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A Review on Diabetic Macular Edema – Pathogenesis and Management

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Abstract

The prevalence of diabetes is rising worldwide. Diabetic retinopathy is one of the major microvascular complication of diabetes mellitus. Diabetic macular edema (DME) is major sight threatening complication of diabetic retinopathy (DR). The pathogenesis of DME is multifactorial. It occurs due to interplay of various growth factors which mediate angiogenesis, endothelial cell proliferation and migration. Management is mostly primary control of DM, laser photocoagulation and pharmacotherapy mostly targeting the anti-VEGF pathway. Besides multiple factors influence the visual outcome of DME, the presence of anti-VEGF non responders have made it essential for development of alternative pharmacotherapies. This review focus on current understanding of pathophysiology of DME and the novel therapeutic approaches in addition with newer advances in DME management.

Keywords: Diabetic Retinopathy, Diabetic Macular Edema, Inflammation, Anti-Vegf, Laser Photocoagulation

Introduction

Considered to be a global epidemic of modern era, DM has been listed as one of the major causes of blindness, showing a global increase in its prevalence in recent years. (1) It has been stated that 10.28% of 22,896 diabetic patients had diabetic retinopathy, and 6.81% had DME. (2) DME is the presence of retinal thickening in and around the center of the macula and can present at any stage of diabetic retinopathy (DR). Early detection and prevention of DME is crucial to prevent irreversible damage to photoreceptors. Laser photocoagulation has been the standard of care of DME patients but with the advent of anti-vascular endothelial growth factor and steroids, focus has been shifted in the recent years to the pharmacotherapies. (3) But with the growing prevalence of DME and increasing number of non-responders there has been

an impetus to shift the emphasis to novel therapeutic targets and approaches. This review focuses on an overview of the pathogenesis of DME and the current management strategies along with future perspectives.

Pathogenesis of Diabetic Macular Edema

Pathogenesis of DME is multifactorial with multiple complex metabolic pathways being involved. Persistent hyperglycemia associated with a DM of any type is the leading cause of chronic complications and pathology. Due to insufficient action of insulin in a diabetic patient, Glucose tends to build up in the bloodstream, leading to hyperglycemia. Glucotoxicity leads to chronic complications through multiple pathways, namely, through the formation of advanced glycation end products (AGEs), activation of protein kinase c, disturbances in polyol pathways, and overactivation of the hexosamine pathway. (4)

In one of the pathways intracellular levels of diacylglycerol (DAG), which acts as a physiological activator of protein kinase C (PKC) are upregulated due to hyperglycemia. (5) The activation of PKC results in the upregulation of VEGF which in turn leads to impaired vascular permeability, hypoxia and altered blood retinal barrier (BRB). (6)

The other metabolic pathway is the polyol pathway where excess glucose is converted to fructose. In this pathway, glucose is first converted to sorbitol by the aldose reductase, oxidizing NADPH to NADP+ in the process. The excessive consumption of NADPH reduces glutathione regeneration, causing elevations in reactive oxygen species which adds to the metabolic stress and resultant structural abnormalities. (7)

One of the pathways is the hexosamine biosynthesis pathway, where fructose-6-phosphate is converted to UDP-N-acetylglucosamine, providing building blocks for N and O- linked glycosylation. This promotes insulin resistance and inflammation by inducing the expression of nuclear factor dependent genes (8).

Recently, upregulation of arginase in diabetic patients has been linked to oxidative stress and vascular dysfunction (9). Another recent theory based on a work done by quadra-omics approach discovered the activation of TGF-B, VEGF, NF-B and arginase with the inhibition of miRNA Let-7a-5p (10). These pathways lead to increased oxidative stress by producing reactive oxygen species causing defective angiogenesis and activating pro-inflammatory pathways.

The tight junctions associated proteins and blood retinal barrier play a critical role in maintaining the normal biological function of retina. The various biochemical mechanisms lead to vascular and neurodegenerative changes in retina like alteration in vascular endothelial cells, tight junctions, pericytes and basement membrane, ultimately leading to tissue ischemia, vascular leakage, and disorganization of the BRB. These results in the leakage of fluid, proteins, and lipid from retinal vessel causing a cytotoxic edema along with the concomitant swelling of muller cells which leads to vasogenic edema. Chronic DME can cause damage to photoreceptors and irreversible disorganization of retinal layers (11).

Diagnosis of Diabetic Macular Edema

The ETDRS defined color fundus mydriatic 7 standard field 7SF 30 degrees as the first-line gold standard retinal examination method (12). Fluorescein angiography is widely used for the detection of microvascular abnormalities in the retina and the choroid.

The ultra-wide field imaging utilizes confocal laser scanning ophthalmoscopy to produce images with broader peripheral view. It helps in early detection of diabetic retinopathy by imaging peripheral lesions as well. Nowadays, smart phone-based cameras are used for DR Screening to decrease the load on medical staff.

Optical coherence tomography provides an optical biopsy of retina. It is non-invasive cross-sectional diagnostic modality with early and definitive diagnosis of DME.

Treatment of Diabetic Macular Edema

A good control of blood sugar levels along with other modifiable risk factors like hypertension, hyperlipidemia, etc.) is one of the most essential factors to decrease the risk of DR progression. This has been very well confirmed in trials like the Diabetes Control and Complications Trail (DCCT)

Anti-Vegf Agents

As discussed earlier, VEGF play a very important role in pathogenesis of DME by increasing vascular permeability and formation of new blood vessels. Intravitreal antivegf agent is currently the first line pharmacotherapy for the treatment of DME.

Pegaptanib sodium (Macugen, Eyetech pharmaceuticals, Melville, New York) was one of the first anti-VGEF inhibitor to undergo clinical trials in the treatment of age-related macular degeneration and DME (13). It is an anti-VEGF aptamer that selectively inhibits the action of VEGF 165, isotope of VEGF-A. However, due to the drug's low clinical efficacy in comparison to other anti-VEGF medications, it is not utilized in clinical practice.

Bevacizumab (Avastin, Genentech, San Francisco, CA, USA) is often used off label in retinal disorders. The study on intravitreal Bevacizumab or Laser therapy in the management of DME (BOLT STUDY) showed superior efficacy of the drug over laser therapy (14). Despite being off labelled and with few reports of inflammation and endophthalmitis it is often used due to financial constraints.

Ranibizumab (Genentech, San Francisco, CA) is a fragment of an antibody that also binds to and inhibits the action of VEGF. Ranibizumab suppresses all isoforms of VEGF-A. Several clinical trials like RESOLVE, RIDE and RISE have evaluated the efficacy of ranibizumab in the management of DME (15,16). Trials with ranibizumab port delivery system (PDS) for continuous delivery of the drug in vitreous cavity to reduce the treatment burden and improve patient satisfaction has been underway (17).

Aflibercept (Eylea, Bayer Health Care, USA) is another anti-VGEF drug which is a fusion protein authorized for intravitreal treatment for DME. The VIVID and VISTA trials demonstrated the superiority of 2mg/0.05 ml aflibercept over macular laser with good functional and anatomical outcomes (18).

The Diabetic Retinopathy Clinical Research Network (DRCR.net) protocol T trial, compared the effectiveness and safety of all the anti-VGEF for DME (19). The improvement in visual acuity and central subfield thickness was greater for aflibercept as compared to bevacizumab and ranibizumab. Ocular and systemic safety was comparable in all three drugs but aflibercept had a slightly higher edge over other two in patients with initial poor visual acuity.

A new Anti- VEGF therapy for DME is brolucizumab (Beovu, Novartis, Switzerland). It is a single chain antibody fragment with a dose of 6 mg. Molar dosage is approximately 11 times that of aflibercept (2 mg)

and 22 times that of ranibizumab (0.5 mg) (20). Non inferiority of brolucizumab over aflibercept in DME has been proven in many clinical trails like KITE and KESTREL (21). However, intraocular inflammation with the use of brolucizumab as compared to eylea has been reported in studies (22).

Faricimab, a bispecific antibody that targets both angiopoietin – 2 (Ang-2) and VEGF-A is a new intravitreal agent used to treat nAMD and DME. Tie – 2 receptor is important for vascular stability and maturation and is antagonist to Ang-2. In conditions of hypoxia Ang-2 expression is elevated which causes endothelial disfunction, vascular leakage and angiogenesis. Faricimab blocks both VEGF -A and Ang-2 and restores vascular stability that may potentially lessen the treatment burden while improving visual acuity with its longer duration of action. Faricimab was shown to be non inferior to aflibercept at one year in YOSEMITE and RHINE trials for DME (23).

Conbercept (Lumitin) KH902 is a fusion protein which inhibits all variants of VEGF-A, VEGF-B, VEGF-C and PIGF. It has a solid affinity for VEGF and remains persistent in the vitreous for a longer duration of action (24). Many trials have been done in China where it has shown efficacy in DME in eyes which were not responding to other Antivegf (25). However, it has not been introduced to market of other countries. Conbercept has shown a beneficial effect on blood flow status in the macula and facilitate the restoration of blood flow in ischemic areas.

Biosimilars

Biosimilars are drug made from living cells and are similar to the original molecule in terms of safety, efficacy, biological activity and immunogenicity. The first ranibizumab biosimilar RAZUMAB was approved in India (26). Other biosimilars like FYB201 (Cimerli, ranibizumab-erqn) and SB11(Byooviz, ranibizumab-nuna) are FDA approved, and many others are still being investigated (27,28). Many biosimilars of aflibercept are also being investigated. MYL-1701P (Mylan, Canonsburg, USA) is a biosimilar to aflibercept currently undergoing trial.

Steroids

Steroids have an anti-inflammatory and anti-VEGF effects for protection of BRB and reduction in capillary permeability. Currently available corticosteroids for the treatment of DME include intravitreal triamcinolone acetonide, dexamethasone implant and fluocinolone acetonide intravitreal inserts. Intravitreal steroids carry a risk of intraocular pressure rise and cataract formation. Hence, they are used only in patients who are unresponsive to antivegf or patients with recent history of stroke or pregnant women (29). Intravitreal triamcinolone acetonide is less commonly used due to its short duration of action and higher chances of IOP rise. Biodegradable Intravitreal dexamethasone implant have shown a significant improvement in BCVA in treatment- naïve patients and substantial reduction in central macular thickness (CMT) 6 months following treatment (30). However, intravitreal fluocinolone acetonide implants tend to last much longer, up to 36 months, thus alleviating some of the treatment burden but DEX implants appear to be superior to fluocinolone acetonide (FA) implant due to their lower risk of ocular hypertension and cataracts. Lipid based nanocarriers of TA are a novel approach showing promising results in the treatment of DME in near future (31).

Systemic Therapy

Apart from systemic lipid lowering drugs like statins, systemic infliximab, an anti-TNF biologic has been investigated for refractory DME (32). One randomized controlled trial has shown Oxygen therapy with a flow rate of 10 L/min to be effective for DME (33).

Laser Therapy

Laser therapy has been the gold standard treatment for DME. Exact mechanism of action remains unknown, but theories suggest that laser therapy destroys tissue, so less oxygen reaches the target, it gets hypoperfused, and the remaining tissues get hyperperfused. Adverse effects of laser therapy included atrophy, scarring, scotoma and fibrosis due to burning of the tissues.

To reduce the side effects of traditional laser therapy newer laser therapies like the semi-automated pattern scanning retinal photocoagulation system (PASCAL, Pattern scan laser), Selective retinal therapy (SRT) and Subthreshold Diode Micropulse laser are being tried in various randomized clinical trials (34).

Pars Plana Vitrectomy

In patients of DME with poor response to medical therapy pars plana vitrectomy (PPV) is the last resort that aims to remove the glycation end products and reduce tractional elements (35). Mechanism with which PPV works is by improving oxygen and capillary blood delivery to retina, suppressing VEGF production.

Future Insights in DME Management

Photo biomodulation therapy (PBM), a non-invasive treatment, to promote tissue repair and activate biological processes by increasing mitochondrial activity, decreasing oxidative stress, and regulating inflammation in the retinal cells to improve retinal function and reduce vascular leakage. It is a photochemical process in which is light is taken by chromophore cells (36).

OCS-01 eye drops (oculis SA) is a topical corticosteroid formulation with a potential alternative to the more invasive intravitreal steroids which is currently undergoing trials (37).

Antivegf agents like OPT-302 (Sozinibercept, opthea), MYL-1701P (momenta pharmaceuticals and mylan), IBI 324 (innovent biologics) are currently undergoing trials for DME (38).

Other newer promising therapies in future included Gene therapy, tyrosinase kinase inhibitors, Kallikrein-kinin inhibitors and senolytic therapy (38).

Conclusion

DME is considered among the leading cause of vision loss worldwide. Current guidelines show that DME is primarily treated with anti-VEGF therapy, but it carries a significant burden and inadequate responses in some DME patients. Emerging new therapies may offer new mechanism of action with better efficacy, safety and durability, further refining outcomes for the growing number of patients affected by DME. Large clinical trials ought to yield adequate proof to support these innovative treatments and therapeutic modalities.

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