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Review Article

QUANTIFYING THE CHOROID BY ADVANCED OCT, A PROGNOSTIC TOOL FOR DIABETIC EYE DISEASE

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A B S T R A C T

Diabetic retinopathy (DR), the leading cause of visual disability in diabetics in India and the world, is an important complication of diabetes mellitus (DM). Beside the retinal ascular malfunction diabetes can lead to multifaceted damage to whole of ocular tissue. Choroid needs a crucial assessment in this regard to elucidate the paradigm of functions and pathophysiology that have occurred from chronic diabetic changes. Although we are concerned about the Diabetic Macular Edema (DME) because it is directly linked with functional visual outcome. Beside retina, Recent researches have significantly influenced our understandings on co are the modern imaging tools such as the optical coherence tomography (OCT) and its advanced modalities like Enhanced Depth Imaging(EDI) emphasised on better imaging of choroid and it is established that choroid is more vulnerable in diabetics and prone to damage before any retinal disorder like DME develops. The review highlights the choroidal microanatomy and its relates its thickness proportional to its function. It also revitalizes the understandings of diabetic changes that take place in retina choroidal interphase to bring forth the ultimate fate of irreversible damage to choroid.

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INTRODUCTION

Diabetes mellitus remain the most familiar metabolic disorder of medical science in today's world. The background and exact etiology or inception could not be pointed out or a matter of debate. The ominous hyperglycaemia, which is the basic biochemical alteration of human circulation keeps a physician in a combat to salvage his vital organs. When sets in at an early age diabetes is labelled as genetic in origin or better known as a type 1 DM (from extensive genetic and pathologic research it is found to be insulin dependent. Origin is also postulated to be multifactorial or heterogeneous. But from the high prevalence rate the non-insulin dependent DM (type 2) is established as a major cause of health ailments. it is estimated that 387 million people is suffering from diabetic illness in today's world, if unattended this toll could rise to 592 million. By 2035[1].

India has become the "Diabetic Capital" of the world, because of its huge population has under controlled hyperglycaemia. World health organization (WHO) has estimated the impact by a joint collaborative study with all India ophthalmological society (AIOS) in 2014. It shows there is a direct relationship between duration of DM with the functional outcome.

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When visual acuity is 6/18 put in a threshold it was found 42.11% cases have acuity poorer that the threshold. The age group of 61-70 are predominantly vulnerable to the diabetic eye complications. [2]. Apart from that we have to also ponder on the data which showed prevalence of diabetic eye diseases is ≥ 25% in eastern India.[3].

Under this circumstance it's a major onus lies on the ophthalmologists to conquer the avoidable blindness and save the precious vision. To save the already diseased eye from chronic damage resulted from diabetic changes its imperative to ascertain the eye by a thorough evaluation. Because diabetes can involve all tissues from an avascular lens to the highly vascular choroid. The necessity of a healthy choroid is unarguably established and its contribution in optimum visual functioning is noteworthy. The article tries to highlight the role of assessment of choroid or specifically its functional capacity in terms of SD-OCT based thickness estimation. Chronic diabetes can lead to thinned out choroid which eventually put the inner retinal layers at risk. Enhanced Depth Imaging (EDI OCT) is a fast, efficient, non-invasive tool estimating the sub retinal microanatomy and as certain the alterations in both proliferative and non-proliferative cases.

Choroid: Its anatomy and physiology

The human eye is a highly sophisticated structure which constitutes some innate distinguished property pertains to its

contribution in visual and higher functions. Various disease process can lead to myriad pathophysiological changes. The choroid is not an exception. It is lying in between the avascular sclera and highly sensitive retina. The central thickness is 0.22 mm and 0.10 mm peripherally. The vascular coat is a multi-layeredstriated settlement and it has specific functions for every stratum.beside the vessels choroid also houses cells like – lymphocytes, plasma cells, fibroblasts. But the importance of melanin containing cells or melanocytes remain unarguably superior. Although the stroma and nerves are not histologically well delineated even by electron microscopic findings. But grossly the layers are understood like- (IMAGE 1)

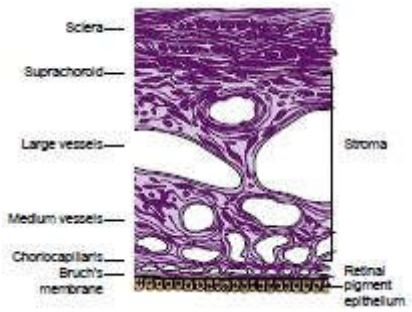

Image 1 basic anatomy of Choroid, a cross sectional view showing the elementary layers of an adult eye

1. **Suprachoroidal lamina:** it contains dense collagenous fibres, melanocytes, fibroblasts, it is a potential space in which the posterior ciliary vessels and nerves can be found.
2. **Stroma of choroid-** made up of loose collagenous tissue with constellation of numerous pigment cells, macrophages, plasma cells, the stroma is the area of major bulk of large vessels, like. -outer layer is called "Haller's layer" and inner layer is called "Sattler's layer".
3. **Choriocapilleris-** it's a layer of fenestrated array of capillaries originating from larger vessels. These are of small calibre with endothelial lined inner surface. Endothelial cells are connected by zonule occudentes. These vessels contain pericytes over the basement membrane. The finer branch of these capillaries serve nutrition to the specific lobules of stroma, and important to note that these are not freely anastomotic vessels.
4. **Bruch's membrane-** a multilayer membrane lying in between RPE and choroid.it is the barrier or gateway of nutrients to be transferred into the deeper retina.

The major arterial supply of choroid derived from the ciliary artery system, or specifically posterior ciliary artery, which has got the following peculiarities (IMAGE 2).

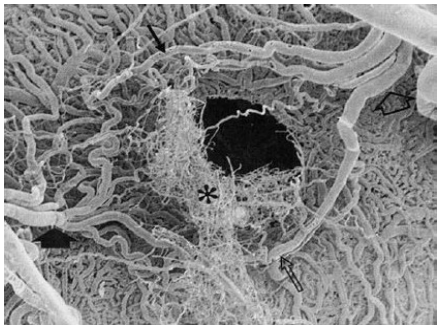

Image 2 scanning laser microphotograph showing circle of Haller and Zinn formed by the branches of lateral paraoptic branch of Posterior ciliary artery(PCA, empty arrowhead) and a medial paraoptic PCA(black arrowhead) forming a superior and inferior anastomotic arterial arcade. Retro laminer capillary plexus (*) arising from this arcade.

1. 2-3 branches originate from the main trunk and they supply in both nasal and temporal aspect of the hemisphere of the choroid.
2. The subsequent divisions give rise to 10 -20 sub branches which are called short PCA. These enter into the posterior pole and assume a preoptic and perivascular pattern before branching peripherally in aradial manner for each lobule.
3. The sole blood supply of and around optic nerve head (ONH) and foveal zone are dependent on choroidal system. Branches from PCA run towards nasal and temporal side of the ONH to make an ellipsoidal anastomotic circle [4,5], which is called circle of Haller and Zinn. So the optic nerve is equally vulnerable to the ischemic condition and chronic vascular insufficiency apart from glaucomatous damage. Similarly perimacular pattern of choroidal branches are of utmost importance because the PCA follow an oblique course in sclera to reach the virtual suprachoroidal space and give recurrent branches to the macula and up to the anterior choroid beyond Ora serrata.

Peculiarities that distinguishes the choroidal vesicular network

- Bruch's and RPE interrelation and highly orchestrated microanatomy contribute a crucial interplay developing a healthy passage of gases and micronutrients by a complex physiological system. Bruch's membrane is considered a fibrocollagenous sheet though which the finest intercapillarypiller blood channels provide nutrition to the RPE layer. [6]
- The short PCAs which are distributed in a spiral shaped configuration is consistent with the vascular pattern of arterial phase of ICG. This distribution differs from other branches of choroidal vessels which expand in a 'V' pattern [7]. Thus the spiral pattern turns ominous in ischemic insult (IMAGE 3).

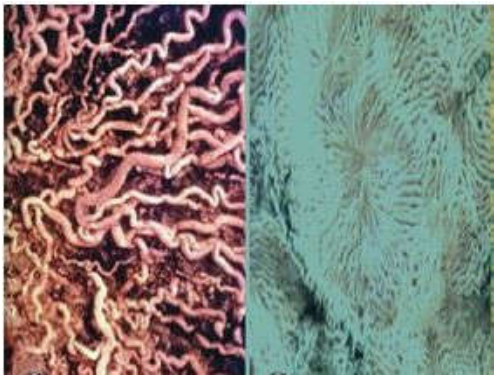

Image 3 V shapped branches of PCA (left) and subfoveal capillary lobules (Right)

- In vivo studies have shown that there is no lobular segmental distribution without any functional anastomosis between them. So these behave like 'end arteries' [7]. Lobules in the equatorial part of the choriocapillaris are larger (200 μm) than those located both at the posterior pole (100 μm), and in the submacular area (30–50 μ) [8]. The borderline area in between the corresponding territories is indeed a 'watershed area'and vulnerable to vascular insufficiency. CNVM arise from this watershed area in about 88% cases [9]

- Interdigitation between the choriocapillaris and venules are present in humans. [10] subfoveal venous network is torturous and denser becomes less dense with increasing distance from the macula and the vessels become straighter, losing the tortuous aspect.

Diabetic retinopathy defeats choroid, ruins retina

From the earlier researches it found that beside retina choroid is equally at-risk of diabetes related vascular insufficiency. As choroid has autonomic innervation and retina lacks it, nevertheless vascular modification (like dilating vessels when inflammatory mediators narrow the calibre) saves choroid to a certain extent but not the inner retinal layers. But as retinal and choroidal vessels share intrinsic structural similarity (pericytes,) that make the retinal vessels already jeopardised. The idea behind this review is to identify the choroidal damage early.

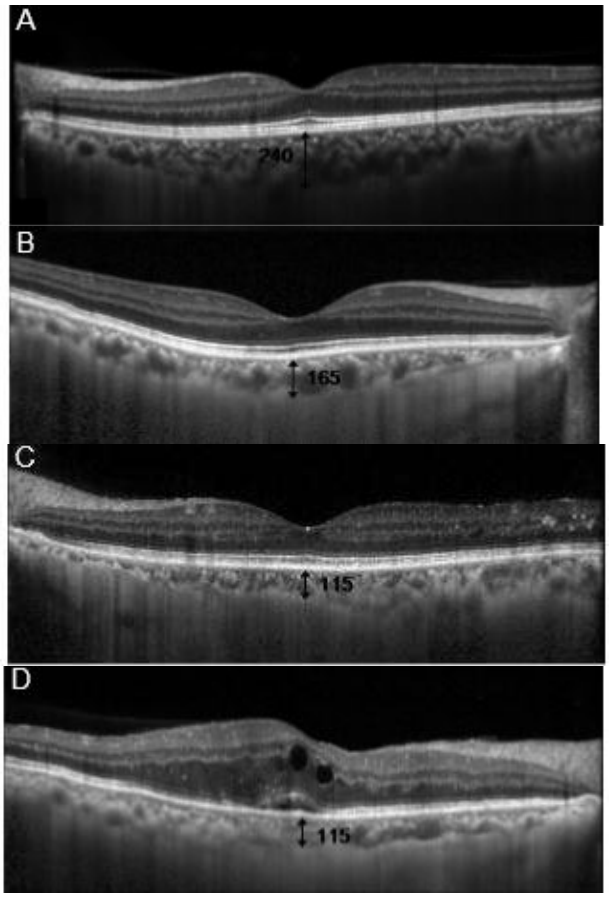

Image 4 (A,B, C, D)- showing Sequence of enhanced depth imaging OCT(EDI OCT) images of normal subfoveal choroid thickness (A) and moderate (B) to severe NPDR(C) and finally prolferative DR (D). establishing the evidence of decreases trend of choroidal thickness in progressive diabetes.

Diabetic retinopathy shows many of the characteristics of an inflammatory disease Diabetic retinal vascular leakage, capillary nonperfusion, and endothelial cell damage are caused, in part, by retinal leukocyte stasis in early experimental diabetes. While vasoproliferation was once considered to be mainly a consequence of ischemia, current evidence also supports a contribution of inflammatory mechanisms. Both clinical and preclinical studies have associated the development of DR with elevated ocular levels of inflammatory mediators. McLeod *et al*. [11] reported that levels of intercellular adhesion molecule-1 (ICAM-1) animportant adhesive molecule for circulating leukocytes, were elevated throughout the vasculature of diabetic patients. These patients also showed elevated vitreouslevels of vascular endothelial growth factor (VEGF) [12], which upregulates ICAM-1expression [13]. In a high velocity flow system like choroid leucocyte activation and adhesion prove fatal because-

- Leukocytes mediate retinal vascular remodelling during development and vaso-obliteration in disease.
- VEGF and leukocyte invasion are important factorsinregulatingbothischemia-mediatedocular neovascularization and vascular damage in DR.

A series of investigations into the mechanisms underlying vascular damage in diabetes have suggested that an inflammatory process, similar to that which mediates vascular pruning, contributes to breakdown of the Blood Retinal Barrier (BRB), with both VEGF and inflammatory leukocytes again exerting important influences [14]. It is imperative to note that adequate oxygen penetration into outer retina is sole responsibility of choroid, of which the nerve endings are equally prone from hyperglycaemic damage. Beside apoptotic mechanism oxygen deficiency continues and that results in choroidal remodelling. Beside hypoxia high O2 tissue levels would result in reactive oxygen species (ROS) generation and cellular damage. Therefore, an optimal O2 concentration is needed to avoid hypoxia or ROS mediated cellular injury. The retinal tissue is very active metabolically and, therefore, exquisitely dependent on adequate O2 supply for its nutrition. [15].

EDI OCT- the new frontier in choroidal imaging

EDI‑OCT is a non-invasive imaging technique that provides important information of posterior segment of eye with greater and finer details. Allows for high‑resolution imaging of the ocular fundus with approximate axial resolution of 3–4 microns. [16,17]. It enhances details of the choroid by displacing the zero delay line, which is the point of maximal OCT signal sensitivity [18]. For a conventional OCT the zero delay line is positioned at the posterior vitreous level to provide a clear image of vitreoretinal structures. By using EDI modality, the zero delay line is displaced deeper in the tissue to provide choroidal images with greater resolution. [19] Image averaging, eye tracking, high‑speed scanning, and low speckle noise result in an enhanced visualization of the choroidal morphology and enables reproducible quantitative measurement. Recent publications have described choroidal tumour imaging with EDI‑OCT, particularly of choroidal pathology due to its higher degree of penetration into deeper tissue. However, because a layer-by-layer architecture is not distinct, the main structures measured in the OCT images have been the overall choroidal thickness, choroidal area and the shape of the chorioscleral border [20]. The frequently used machines are Swept source optical coherence tomography (SS-OCT) and spectral domain OCT, the former is better in choroidal imaging because it employs narrow width infrared light that enables the measurement of interference at different optical frequencies or wavelengths sequentially over time.[21]. Over 30000 axial scans can be acquired in a second thus deeper penetration even up to scleral tissue yielding higher resolution image of choroid.

Assessment of individual risk

It is noteworthy from epidemiological point of view that India is suffering a huge burden of diabetic illness, which constitutes diabetic eye diseases a handsome share. A nationwide survey conducted by AIOS in 2014-15 on the prevalence of DR in India, reinforces the impact of the dreadful cause of avoidable blindness. It showed that the information put government to act promptly by increasing awareness and raising funds to strengthen eye health care set up for early diagnosis and monitoring DR cases.

The project is unarguably laudable but it is more imperative to think of the tissue which get involved with retina but escape indirect ophthalmoscopy or 90D fundus examination. Choroid thus being already endangered but get unnoticed though its involvement occurs prior to retinal changes [22]. It was known from previous studies that age and axial length have directly related to choroidal thickness. Duration and glycaemic control over diabetes is proven to be a controlling factor for choroidalhealth, Hyo Kyung Lee *et al* [23] showed that the central sub fovealchoroid is thinner when eyes show diabetic changes on the retina.However, they did not point the presence of diabetic macular oedema or severe proliferative changes pertaining to the choroidal thinning. Age of the individual is a decisive factor for the cumulative impact of the disease (IMAGE 4). McCourt *et al*. [24] that choroidal thinning in diabetic retinopathy was not significant after adjusting for age.

The retina which became vulnerable is being damaged by a double edged sword. Primary attack develops from the nutritional dearth. As the outer retina is solely dependent on choroid and specifically the perifoveal avascular zone which receives necessary nutrition from choroid considerably gets affected. Secondarily the retinal vessels which are distributed mainly distinct layers setting up capillary networks already start vascular changes owing to retinal hypoxia. Furthermore, choroidal thinning could explain the increased susceptibility to retinal hypoxia and ischemia in diabetics [25]. It was reported that choroidal blood flow in diabetes patients can be measured with laser Doppler flowmetry and indocyanine green angiography [26-28]. Both of which invasive and require advancement of damage to be identified. And surprisingly the choroidal damage is irreversible. Laser, the gold standard of treatment in DME or retinopathy cases induces its benefit by local tissue reaction in RPE level, if the choroid is compromised it is onerous to provide nutrition to ill retina and minimises the effect of efficient laser therapy. As the diabetic eye care is cumbersome issue if disease sets in beside strict control over glycaemic level, blood pressure and lipid level the management protocol is on a paradigm shift. The American Society of Retina Specialists, a large conglomeration of retina specialists both from and outside the USA, has been conducting a pattern and trend (PAT) survey on current vitreoretinal disease management issues among its members for several years. It standardised the therapeutic approaches keeping in mind the retinal microstructural jeopardy in DR and preventing farther damage by extremely population based meta-analysis and it emphasised on intravitreal VEGF rather than laser in variety of DME both centreinvolved or not. It is also analysed from PAT survey that in India OCT is the commonly performed investigation (89.71%) to establish macular and choroidal pathology and this trend is helpful to diagnose choroidal illness early and decrease the treatment cost.

A study of patients with no diabetic change by Langham ME *et al* [29]. observed decreased choroidal blood flow as the result of diabetic retinopathy We posit, therefore, that earlier choroidal circulation alteration could induce choroidal thinning at a later stage. Variability of susceptibility to choroidal circulation, in fact, might explain the above-noted different result of Esmaeelpour *et al* [30] who showed increased subfoveal choroidal thickness after an episode of PRP and also postulated the regulatory homeostatic mechanism of recirculation of choroidal blood from periphery to centre. It is presumed that age could have influenced the inconsistency observed between the two studies, particularly as older age is a demonstrated important factor related to choroidal atrophy.

Assessment of individual risk is incomplete without emphasising on the blood pressure and Intraocular pressure of an individual. As we aware of that diabetic retino choroidal interphase is susceptible to metabolicassault, like blood glucose, blood gases and pH, visual stimulation and vasoactive agents including angiotensin II and nitric oxide.[31], Usui *et al*[32] reported a significant negative correlation between the choroidal thickness and Systolic Blood Pressure(SBP) during the diurnal variations in these two parameters. , Li *et al*[33] reported that they found no significant correlation between the SBP or DBP and the choroidal thickness.

Changes in the IOP could also influence the choroidal parameters. But recently a report showed that the diurnal variation of the IOP and choroidal thickness were out of phase, [34]. Even the consistent elevated IOP hardly effects on choroidal health.

CONCLUSION

We can conclude that diabetic eye diseases are a silent thief of vision, and it needs regular monitoring and periodic follow up to identify and delineate minute and finer pathologic changes. OCT remain the gold standard for diagnosis of diabetic retinal micro jeopardy but evidence base knowledge on different tissues like choroid are also of prime importance because of their irreversibility of damage. This review has emphasised on the ailing choroid from chronic diabetic illness, and also the importance of early investigation the particular tissue for its normal functioning health and outer blood retinal barrier. EDI OCT is the latest imaging modality to be employed and thus vision is salvageable in a diabetic eye in an early stage obviating the further expensive therapy and resultant morbidity.

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