Research Article

Review in Type 1 Diabetes Mellitus

Wagiha H. Massoud, Hossam El-Deen M. Moharrm, Mohamed A. Ali and Sondos M. Ali Mohamed Salah Eldeen
Department of Ophthalmology, El-Minia Faculty of Medicine

Introduction

Retinal photoreceptors are cones and rods. Cones are responsible for color vision and best function relatively in bright light. They allow the perception of color, perceive fine details and more rapid changes in images. Cone cells are densely packed in the fovea centralis, their number six to seven million. (Valberg, 2007)

Cones are three types, namely: S-cones, M-cones and L-cones. Each cone is therefore sensitive to visible wavelength of light that correspond to short-wavelength, medium-wavelength and long-wavelength light.(Labin et al., 2014)

S-cones represent a minority of the cone photoreceptors in the human retina about 10% of cones. They are more vulnerable to damage by certain retinal disease than L and M-cones. (Hunt & Peichl, 2014)

The eye is one of the body organs affected in diabetes mellitus. More than 90% of patients with type 1 diabetes of 15 years and longer duration show features of retinopathy. (Keech et al., 2007)

Electroretinography measures the electrical responses of various cell types in the retina, including the photoreceptors (rods and cones), inner retinal cells (bipolar and amacrine cells), and the ganglion cells. It is used for the diagnosis of various retinal diseases and extensively used in eye research, as it provides information about retinal function.(Marmor et al., 2004)

Optical coherence tomography angiography (OCTA) is a non- invasive technique allows visualization of retinal and choroidal vasculature via motion contrast imaging. This relatively new imaging technique maps erythrocyte movement over time by comparing sequential OCT B-scans at a given cross section.(De Carlo et al., 2015)

Aim of the work

The aim of this study is a trial to detect early parameters in S-cone response and OCTA predicting retinopathic changes in diabetic patients type-1.

Anatomy of Macula

Macula is a round area at the posterior pole of the eye, lying inside the temporal vascular arcades. It measures between 5 and 6 mm in diameter, and sub serves the central 15–20° of the visual field (figure 1). Histologically, it shows 2-3 layers of ganglion cells, in contrast to the single ganglion cell layer of the peripheral retina. The inner layers of the macula contain the yellow xanthophyll carotenoid pigments lutein and zeaxanthin in far higher concentrations than the peripheral retina (hence the full name 'macula lutea' – yellow plaque) (Bowling, 2015).

Branch retinal arteries lack an internal elastic lamina. They are about 200 μm in diameter and in the peripheral retina they bifurcate to third and fourth orders and finally to pre-capillary arterioles that lack a pre-capillary sphincter. However, this arrangement is altered in the central retina where small pre-capillary arterioles emerge abruptly from the larger radial arteries. These vessels merge into highly complex capillary networks consisting of two to four plexi. (Archer et al., 2007).

Pathophysiology of diabetic retinopathy

Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) clinical trials confirmed the strong relationship between

chronic hyperglycemia and the development and progression of diabetic retinopathy, but the underlying mechanism that leads to the development of microvascular damage as a result of hyperglycemia remains unclear.
A number of interconnecting biochemical pathways have been proposed as potential links between hyperglycemia and diabetic retinopathy. these include increased polyol pathway flux, activation of diacylglycerol- (DAG-)PKC pathway, increased expression of growth factors such as vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1), hemodynamic changes, accelerated formation of advanced glycation end products (AGEs), oxidative stress, activation of the renin-angiotensin-aldosterone system (RAAS), and subclinical inflammation and leukostasis (Tarr et al., 2013).

Optical coherence tomography angiography
Optical coherence tomographic angiography (OCTA) is a recently developed imaging modality that can facilitate noninvasive study of retinal and choroidal vasculature in details. It differentiate the retinal vasculature in both normal eyes and various retinal vascular pathologies (Jia et al., 2012).

It compares the variation between consecutive B scans that reveals the motion of erythrocyte. Due to its high resolution, retinal microvasculature can be displayed on separate layers and quantitative metrics can be achieved by automated image analysis (Lei et al., 2018).

These techniques aim to contrast blood vessels from static tissue by assessing the change in the OCT signal caused by flowing blood cells. These intrinsic contrasts can be broadly classified as Doppler shift and speckle variance/decorrelation. (Gao et al., 2016)

Diabetic Retinopathy in OCT Angiography
Diabetic Patients without Retinopathy:
The Avascular Zone
In diabetic patients, even in the absence of retinopathy, angio-OCT shows that the avascular foveal area is larger than in healthy individuals. A sharp macular capillary network is suggestive of an incipient retinopathy because, even before the onset of diabetic retinopathy, as there are changes in the macular capillary network. The size of some capillaries increases, some are thicker while others are closed and thus we see a looser network with larger and sparser meshes (Lumbroso et al., 2015).

There is an increase in the size of the foveal avascular area that normally is about 500 microns large. This is an early sign that appears before the onset of the micro-aneurysms and at this stage the condition is still reversible. As retinopathy evolves, the capillary network of the macula becomes increasingly evident and more marked alterations will appear such as mild congestion of capillaries and some dilation. The presence of small non-perfused areas at the posterior pole will lead to the occlusion of small branches; the network becomes at first more irregular, and later, the small areas of ischemia will grow and then merge with the central enlarged avascular area (figure 6) (Lumbroso et al., 2015).

One of the major factors affecting FAZ measurements is segmentation of the FAZ boundary. Numerous methods for quantifying pathologic changes of the FAZ on OCTA have been proposed some involve measuring the ischemic area, such as FAZ diameter and total area, and others quantify the irregularity of the FAZ shape, such as axis ratio. FAZ enlargement in DR is an asymmetric process and therefore assessing both size and shape is likely important for the detection of pathologic change (Lu et al., 2018)

Background Diabetic Retinopathy:
In patients with background retinopathy, capillary non perfusion areas, similar to the non-perfused areas, highlighted by fluorangiography, are evident. Angio-OCT shows a larger number of capillary loops and arteriovenous anastomoses. At the level of the deep capillary vascular plexus, the capillary drop out is more evident. Changes in size, in flow and in the morphology of the plexus are evident. Often the scarce capillaries have the shape of a fan. The connections between superficial and deep vascular network are very evident; these are not seen on the fluorangiography. Angio-OCT offers a much better view of shunts, deep connections and vascular loops. The deep new vessels are more clearly seen than with angiography (Lumbroso et al., 2015).

Rare retinal hemorrhages are visible as masked areas but they are less evident than they appear in fluorangiography. Angio-OCT does not show up all the micro-aneurysms: those that are evident are generally the larger micro-aneurysms where there is probably residual blood flow (Lumbroso et al., 2015)

Advanced Diabetic Retinopathy and Retinal Ischemia

The areas of retinal ischemia, examined with angio-OCT are much sharper than as with fluorangiography because there is no masking effect by dye leakage. Details are appreciated that cannot be seen with fluorangiography because hidden by the dye in the intermediate and later stages of the examination (Lumbroso et al., 2015).

Ischemic areas show sparse capillaries evident against a grey background. Often the capillaries inside the non-perfusion areas are truncated, with abrupt interruptions, or with shunts. Connections with the deep network are well seen. In angio-OCT the ischemic areas can be easily identified on the basis of texture and of flow alterations. Initial neo-vascularization are seen as thickened and irregular vessels that may emerge from the surface of the retina or from the optic disc (Lumbroso et al., 2015).

Proliferative Diabetic Retinopathy

The natural evolution of ischemic area in diabetic retinopathy, or in ischemic venous occlusions, is characterized by the progressive formation of new vessels, preceded by the establishment of capillary shunts, that are clearly visible in fluorangiography immediately after the ischemia appears. With fluorangio-graphy however, it is not possible to appreciate the level of these alterations, but only the two-dimensional course, the veins dilatation and the diffusion of the newly formed capillaries (figure 7) (Lumbroso et al., 2015).

In diabetic retinopathy, chronic ischemia leads to proliferative diabetic retinopathy with pre-retinal and pre-papillary neovascular membranes. In fluorangiography, there is a very intense dye leakage that does not allow to see the neovascularization (Lumbroso et al., 2015).

Angio-OCT of pre-retinal and pre-papillary neovascular membranes allows the operator to make a very precise evaluation of the extent and morphology of the network without the problems linked to dye leakage. Flow and morphology of the neovascular network are visible. Angio OCT can be performed during pregnancy and allows to follow evolution after laser pan retinal photocoagulation (Lumbroso et al., 2015)

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