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Retinal imaging; Optical Coherence Tomography Angiography (OCTA) and Fundus Fluorescein Angiography (FFA) in diabetic macular edema, Review

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Abstract

Diabetic retinopathy (DR) is one of the major microvascular complications of diabetes mellitus. The most common causes of vision loss in diabetic retinopathy are diabetic macular edema (DME) and proliferative diabetic retinopathy. Recent developments in ocular imaging have played a significant role in early diagnosis and management of these complications. Fluorescein Angiography (FA) was a gold standard imaging modality and it requires venipuncture. Anaphylaxis and death related to contrast injections was rare and have been reported. OCT angiography (OCTA) used for 3D mapping at microcirculation level by which retinal and choroidal structures via motion contrast imaging and high-speed scanning is detected This article give insight on various studies that summarizes the utility OCT angiography and FA as a diagnostic tool in DR and DME.

Keywords: DR, DME, FA, OCTA, Minia.

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1. Introduction

Diabetes is a chronic metabolic disease and a major public health problem worldwide. According to the World Health Organization (WHO) report, the prevalence of diabetes has risen dramatically over the past three decades. An estimated 108 million people were affected with diabetes in 1980, and this figure rose to 422 million in 2014; diabetes was also a leading cause of death, with 1.5 million deaths directly attributed to diabetes in 2019 (In addition to mortality, the morbidity associated with diabetes is staggering. Diabetes leads to significant injury to vessels and nerve cells throughout the body, including the eye, where the most common vision-threatening manifestations are in the retina, known as diabetic retinopathy (DR). DR was reported to be the fifth most frequent cause of global blindness (0.8 million cases) in 2020 [1]. The chronic hyperglycemia of diabetes mellitus is associated with end organ damage, dysfunction, and failure, including the retina, kidney, nervous system, heart, and blood vessels. The International Diabetes Federation (IDF) estimated an overall prevalence of diabetes mellitus to be 366 million in 2011 and predicted a rise to 552 million by 2030 [2]. Blindness is one of the major consequences of Diabetic retinopathy (DR) in the middle-aged population [3]. Diabetic retinopathy has been described as occurring due to microvascular injury of the retinal capillaries; however, there is accumulating evidence that retinal neuronal dysfunction may be present much before vascular changes are seen [4]. Diabetic macular oedema (DME) is an ocular manifestation of disease-causing visual deterioration. The prevalence of visual impairment due to DME is estimated to be 5.4% in Europe [5]. Cystoid macular oedema (CMO) is defined as a macular thickening and cystic change due to the accumulation of fluid. It could be asymptomatic and only diagnosed using paraclinical techniques [6]. The retina contains two main capillary plexuses: the superficial capillary plexus lies in the nerve fibre layer or ganglion cell layer, while the deep capillary plexus is located within the inner nuclear layer. The foveola and the immediate parafoveal retina lack capillaries, making this area dependent on the blood supply from the choriocapillaris. This area represents the foveal avascular zone (FAZ), and pathologic conditions that feature retinal capillary dropout, such as diabetes, lead to enlargement and irregular margins of the FAZ [6]. One of the key elements in in the diagnostic and therapeutic paradigm of DR is ophthalmic imaging particularly retinal imaging which their role was increased with the innovations and advances in technology over the past few decades [7]. Over the last few years, a lot of work has been done on early diagnosis of DR and on looking for new ocular diagnostic tools useful in

evaluating patients affected by diabetes (Mastropasqua 2017Recently published literature on DME has focused on several novel clinical, laboratory, and imaging biomarkers. From these biomarkers that help in assessing the disease severity and response to therapy include cytokines levels and inflammatory markers in serum, vitreous, aqueous, and tear fluid [8]. Optical coherence tomography angiography (OCTA) is a quick and noninvasive technology that may see the microvasculature of the retina in vivo (Spaide et al., 2018). Recently, there was an interest in assessing the prognostic value of the changes on OCT [9]. Fundus fluorescein angiography (FFA) is an invasive diagnostic procedure. It helps to analyse the anatomy, physiology, and disease of retinal and choroidal circulation. It aids in the diagnosis of many eye disorders. It contributes to decision-making while planning the management of ocular pathology. It is also valuable as a teaching tool. Although it is a safe technique. there are adverse effects [10]. Reviewing several research that condense the value of FA and OCT angiography as diagnostic tools for DR and DME is possible now.

1.1. Retinal Anatomy

The retina is a multilayered sheet made up of support cells, photoreceptors, and neurons. Since it is one of the body's most metabolically active organs, ischemia and nutritional imbalances can cause severe damage to it [11]. The blood supply for the outer third of the retina is derived from the choriocapillaris, a vascular network situated between the sclera and the retina. Branching off of the ophthalmic artery (the initial branch of the internal carotid artery), the central retinal artery supplies the inner two-thirds of the retina (Vislisel and Oetting, 2010). The optic nerve is the departure site for the central retinal artery, which branches out temporally above and below the macula, the sensitive area of the retina that is responsible for central vision. Hyperglycemia is thought to produce endothelial damage, selective loss of pericytes, and thickening of the basement membrane, all of which lead to leaky, incompetent blood vessels, even if the precise pathophysiology of diabetic microvascular illness remains unknown [12]. The optic nerve, a white, circular to oval region that is roughly 2 by 1.5 mm in size, is located in the middle of the retina. The retina's main blood veins radiate outward from the optic nerve's core. In the middle of the macula lies the somewhat oval-shaped, reddish region devoid of blood vessels called the fovea, located about 2.5 disc diameters to the left of the disc [13]. The posterior pole is home to the fovea, which designates the roughly central point of the region centralis. At 4 mm temporal distance from the optic disc's centre, it is situated around 0.8 mm below the horizontal meridian. It measures 1.85 mm in diameter, or 5 degrees of the visual field, and 0.25 mm on average in thickness. The foveola is a centrally concave depression that is caused by weaker retinal layers at the centre of the fovea [13]. In the macula, there are up to four retinal vascular networks. The "deep" and "intermediate" capillary plexuses, also known as ICP and DCP, are the two deeper capillary networks above and below the inner nuclear layer (INL), respectively, and are connected to the superficial vascular plexus (SVP). According to [14], the radial per papillary capillary plexus (RPCP), a regional layer, is the fourth network. The anatomy of circulation in the retina [15].

1.2. Diabetic macular manifestation

1.2.1. Cornea

A cornea's biomechanics are impacted by poor glucose control in diabetics, which may lead to elevated IOP readings regardless of CCT. In clinical practice, corneal biomechanics measurement should be considered [16]. Diabetes mellitus (DM) is a primary systemic risk factor for diabetic eye disease (DES), according to research on dry eyes. In diabetics over 65, the reported prevalence of DES is 15–33%; it rises with age and is 50% more common in women than in males [16].

1.2.2. Anterior segment

Using gonioscopy and slit lamp examination, specific findings in the anterior segment were revealed. These included an increased frequency of pigment deposition on the anterior surface of the iris, trabecular meshwork, and posterior surface of the cornea, as well as ectropion uvea [17]. Lens: The degree of lens opacity was substantially higher in the diabetes mellitus patients than in the normal control group [18]. Open-angle glaucoma is more common in Africa (4.2%) than in Asia (2.1%), which is significant given the rise in diabetes prevalence in these areas [19].

1.2.3. Abnormalities of the cranial nerves

Third, fourth, or sixth cranial nerve palsy are associated with diabetes mellitus; this association is stronger in older adults with Type 2 diabetes who have poor glycemic control [20].

1.2.4. Macular degeneration associated with ageing

Among the most common causes of permanent vision loss in the elderly is macular degeneration associated with ageing. Geographic atrophy is not associated with diabetes, although late neovascular AMD is [21]. A 5-year prospective study demonstrated decline in the visual field as well as colour vision [22].

1.3. Refraction

Diabetes is frequently associated with visual acuity impairment, which is not usually related to diabetic retinopathy. Hyperopia, a transient alteration in refraction, is a well-known symptom in newly diagnosed diabetics [23]. Contrast sensitivity is a measure of a person's capacity to distinguish between relative variations in light intensity and offers a more thorough evaluation of their spatial vision [24].

1.3.1. Anterior ischemic non-arteritic optic neuropathy

The most frequent cause of acute optic neuropathy, which is characterised by abrupt, painless unilateral vision loss, is non-arteritic anterior ischemic optic neuropathy [25].

1.3.2. PVD

Diabetes mellitus predominantly affects the body's extracellular matrix and connective tissue by non-enzymatic glycation and aberrant collagen cross-linking [26].

1.4. The Diabetic Retinopathy

Clinical indicators of diabetic retinopathy (DR) can vary from biomicroscopic alterations of intraretinal capillaries to a severe proliferation of new arteries out of the retina into the vitreous. These issues can lead to serious consequences such as vitreous haemorrhage and traction retinal detachments, both of which can result in blindness. Traditionally, diabetic

retinopathy (DR) has been separated into two categories: proliferative diabetic retinopathy (PDR) and no proliferative diabetic retinopathy (NPDR) [27]. Proliferative and no proliferative are the two basic categories of diabetic retinopathy. The term "proliferative" describes the presence or absence of neovascularization, or the growth of aberrant blood vessels, in the retina. No proliferative diabetic retinopathy (NPDR) is an early disease state devoid of neovascularization. When the condition worsens, it may develop into proliferative diabetic retinopathy (PDR), which is characterised by neovascularization and carries a higher risk of major visual effects [28]. Based on retinal findings, the NPDR is further classified into: At least one microaneurysm was found during the retinal exam in the early NPDR. Cotton wool patches, venous beading, numerous microaneurysms, and dot-and-blot haemorrhages are characteristics of moderate NPDR.

1.4.1. Significant NPDR

Cotton wool patches, venous beading, and significant intraretinal microvascular abnormalities (IRMA) are characteristics of the most severe stage of NPDR. A diagnosis is given if the patient shows any of the following: venous beading in ≥2 quadrants, IRMA in ≥1 quadrant, or diffuse intraretinal haemorrhages and microaneurysms in 4 quadrants. This is known as the "4-2-1 rule." Of those who fall into this category, 52–75% will advance to PDR within a year [29].

1.4.1.1. PDR

New blood vessels grow in the retina as a result of ischemia of the inner retinal layers brought on by the closure of some retinal capillary bed segments in proliferative diabetic retinopathy (PDR) [30]. Although new vessels can arise anywhere in the retina, they are most commonly seen posteriorly, within about 45° of the optic disc. It is hypothesised that the ischemic retina produces a new vessel-stimulating factor, such as vascular endothelial growth factor, which can act locally and diffuse through the vitreous to other areas of the retina, to the optic disc, and into the anterior chamber. Early in their formation, new vessels seem bare; later on, the fine white fibrous tissue that surrounds them is typically apparent. In order to reduce the generation of vaso proliferative agents, the ischemia retina is treated with thermal laser photocoagulation [31].

1.5. Image of the Retinal Organ

1.5.1. FFA Fundus fluorescein angiography

For the assessment of chorioretinal diseases, fundus fluorescein angiography (FFA) has been used for over 30 years [32]. An established test for identifying NPA or NV in the retina is fluorescein angiography (FA). However, as stated by [32], it is an intrusive examination that cannot be repeated that day or in the near future and may result in consequences. Retinal artery blockage and/or leakage can be conclusively documented using fluorescein angiography (FA). During an FA, a fluorescent dye is administered intravenously, and while the vessels are being perfused, a special camera takes fundus pictures over a period of several minutes. Its use as the primary imaging modality in DR grading may result in an apparently significantly higher DR severity, with subsequent increased procedures and associated costs [33]. FA detects significantly greater pathology than Colour imaging, and treatment and follow-up recommendations are based on CI. An estimated 5% of intravenous fluorescein adverse reactions are severe, with 0.05% of cases falling into this category. A national survey's results were reported to show an overall frequency rate of 1:63 for a moderate reaction, 1:1900 for a severe reaction, and 1:222.000 for death. Variable rates ranging from 3% to 20% have been reported in the literature. Some studies estimate that urticaria occurs in 0.5% to 1.2% and respiratory distress in 0.02% to 0.1% of the exposed patients [34]. Since its introduction in 1961, FA has been the imaging modality of choice. Though rare, instances of anaphylaxis and death linked to contrast injections have been observed [35]. Contradictory findings have been reported about the possible utility of spectral-domain (SD) OCT as a substitute for identifying macular nonperfusion in diabetic patients (Varma et al., 2014). The normal flow of nutrients to the outer retina may be disrupted by macular ischemia, yet there is still debate over the photoreceptor status on SD-OCT [36]. Proliferative diabetic retinopathy in a patient treated with widefield fluorescein angiography. Take note of the multiple sites where there is leakage around the disc and along the arcades, which correspond to the disc's neovascularization and other areas. Large regions of the periphery lack blood supply, and numerous laser scars from panretinal photocoagulation have been directed towards these areas [37].

1.6. Spectral Coherence Tomography Angiography (OCTA)

By identifying motion contrast in flowing blood, Optical Coherence Tomography Angiography (OCTA), a functional extension of OCT, allows microvasculature visualisation [38]. A distinct and continuous microvascular network surrounds FAZ thanks to this noninvasive technique for studying the retinal circulation [39]. OCTA is a novel analytical approach that leverages high-resolution imaging methodologies. There is no requirement to inject any contrast agent in order to observe the retinal and choroidal circulations. Endoluminal flow can be detected at any moment by OCTA. The contrast material it employs is the blood flow within the vessels. Unlike FA, which produces 2D images, OCTA produces 3D images. Unlike FA, which is a dynamic approach with a duration in time that includes early, intermediate, and late stages, OCTA is static and independent of time, meaning that there is no difference between images at a given point [40]. Parafoveal superficial and deep retinal artery density is reduced in mild NPDR (A, B), severe NPDR (C, D), and PDR (E, F) patients' OCTA pictures [41]. OCTA photographs of the retinal networks and structures, including information on vascular density and thickness, in a diabetic patient and a normal subject (3 x 3 mm scan area). A. An individual in good health did not exhibit any anomalies on structural OCT or angiography, and the image quality was satisfactory. B. An individual with diabetes did not exhibit any abnormalities on structural OCT. An angiography scan revealed capillary loss (yellow arrow), morphological defects (red arrow), and a distorted foveal avascular region (yellow star) [42]. The segmentation of the retina and choroid within the macular area is demonstrated by OCTA with en face pictures utilising Optovue, Inc., Fremont, CA, USA [43-46].

Compared the foveal avascular zone (FAZ) pictures obtained from fluorescein angiography (FA) and optical coherence tomography angiography (OCTA) in patients with and without diabetic macular ischemia (DMI). To sum up, OCTA could offer more detailed pictures pertaining to macular health, making it a novel imaging method for DMI diagnosis and possibly displacing FA in this regard. When compared to diabetic participants with established macular ischemia, the results also provide enhanced estimation of FAZ area in diabetic patients without DMI [47-50].

2. Conclusions

A multimodal approach to the detection and treatment of different retinal diseases has been made possible by recent developments in imaging technology. The non-perfusion regions and aberrant retinal vasculature are easily distinguished by OCTA, a non-invasive, dyeless technique.

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