensitivity estimated at different ranges of spatial frequency [14, 16, 41]. The reduction of the contrast sensitivity can occur even when the visual acuity is preserved in diabetic patients [42,43].”

9) One thing that emerges clearly from the study are the difficulties and variability of the 100-hue and CS test with sinusoidal gratings. Definitely worth more in depth discussion.
A) Done. We inserted in the Discussion section a sentence about the difficulties to apply both tests as follows (Page #13, Line# 284):
“In this study we applied two commonly used visual tests to evaluate the visual functions of diabetic patients. Both tests have advantages and disadvantages that apply to diabetic patients. An important disadvantage is that both tests require long time to be finished and are very demanding tests in terms of patient’s attention and commitment. These factors may contribute to the data variability. But they have been applied in several studies and our results can be almost directly compared to previous results. Few studies had incorporated both tests and correlated their results for the same patient groups.”

10) It is also difficult to understand what is really useful in showing the differences in the ellipse plots in Fig. 3c. More discussion is needed to show the benefits.
A) Done. We inserted in the Discussion section the following sentences (Page #15, Line #357):
“The ellipses represented the area where the most of the results for each group of patients could be found. We observed an overlap area in the results two-dimensional space, which we consider as an intermediate risk area for a newly diagnosed patient. The areas without overlap between the groups can be considered to indicate high (exclusive diabetic area) or low (exclusive control area) risk to develop visual loss due to diabetes.”

11) In conclusion, the paper makes a useful contribution to our understanding of CS
and CV changes in diabetes, but the discussion is not sufficiently critical of the techniques employed and the value of the results obtained. It would be useful to acknowledge and compare other tests of CS and CV (such as the Pelli-Robson test chart, CRS and the CAD test which is also used widely in clinical work) which may yield more useful results in diabetes and are also easier to use and the results easier to interpret.

A) Done. We accepted the suggestions and we inserted in the Discussion section the following sentences (Page #14, Line #331):

“In another study, using the CAD test, it was observed that diabetic subjects exhibited equal and highly correlated reduction in red-green and blue-yellow thresholds [24]. It is not easy to compare the result from FM100 and tests such as CCT and CAD. The task in FM100 is performed at suprathreshold levels, while for CAD and CCT the final results are estimated for the threshold level. CAD and CCT investigate the functioning of cells or neuronal processing with highest sensitivity, while in FM100, it is possible that more cells or neuronal processing than those with high sensitivity are contributing to the patient’s performance.”

12) Greater criticism is also needed when examining the correlation between CS and CV losses and changes in metabolic markers. If there is little or no correlation, one should say so and attempt to account for such findings.

A) Done. We wrote about the reviewer’s suggestion made in the Discussion section as follows (Page #16, Line #371):

“There is no full agreement about the correlation between metabolic markers and psychophysical performance. Some previous studies reported some positive or negative correlations between the level of metabolic markers and psychophysical parameters [14,17,44,24], while others found no correlation between psychophysical and metabolic parameters [53]. The variability of the clinical status from patients investigated across the different studies make it more difficult to draw conclusions about the significance of these correlations. Higher values of time of diagnosis, glycated hemoglobin or fasting blood glucose indicate poor control of glucose levels and they have been associated with higher risk of vascular damage [54]. We found more significant correlations between contrast sensitivity and the metabolic markers from eyes without retinopathy. The higher the value of metabolic marker, the worse the psychophysical performance. The impairment of the glycemic control probably impairs the neuronal function by direct or indirect reasons. It is possible that in eyes with retinopathy, the correlations between the visual performance and levels of metabolic marker could be non-linear. Once the retinal damage is incurred and the visual function is lost, the glycemic control probably has little influence on the residual visual function.”

13) Level of interest: An article of importance in its field.

A) No comments.

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

A) Done.

15) Statistical review: No, the manuscript does not need to be seen by a statistician.

A) No comments.

16) Declaration of competing interests: None.
A) No comments.
Reviewer’s Report – Jonathan M. Gibson

Title: Influence of retinopathy in the achromatic and chromatic vision of patients with type 2 diabetes
Version: 2
Date: 17th June 2014

General Comments
1) The authors report a study of measuring colour vision with the FM 100 Test and Contrast Sensitivity in 27 Diabetic patients with and without retinopathy and 32 age matched controls. There is a considerable amount of existing work on colour vision in diabetes and I was not clear what this paper adds.
A) Done. We inserted a sentence in the Discussion section as follows (Page #15, Line #349):
“As the interpretation of the contrast sensitivity test and the FM100 hue test results in diabetic patients with and without retinopathy are still being debated, we correlated the results of both tests in the same group of diabetic patients and controls to evaluate how they changed together.”

and (Page #15, Line #357):

“The ellipses represented the area where the most of the results for each group of patients could be found. We observed an overlap area in the results two-dimensional space, which we consider as an intermediate risk area for a newly diagnosed patient. The areas without overlap between the groups can be considered to indicate high (exclusive diabetic area) or low (exclusive control area) risk to develop visual loss due to diabetes.”

2) Many of the references are quite old.
A) Done. We inserted new references.

Major Compulsory Revisions
3) The paper is generally rather difficult to read and the discussion is poor, with the reader left unclear as to the significance of the findings and asking "so what."
A) Done. We wrote new sentences in the Introduction and Discussion sections in order to clarify our purposes.

4) The authors fail to develop an argument regarding the relevance of their findings. For example what is the importance of psychophysical testing in diabetic patients - is it to detect those patients who might develop retinopathy later, in a pre-clinical phase ? Or does it demonstrate that diabetic retinopathy has a neurological rather than microvascular basis?
A) Done. We wrote a sentence in the Discussion section to clarify the fail pointed out by the referee as follows (Page #13, Line #290):
“We consider that our findings are important because they suggested that patients without retinopathy might develop visual function impairment even before the clinical symptoms appeared, and that contrast sensitivity and colour vision results can be used as a clinical tool to identify the status of the visual function of the newly diagnosed diabetic patient.”
5) The authors state "It has been reported that psychophysical measurements are of great value for monitoring the effects of diabetes on the visual system", but they fail to justify this statement.

A) Done. We enriched the Discussion section with many sentences in order to justify the importance of psychophysical measurements for diabetes monitoring. For example (Page #12, Line #281):

"Several studies identified visual losses of contrast sensitivity and colour vision associated with diabetes in the presence or absence of retinopathy. Visual function can be used as biomarker to indicate the diabetic status."

and (Page #13, Line#290):

"We consider that our findings are important because they suggested that patients without retinopathy might develop visual function impairment even before the clinical symptoms appeared, and that contrast sensitivity and colour vision results can be used as a clinical tool to identify the status of the visual function of the newly diagnosed diabetic patient."

Minor Essential Revisions
6) It was not clear to me in the exclusions section whether patients who had received laser were excluded from recruitment - this would be important as laser is known to affect colour vision. Also whether persons with cataracts were excluded.

A) Done. We inserted in the Methods section the following sentences (Page #7, Line #145):

"Exclusion criteria comprised visual acuity of 20/40 or worse, congenital colour blindness, history of ophthalmological disease, advanced cataracts, and/or any chronic disease not associated to diabetes that could affect the visual system. None of the patient received laser photocoagulation treatment previously."

7) The article is written in US English and may need changing to UK English - i.e. color to colour, etc…

A) Done.

8) Level of interest: An article of limited interest.

A) No comments.

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

A) Done.

10) Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

A) No comments.

11) Declaration of competing interests: I declare that I have no competing interests.

A) No comments.