Crimson Publishers
Wings to the Research

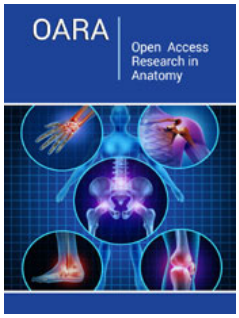
Opinion

Macular Diseases: Current and Future Needs for Outcomes Analysis

Stephen H Sinclair*

Specializes in Ophthalmology, USA

ISSN: 2577-1922



***Corresponding author:** Stephen H Sinclair, MD, Specializes in Ophthalmology, Media, Pennsylvania, United States

Submission: December 13, 2022
Published: March 08, 2023

Volume 3 - Issue 1

How to cite this article: Stephen H Sinclair*. Macular Diseases: Current and Future Needs for Outcomes Analysis. Open Acc Res Anatomy. 000551. 3(1).2023.
DOI: 10.31031/OARA.2023.03.000551

Introduction

The increasing life span of the populations worldwide along with the severe rise in the prevalence of diabetes has promoted macular disease to now become the major cause of mild, moderate, and severe vision loss, not only in the elderly (glaucoma and macular degeneration) but also in the working age group (diabetic retinopathy). This has demanded significant change in the implementation of programs to screen for retinal disease as well as to monitor the progression that will determine when to intervene as well as the chronologic efficacy of the promoted interventions. Until just recently the methods used to define and monitor the progressive retinal disease process have been primarily via fundus examination through a dilated pupil (or fundus color photography through an un-dilated pupil) together with functional evaluation by chart acuity (or contrast sensitivity) and Humphrey photopic, spot contrast perimetry. However, it is now well recognized that these fail to detect the diseases early in the course or to adequately define progression until moderately late in the disease process when there is significant functional vision loss due to multiple level and wide-spread retinal neuronal apoptotic injury, death and atrophy. It must be remembered that all three diseases are focal in their onset and progression, most often initially involving the parafoveal retinal structures, thereby creating para-fixation defects in the field of functional vision. Screening for structural abnormalities, usually performed by fundus examination or color fundus photography, detects the disease only when there is sufficient color defined atrophy or with the occurrence of secondary lesions (e.g., microaneurysms, hemorrhages, IRMA or NV) that are currently the focus of AI image evaluation and disease staging. In addition, images acquired over time are not registered for overlay to define progression of local abnormalities. Because of this, the interventions have been primarily oriented toward the later detected stages, and clinical trials, while demonstrating a slowing of the disease progression, demonstrate minimal improvement in function. For e.g., in multiple studies of diabetic retinopathy, only 25-34% demonstrate improvement of ≥3 ETDRS lines visual acuity, and primarily only among the eyes with severe retinopathy and poor initial vision, and with 23% considered non-responders and 27% having only a “moderate” response. Even when OCT is performed to define the neuronal injury, the process is detected only when there is sufficient neuronal layer atrophy occurring over a sufficient area that the disease injury can be identified, or progression defined. The use of charts to define foveal function is not reliable as the patient moves fixation to overlay the best functioning retinal area over the chart letters, and most commonly testing is done under photopic conditions, whereas repeated studies have shown that vision tasks performed under mesopic conditions with lowered contrast decline first and most severely. Furthermore, chart measurements have been repeatedly shown to fail to correlate with real world visual task management that requires integration of the central visual field perceived elements and motion (e.g., reading, driving, catching or hitting a ball, recognizing faces) [1-3]. For example, reading speed and comprehension are severely reduced with right visual field defects (in the western world), even with good chart acuity, because

of the failure to integrate letter and word form and to manage saccades. Unfortunately, Humphrey visual fields, which measure only threshold sensitivity for contrasted spot detection, do not detect paraxial defects of identified structures with presentations mimicking real world fixation times and with poor management of monocular or binocular fixation. Rarely are they performed under mesopic luminance conditions and with adequate density in the central (macular) field of view.

Desperately needed are new measurements of the neurovascular elements that can identify earlier injury from these focal, progressive disease processes and which can be provided in a routine screening mode in the clinic and can be quantitated to define position, severity and area of structure involvement. Furthermore, these must be overlaid to define the focal effect upon visual function as measured by monocular as well as binocular resolution visual fields that are presented under conditions of contrast and luminance as well as with fixation times that mimic real world tasks. Methods to perform such measurements are on the near horizon and must be clinically integrated into routine ocular screening and monitoring, especially in the arena of treatment evaluation and promotion. Injury to individual neurons that result in apoptosis can now be imaged by fluorescent cell surface tagging at a potentially reversible stage instead of following cell death and structure atrophy as now defined by OCT retinal layer analysis. Bis,zinc-dipicolylamine, currently administered intra-venous, has been demonstrated to pass the blood retinal barrier and stain individual neurons undergoing apoptosis [4]. It is currently undergoing confirmation studies in animals mimicking human retinal structure and is scheduled to begin human trials via a potential nasal spray delivery and with an imaging capability to define fluorescent cells within individual retinal layers (e.g., the transsleral optical phase imaging camera [5,6]. Evaluations of neuroretinal spectral absorption properties on multispectral imaging also are showing relationships visual field abnormalities in glaucoma eyes [7] and in incase studies of early atrophic AMD [Sinclair, Luttrull], AI Spectral Imaging]. Evaluation of alterations of the internal retinal microvasculature, obtained through OCTangio imaging, has been limited by the scan time of current scanners reducing the outcomes to detections only of the microvasculature, interpreted as the microvascular density in the perifovea, hence indicating flow obstruction (or enlargement overall area of the foveal avascular zone). Improvements in the speed of image acquisition (now to less than 100 microseconds) has improved the evaluation of flow characteristics, and with sufficient resolution that now with luminal chip analysis the microvasculature can analyzed to define focal irregularities of lumen diameter (indicating endothelial and pericyte early injury), tortuosity, vessel branching angles, occlusion, and modes of stimulated revascularization versus neovascularization. With repeated measurements, these evaluations of the focal neurovascular structures will allow chronologic evaluations of the progressive injury or improvement with treatment.

Improvements in central field vision testing are now acquired with resolution visual fields performed under luminance and contrast conditions mimicking common photopic and mesopic tasks and with presentations mimicking fixation times. The fields provide adequate density analysis within the central 20 0 diameter field and now with adequate fixation control (when conducted in a head-mounted goggle device), it can potentially be aligned with the structural imaging described above to define the relations of the pathology to the localized visual dysfunction (micro-perimetry is not possible because of the reduced illumination levels prevent adequate imaging). Finally, these results must then be compared with outcome real world functional measures derived from the sub-group analysis of visual function questionnaires relating tasks performed under similar luminance and target conditions, not the overall summary score as is now performed with questionnaires such as the NEI VFQs 14-24 or the Functional Vision Questionnaire, or with measurements of actual task performance under such conditions, (e.g., reading speed, driving simulation, etc). It is our belief that only with such systems made available for routine screening and monitoring that such prevalent macular diseases can be detected, and intervention periods assigned to treat sufficiently early that excellent functional vision is maintained. However, for multiple reasons, patients may miss such potential evaluations and present at later stages, requiring that interventions though out the disease course must be adequately evaluated and rehabilitation methods, improved with a better understanding of the functional deficits, applied [8]. As recently documented in a severe criticism of the current failures of pharmaceutical companies to adequately report the outcomes of trials [9], not only must we define earlier interventions, but adequately monitor the risks along with the benefits, as well as patient perceptions toward adherence when treatments are applied at all stages of the disease process. Furthermore, it must be remembered that in systemic diseases, such as diabetes, the retina neurovascular abnormalities mirror similar processes progressing in other organs, such as the brain cortex (diabetes now representing a major cause of small vessel, non-Alzheimer's dementia), peripheral nerves and small vessel disease in the myocardium. As such, the retina offers the optimal opportunity as an outcome measure for clinical trial design of systemic chemotherapy [10,11].

References

1. Conlin L (2022) The ball is quicker than the eye-Bipolar cell detection and ganglion cell transmission of object motion.
2. Slakter JS, Stur M (2005) Quality of life in patients with age-related macular degeneration: Impact of the condition and benefits of treatment. Surv Ophthalmol 50(3): 263-73.
3. West S, Rubin G, Broman A, Munoz B, Bandeen RK, et al. (2002) How does visual impairment affect performance on tasks of everyday life? Arch Ophthalmol 120: 774-780.
4. Jacky MK, Celia H, Reshil TD, Richard W Yee, Brian D Gray, et al. (2014) Bis (zinc-dipicolylamine), Zn-DPA, a new marker for apoptosis. Invest Ophthal Vis Sci 55: 4913-4921.

5. Dos Santos F, Laforest T, Künzi M, Kowalczuk L, Behar C, et al. (2021) Fully automated detection, segmentation, and analysis of in vivo RPE single cells. Eye 35(5): 1473-1481.

6. Laforest T, Künzi M, Kowalczuk L, Carpentras D, Behar C, et al. (2020) Transscleral optical phase imaging of the human retina. Nature Photonics 14: 439-445.

7. Denniss J, Schiessl I, Nourrit V, Fenerty C, Gautam R, et al. (2011) Relationships between visual field sensitivity and spectral absorption properties of the neuroretinal rim in glaucoma by multispectral imaging. Invest Ophthalmol vis Sci 52(12): 8732-8738.

8. Isaksson J, Jansson T, Nilsson J (2020) Desire of use: A hierarchical decomposition of activities and its application on mobility of by blind and low-vision individuals. IEEE Transactions on Neural Systems and Rehabilitation Engineering 28(5):

9. Rofagha S (2022) Minimizing risks to patients by improving presentation of clinical trial results in geographic atrophy trials. Ophthalmology Retina 6(5): 337-338.

10. Akuffo KO, Nolan J M, Peto T, Stack J, Leung I, et al. (2016) Relationship between macular pigment and visual function in subjects with early age-related macular degeneration. Br J Ophthalmol 101(2): 190-197.

11. Bansback N, Czoski M, Carlton J, Lewis G, Hughes L, et al. (2007) Determinants of health related quality of life and health state utility in patients with age related macular degeneration: The association of contrast sensitivity and visual acuity. Qual Life Res 16: 533-543.