Current Aspects of Epidemiology, Pathogenesis and Treatment in Diabetic Macular Edema

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Summary

This problem-solving article reviews the current knowledge on the epidemiology, physiology and treatment principles of Diabetic Macular Edema (DME), a common diabetic complication and leading cause of blindness in working-age individuals. Although some risk factors for DME have been determined, the exact pathogenesis is still unknown. Proven effective and satisfactory therapy is currently not available. Clinical understanding and the major treatments for DME have not changed for several decades. Scientific progress in recent years outlines some new promising therapeutical strategies for treating DME. In addition new non-invasive high resolution imaging methods of the retina provides much deeper information about morphological findings in DME. New treatment and diagnostic options could be beneficial to detect DME in early stages, prevent its progression and to start the most effective treatment at earlier stages.

Key words: diabetic retinopathy, diabetic, macular edema, blood-retinal barrier, optical coherence tomography, laser coagulation, vascular endothelial growth factors.

INTRODUCTION

According to the World Health Organization data, Diabetic Retinopathy (DR) is one of the most common diabetic complications and also the leading cause of blindness and visual disability in working-age individuals. Because of its chronic nature and the severity, DR has also economic impact, not only for patients, but also for the whole health systems.

The number of diabetic patients continues to increase both in Latvia and in the world and has reached epidemic proportions. An estimated 285 million people of the world's adult population have diabetes in 2010. The number is expected to double by 2030. According to the Centre of Health Economics of Latvia, in 2009 where registered more than 67 000 diabetic patients. In fact, even in developed countries, only less than half of people with diabetes are diagnosed.

Without timely diagnoses and adequate treatment, complications from diabetes rise exponentially. Early diagnosis and proper control of diabetes-associated metabolic abnormalities (i.e., hyperglycemia, hyperlipidemia, and hypertension) are important in preserving visual function, because these conditions have been identified also as risk factors for the development and progression of diabetic eye complications.

The most common cause of moderate central vision and visual acuity loss in DR patients is Diabetic Macular Edema (DME) (12, 13, 15). DME is swelling and thickening of the central part of the retina – macula. The macula is only 5mm in diameter and responsible for high resolution central and color vision. The central point of the macula – fovea has the highest concentration of photoreceptors. Macula is the most metabolically active part of the retina, and as a consequence also the most sensitive part in respect of any metabolic disturbance.

DME can occur in patients with both types of diabetes (type 1 and type 2) either nonproliferative or proliferative diabetic retinopathy at any stage, but its obvious that the most important factors for the beginning and progression of DME are the disease duration and the degree of metabolic control maintained over the years. It is estimated that, over 15 years of diagnosed diabetes, approximately 20% of people with type 1 diabetes, 25% of people with type 2 diabetes taking insulin, and 15% of people with type 2 diabetes not taking insulin, will develop DME. The prevalence reaches approximately 30% in those who have had either type of the diabetes for 20 years (9). In a younger onset diabetic cohort study, macular edema was associated with a prevalence of visual impairment of 50% and blindness of 20% (14). If left untreated 24% of eyes with severe DME will have a moderate visual loss within 3 years (2).

When DME involves the center of the fovea, there is a higher risk of visual loss. Therefore there are defined signs of clinically significant DME – 1) retinal thickening at or within 500µm of the fovea, 2) and/or hard exudates at or within 500µm of fovea with associated thickening, 3) and/or an area of thickening the equivalent of one optic disc area or more, any part of which is within one optic disc diameter of the fovea. The clinical terms of focal and diffuse are used frequently to differentiate two main types of DME. Focal macular edema is characterized by well-defined areas of leakage associated with a leaking microaneurysm. Diffuse DME is characterized by widespread and poorly demarcated thickening caused by extensive capillary leakage. Focal DME has been reported to be more common than diffuse DME and is associated with less macular thickening, better visual acuity, and less severe retinopathy severity (8). The most severe form is ischemic DME. It is characterized with

the perfusion loss of the capillary network surrounding the center of the macula – fovea. Ischemic maculopathy is generally regarded as untreatable, since irreversible vision loss has already occurred at the time of diagnosis. The pathogenesis of DME is complex and not yet fully understood. Although some risk factors of DME have been determined, the exact pathogenesis is still unknown. According to existing knowledge base, DME is the result of microvascular retinal changes due to hyperglycemia and hypoxia (2). Endothelial dysfunction and basement membrane damage are key features of DR and is considered to be a major cause of the associated vascular complications and development of DME. Endothelial cells are comparatively vulnerable to hyperglycemia because they have very limited regulation capability of the intracellular glucose. Hyperglycemia induced intramural pericyte death and thickening of the basement membrane lead to damage of the vascular walls (7). This leads to edema, caused by extravasation of fluid and plasma constituents. With a time lipoproteins accumulate in the macular area and forming hard exudates (3).

Dominant biochemical mechanisms by which hypoxia and hyperglycemia may cause endothelial damage are: 1) increased polyol pathway activity and associated changes in intracellular redox state, 2) increased nonenzymatic glycation of both intracellular and extracellular proteins, 3) increased diacylglycerol synthesis with consequent activation of protein kinase C and 4) oxidative stress due to increased formation of reactive oxygen species in the mitochondria (18).

Chain reaction of metabolic disturbances changes the formation of the blood–retinal barrier. The breakdown of the blood–retinal barrier produces increased vascular permeability and the accumulation of fluid within the intraretinal layers of the macula which extends hypoxia and decrease of visual acuity (1). The blood–retinal barrier consists of two parts – outer blood–retinal barrier (retinal pigment epithelium) and inner blood–retinal barrier (vascular endothelium) which is the main barrier against the passage of macromolecules and circulating cells from blood to the extracellular space. The movement of fluid through the blood–retinal barrier has two dominant components: a passive (bidirectional) transport and an active transport directed from the retina to the blood. DME develops when the inflow of fluid into the retina exceeds the outflow. Passive transport (permeability) has been shown to increase in relation to the progression of retinopathy. Unlike active transport, passive permeability is related to the degree of retinopathy. In eyes with severe nonproliferative diabetic retinopathy passive permeability is significantly increased compared with moderate retinopathy. The active resorptive functions of the blood–retinal barrier in diabetes are likely to be increased to counteract edema formation, but this increase is too little. Passive permeability through the endothelium can be increased by three general mechanisms: 1) increased transcellular transport, 2) dysfunction of the intercellular junctions, and 3) increased endothelial cell destruction. Although

other factors such as impairment of the perivascular supporting cells might influence vascular permeability, the primary damage is likely to predominantly affect endothelial cells (6, 10, 21).

Additionally, increased vasopermeability resulting in DME may be induced by vitreomacular traction. Evidence of a vitreous origin of development and exacerbation of DME arises from several clinical studies. The prevalence of posterior vitreous detachment (PVD) in patients with DME is significantly lower than in diabetic patients without macular edema. Spontaneous vitreomacular separation can cause resolution of DME (22).

For many years our standard methods to diagnose DME were limited to Ophthalmoscopy, Fundus Photography and Fluorescein Angiography. In the recent years new imaging equipment – Optical Coherence Tomography (OCT) become available in clinical practice. Today OCT is a primary tool for early detection and follow-up of DME. OCT gives high-resolution and 3D cross-section images of the retina and is very sensitive to small changes in retinal structure and thickness. This method also provides with important additional information about the retina and vitreoretinal relationships.

Already for several year decades laser coagulation is a golden standard ophthalmic treatment method for DME. Conventional laser treatment is made according to the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol or with some modifications (24). In general laser coagulation treatment approach has not changed during about 25 years. Since Latvia was the first country among Baltic countries, where laser coagulation was introduced (1986, Dr. Ivars Luksa), we have very extensive experience with this method of treatment. Unfortunately, we have to conclude, that it only targets advanced stages of disease. Our personal practice confirms data of several randomized clinical trials, that laser treatment of DME has been shown to be effective in preventing visual loss, however it is not a cure and can't prevent loss of vision for all patients. Treatment by laser coagulation is more effective in focal edema, but is disputable in diffuse edema and proven to be ineffective in ischemic diabetic maculopathy. ETDRS study showed that despite successful treatment and decreased retinal thickening, only 17% of patients recovered three or more lines of visual acuity relative to their entry levels of vision. Study concluded that visual improvement was observed in a minority of cases, but for the majority of cases the goal of laser coagulation is limited to stabilizing visual acuity for a certain period of time (5).

The low frequency of improvement following by laser coagulation for DME has prompted interest in other treatment options, including use of intravitreal steroids (11) oral protein kinase C beta inhibitors (19) pars plana vitrectomy (17) and intravitreal agents directed against Vascular Endothelial Growth Factor (VEGF) (16).

New therapeutical strategies are targeted on the inhibition of pathophysiologic pathways leading to microvascular damage specific to DME. Recent scientific findings are showing that VEGF has perhaps the most

important role in the pathophysiology of DME. VEGF is a glycoprotein secreted by retinal pigment epithelium cells, pericytes and endothelial cells. It is a powerful inducer of vascular permeability, and a well studied pro-angiogenic factor. VEGF is perhaps the most potent mediator of vascular permeability. It is 50,000 times more potent increasing vascular permeability than histamine (4). VEGF increases vascular permeability via multiple mechanisms, including: leukocyte mediated extra-cellular injury, formation of fenestrate, and the dissolution of tight junctions and transcellular bulk flow. The normal human retina contains little VEGF and hypoxia causes upregulation of this mediator. VEGF levels are elevated in the eyes of patients with DME, and in animal models of diabetes this elevation coincides with the breakdown of the blood-retinal barrier. Moreover, injection of VEGF into healthy eyes of animals can induce diabetes-associated ocular pathologies (23). Vinore (25) used immunohistochemical staining for VEGF to demonstrate an increase in VEGF staining of the retina from diabetic patients in contrast to that observed in normal human retinas. Several studies indicate that VEGF inhibition may treat the underlying disease and reverse the neovascular and the permeability changes in DME. The use of VEGF inhibition as a treatment for different human diseases has been studied for many years and different therapeutic agents targeting VEGF have been developed. Since VEGF is thought to be the primary endogenous mediator of DME and proliferative DR, several pharmacologic therapies that inhibit VEGF and are already used for treatment of other microvascular eye diseases treatment have been proposed. Our personal experience proved that these medications are effective and safe therapy for treatment of other retinal microvascular disease, like Age Related Macular Degeneration (AMD). The most widely used and clinically proven to be effective anti-VEGF agents for intravitreal injections are ranibizumab, pegaptanib and bevacizumab. Lucentis® (ranibizumab) is an intravitreal recombinant, humanized, monoclonal anti-VEGF antibody fragment. It is approved by the FDA for treatment of wet AMD. Macugen® (pegaptanib), an intravitreal, anti-VEGF aptamer, was the first anti-VEGF agent proved to be effective in patients with wet AMD. Avastin® (bevacizumab) is a humanized monoclonal anti-VEGF antibody and was approved by the FDA in 2004 for intravenous therapy of metastatic colorectal cancer. In early 2004, Rosenfeld initiated the use of bevacizumab in the treatment of wet form of AMD (20). Although Avastin is off-label product for ocular use, it's the most widely used medication for intravitreal use, mostly because of economical aspects. Despite that, until today none of anti-VEGF agents are officially approved for intravitreal use in treatment of proliferative DR or DME, they are extensively studied for this indication and in some practices already successfully used. Some, already published studies are showing promising results with this new treatment approach as a single therapy or in combination with laser coagulation.

CONCLUSIONS

Although intravitreal delivery of anti-VEGF agents seems to be effective and relatively safe procedure, the long-term local and systemic effects of these agents in the diabetic population needs to be investigated.

Also further studies on different dosage regimen and administration frequency would be beneficial to establish new treatment standards for DME.

Combination of new diagnostic possibilities (OCT) and new treatment approach (anti-VEGF) could give the opportunity of intervention for DME at earlier non-sight-threatening stages. This could give a significant economical input and also increase the quality of life for diabetic patients.

Conflict of interest: None

REFERENCES

1. Antcliff RJ, Marshall J. The pathogenesis of edema in diabetic maculopathy // *Semin Ophthalmol.*, 1999;14:223-232
2. Bhagat N, Grigorian RA and Tutela A. Diabetic macular edema: pathogenesis and treatment // *Survey of Ophthalmology*, 2009; 54: 1-32
3. Cunha-Vaz J.G. Pathophysiology of diabetic retinopathy // *British Journal of Ophthalmology*, 1978; 62, 351-355
4. Donald R. Senger. Vascular Endothelial Growth Factor: Much More than an Angiogenesis Factor // *Molecular Biology of the Cell*, 2010; 21(3): 377-379
5. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema: ETDRS report no. 4. // *Int Ophthalmol Clin*, 1987; 27:265-72
6. Engler CB, Sander B, Larsen M, Koefoed P, Parving HH, Lund-Andersen H. Probenecid inhibition of the outward transport of fluorescein across the human blood-retina barrier // *Acta Ophthalmol (Copenh)*, 1994; 72:663-667.
7. Hans-Peter Hammes, Jihong Lin, Oliver Renner, Moshe Shani, Andrea Lundqvist, Christer Betsholtz, Michael Brownlee, and Urban Deutsch. Pericytes and the Pathogenesis of Diabetic Retinopathy // *Diabetes*, 2002; 51(10):3107-12
8. Kang SW, Park CY, Ham DI. The correlation between fluorescein angiographic and optical coherence tomographic features in clinically significant diabetic macular edema // *Am J Ophthalmol.*, 2004; 137(2):313-22
9. Klein R, Klein B, Moss S, Davis M, DeMets D. The Wisconsin Epidemiologic Study of Diabetic Retinopathy, IV: diabetic macular edema // *Ophthalmology*, 1984; 91:1464-1474
10. Koyano S, Araie M, Eguchi S. Movement of fluorescein and its glucuronide across retinal pigment epithelium-choroid // *Invest Ophthalmol*

- Vis Sci, 1993; 34:531–538.
11. Martidis A, Duker JS, Greenberg PB, Rogers AH, Puliafito CA, Reichel E, Bauman C. Intravitreal triamcinolone for refractory diabetic macular edema // *Ophthalmology*, 2002 May; 109(5):920–7
 12. Mokdad AH, Ford ES, Bowman BA, Nelson DE, Engelgau MM, Vinicor F, Marks JS. Diabetes trends in the U.S.: 1990–1998 // *Diabetes Care*, 2000; 23:1278–1283
 13. Moss S, Klein R, Klein B. The 14-year incidence of visual loss in a diabetic population // *Ophthalmology*, 1998; 105:998–1003
 14. Moss SE, Klein R and Klein BE. The 14-year incidence of visual loss in diabetic population // *Ophthalmology*, 1995; 97: 415–419
 15. Negi A and Vernon SA. An overview of the eye in diabetes // *Journal of the Royal Society of Medicine*, 2003; 96:266–272
 16. Nguyen QD, Tatlipinar S, Shah SM, Haller JA, Quinlan E, Sung J, Zimmer-Galler I, Do DV, Campochiaro PA. Vascular endothelial growth factor is a critical stimulus for diabetic macular edema // *Am J Ophthalmol*, 2006;142(6): 961–9
 17. Pendergast SD, Hassan TS, Williams GA, Cox MS, Margherio RR, Ferrone PJ, Garretson BR, Trese MT. Vitrectomy for diffuse diabetic macular edema associated with a taut premacular posterior hyaloid // *Am J Ophthalmol*, 2000; 130(2):178–86
 18. Peter Kroll, Marburg. Current Aspects of Pathogenesis and Treatment in Diabetic Retinopathy // *Ophthalmologica* 2007; 221:77
 19. PKC-DRS2 Group, Aiello LP, Davis MD, Girach A, Kles KA, Milton RC, Sheetz MJ, Vignati L, Zhi XE. Effect of ruboxistaurin on visual loss in patients with diabetic retinopathy // *Ophthalmology*, 2006;113(12):2221–30
 20. Rosenfeld PJ, Moshfeghi AA, Puliafito CA. Optical coherence tomography findings after an intravitreal injection of bevacizumab (Avastin) for neovascular age-related macular degeneration // *Ophthalmic Surg Lasers Imaging*. 2005; 36:331–335
 21. Sander B, Larsen M, Moldow B, Lund-Andersen H. Diabetic macular edema: passive and active transport of fluorescein through the blood–retina barrier // *Invest Ophthalmol Vis Sci* 2001;42: 433–438.
 22. Schepens CL, Avila MP, Jalkh AE, Trempe CL. Role of the vitreous in cystoid macular edema // *Surv Ophthalmol*, 1984; 28(suppl):499–504.
 23. Tolentino MJ, Miller JW, Gragoudas ES, et al. Intravitreal injections of vascular endothelial growth factor produce retinal ischemia and microangiopathy in an adult primate // *Ophthalmology* 1996; 103: 1820–8.
 24. Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema: Early Treatment Diabetic Retinopathy Study report number 1. // *Arch Ophthalmol* 1985; 103:1796–806
 25. Vinore S, Youssri A, Luna J, et al. Upregulation of vascular endothelial growth factor in ischemic and non-ischemic human and experimental retinal disease // *Histol Histopathol* 1997; 12:99–109

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