WHO GETS DIABETIC MACULAR OEDEMA; WHEN; AND WHY? PATHOGENESIS AND RISK FACTORS

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ABSTRACT

Diabetic macular oedema (DMO) presents an enormous rise in the last decades with an increasing number of diabetic patients. It has a negative impact on the health-related quality of life beside the related visual loss. Additionally, it incurs more health centre visits, higher health costs, and lower working performance. Therefore, early diagnosis and preventive measures gain more and more importance in the management of DMO. Risk factors for DMO can be divided into systemic and ocular risk factors. The leading systemic risk factors include age, type and duration of diabetes, insulin use, and glucose regulation. Hypertension, nephropathy, hyperlipidaemia, anaemia, cardiovascular disease, smoking, and amputation are other risk factors reported. In addition, susceptibility in cases with endothelial nitric oxide synthase polymorphism and vascular endothelial growth factor C634-G polymorphism has been reported. The severity of diabetic retinopathy, microaneurysm turnover, cataract surgery, incomplete vitreous detachment, and peripheral retinal ischaemia are among ocular risk factors. Though avoiding changes in the metabolic memory related to hyperglycaemia in the early period seems to be the most efficient treatment, nowadays close follow-up of patients with high risk and effort to control the modifiable risk factors seems to be the ideal treatment.

Keywords: Diabetic macular oedema, risk factors, hyperlipidaemia, hypertension, cataract.

INTRODUCTION

The modified dietary changes and Western type lifestyle leads to an enormous increase in the incidence of diabetes. It is estimated that there were 347 million people affected by diabetes worldwide in 2011 and this is expected to double by 2030.[1,2] This alarming rise in the number of diabetic patients is accompanied by the rapid increase in the number of patients affected by its microvascular complications, diabetic retinopathy (DR) and diabetic macular oedema (DMO). DMO is the most common cause of visual acuity decrease in diabetic patients. About one diabetic patient in four can be expected to develop DMO in a lifetime.[3]

According to statistics, 40% of people with diabetes have retinopathy, and diabetes is the leading cause of new blindness in adults 20–72 years of age.[4] In 2012, DMO was estimated to affect approximately 21 million cases worldwide which constitutes 7% of all people with diabetes.[5] Comparing the prevalence of DMO between Type 1 and 2 diabetes mellitus (T1DM and T2DM), 14% of people with T1DM have DMO, while it affects only 6% of people with T2DM. However, since the number of T2DM cases significantly outnumbers that of T1DM, there are more T2DM patients with DMO.[6]

In addition to visual loss, the negative impact of DMO on the diabetic population, especially on patient health-related quality of life (QoL), is a serious issue as well. Patients with DMO consume significantly more healthcare resources, incur higher costs, and have a low work efficiency compared to diabetic patients without retinal complications. The yearly number of ophthalmological examinations of diabetic patients are 3-times higher than controls. The health costs are 30% higher in DMO cases compared to diabetic patients without retinopathy.[7,8]

As these data show, visual disability from diabetes is a significant public health problem which is largely preventable, and the QoL can be preserved if managed with timely intervention. Therefore, determining the risk factors, close follow-up, early diagnosis, and taking preventive precautions for patients at higher risk to prevent the visual disability related to DMO has gained more importance despite encouraging and hopeful developments for the treatment of DMO in the pipeline.

DMO can be seen at any stage of DR, either nonproliferative or proliferative, with two types: focal oedema (FO) arising from microaneurysm (MA) leakage, and diffuse oedema related to increased capillary permeability. Focal macular oedema has been defined as an area of retinal thickening less than two disc areas in diameter, not affecting the centre of the macula. Diffuse macular oedema has been defined as having two or more disc areas of retinal thickening with involvement of the macular centre. FO has been reported to be more common than diffuse DMO and associated with better visual acuity, less severe retinopathy, and less macular thickening. The decision for treatment is based on the criteria of clinically significant macular oedema (CSMO) defined by the Early Treatment for Diabetic Retinopathy Study (ETDRS) in 1985 with clinical exam or colour fundus photographs. According to their definition, one of the following three criteria should be fulfilled:

1. Any retinal thickening within 500 µm of the macular centre.

2. Hard exudates within 500 µm of the macular centre with adjacent retinal thickening.

3. Retinal thickening at least one disc area in size, any part of which is within one disc diameter of the macular centre.[9-11]

In recent years optical coherence tomography, which has allowed assessment of early DMO, including subclinical DMO, has become an adjunctive tool in addition to colour fundus photography and fundus fluorescein angiography (FA) to determine its classification and thus its management strategy.[12]

Diabetes affects all cell types in the retina including neurons, glial cells, and blood vessels. Chronic hyperglycaemia initiates a complex series of responses including activation of protein kinase C, activation of aldose reductase, formation of advanced glycation end products, increased

hexosamine pathway flux, and activation of renin-angiotensin system. These together induce overproduction of reactive oxygen species, which increase oxidative stress leading to retinal damage. The structural changes related to hyperglycaemia are thickening of the capillary basement membrane, loss of microvascular pericytes, MA formation, and breakdown of the blood-retinal barrier which initiates the DMO. Furthermore, vascular endothelial growth factor (VEGF) and other inflammatory cytokines such as tumour necrosis factor and interleukin 1β, insulin-like growth factor, hepatocyte growth factor, and histamine also contribute to vascular permeability by disrupting the tight junction proteins in the endothelium.[13-15]

Under normal conditions the inner retina is continuously dehydrated by glial cells such as Müller cells, and the outer retina is kept dry by pumping of retinal pigment epithelium. Special water channels called 'aquaporins' enhance permeability of membranes and mediate rapid and extensive fluid exchange.[16] Intraretinal fluid collection may develop as a result of enhanced fluid leakage due to breakdown of the blood-retinal barrier and by the impaired removal of fluid from the retinal tissue to systemic circulation. The permeability of the retinal capillaries increases approximately 12-fold but the activity of the pigment epithelial pump increases only 2-fold in diabetes, and in the macular centre there is no venous side of vasculature and water can leave the extravascular space only via action of the retinal pigment epithelial pump.[17]

Generally, fluid collection develops in interstitial spaces (extracellular fluid, vasogenic oedema) causing cellular compression or it may collect within cells (intracellular, cytotoxic oedema) resulting in cellular swelling. Vasogenic oedema can be explained by Starling's law. According to Starling's law, oedema will form if the hydrostatic pressure gradient between vessel and tissue is increased or the osmotic pressure gradient is decreased.[18] The increased capillary permeability in diabetes enables leakage of macromolecules, predominantly albumin, from the blood into the tissue interstitial space. This accumulation of albumin in the tissue increases the osmotic pressure difference between tissue and blood, which pulls water into the interstitial space.[19] VEGF is the primary cytokine responsible for the increased permeability of retinal capillaries which makes it an essential target in the treatment of DMO.[20] VEGF is controlled

by oxygen tension in the tissue; its production is induced by hypoxia. Reducing the VEGF concentration in the retina seems to be the ideal way to reduce the leakage of plasma proteins from the blood into the tissue interstitial space.[18]

Intracellular oedema leakage will not be seen on FA, as the fluid is intracellular and can be explained by hypoxia-induced K+ channel disturbances. The redistribution of K+ channels results in a net accumulation of K+ ions within cells, building an osmotic gradient. This gradient drives water from the blood and vitreous into the glial cells via aquaporins, and causes glial swelling oedema and cyst formation.[21] A prevailing view is that cyst formation secondary to macular oedema is formed by swollen and dying Müller cells. When present, these cysts are predominantly located in the inner nuclear layer and Henle fibre layer.[22]

DMO: WHO, WHEN, AND WHY?

The answer of this question is multifactorial, including systemic or ocular factors. Systemic factors include age, duration and type of diabetes, and insulin use. According to the Wisconsin epidemiologic study of DR10 data, cumulative DMO risk increases with age in 25 years. In cases with duration of disease >20 years, DMO prevalence is 32% for patients younger than 30 years at the time of diagnosis and using insulin. For patients who are older than 30 years at the time of diagnosis with either T1 or T2DM, the prevalence of DMO is 38% for insulin users and 18% for non-insulin users.[23] ETDRS group reported the incidence of DMO for 10 years follow-up as 20.1% in T1DM cases, 25.4% in insulin-dependent T2DM patients, and 13.9% in non-insulin-dependent T2DM patients.[24]

There are not so many studies evaluating DMO prevalence and its correlation with the disease duration in Europe. From the 775 patients participating in the Exeter Diabetic Retinopathy Screening Programme in the United Kingdom, 6.1% were diagnosed to have DMO at the time of screening. This ratio is 11.5% for T1DM cases, 4.1% for non-insulin-dependent T2DM patients, and 9.1% for insulin-dependent T2DM patients.[25] The Epidemiology of Diabetes Interventions and Complications research group found that at 4-year follow-up, patients in the Diabetes Control and Complications Trial (DCCT) who received intensive insulin treatment showed better retinopathy outcomes than those receiving conventional treatment.[26] However, insulin treatment is always associated with higher DMO incidence. Previous studies could not detect a direct association with insulin use and DMO, and proposed that DMO incidence was higher among insulin users as those are usually uncontrolled patients with severe DR, and strict glucose regulation with insulin resulted in decrease in DMO incidence with time.[7,23] However, recent studies proposed that insulin causes impairment of the blood retina barrier by increasing binding of hypoxia-induced factor to the VEGF promoter region. In the long term, insulin demonstrated positive effects on DMO due to its anti-inflammatory, antiapoptotic, oxidative stress diminishing effects.[27,28] DCCT[15] and the United Kingdom's Prospective Diabetes Study[16] reported an increase in DMO in T2DM cases with especially >3% decrease in glycated haemoglobin (HbA1c), but no progression was detected in patients without retinopathy at the beginning.[29] Therefore, close follow-up is recommended for cases starting insulin treatment.

In addition to DM type, duration, and insulin use, the degree of metabolic control, dependent on blood glucose and HbA1c level, is the most important risk factor for DMO.[30] The 4th and 7th year follow-up data of DCCT[15] group showed that patients receiving intensive insulin treatment presented slowdown of DR progression, which continues even after the intensive treatment has been stopped. Similarly, the endothelial dysfunction related to poor glucose regulation in the first 5 years of the disease persists after normoglycaemia.[31] The study of Madsen-Bouterse et al.[32] showed persistence of mitochondrial DNA damage even after normoglycaemia following 6 months of poor glucose regulation. These findings bring up the 'metabolic memory' concept which is a result of oxidative stress, advanced glycosylation end products, and epigenetic changes related to chronic hyperglycaemia in diabetes. It also emphasises the importance of preventing these stationary metabolic memory changes by early diagnosis and intensive glucose regulation.[33] Despite positive effects of DM regulation in the early period, the treatment itself may sometimes have some risks. For example, the thiazolidinediones which were increasing the insulin sensitivity were claimed to increase DMO risk in some studies.[34] However, recent studies proved that they induce neither clinical nor subclinical DMO.[35]

DMO prevalence has been studied in many ethnic groups as well. Black and Hispanic patients seem to be more prone to DMO compared to Chinese and Caucasian patients.[36] The three population study (Los Angeles Latino Eye Study, Projecto VER, Beaver Dam Eye Study) of Varma et al.[37] found higher prevalence of DR among Hispanics after eliminating the traditional risk factors. In the United States, the cross-sectional Veterans Affairs Diabetes Trial examined the association between ethnicity and DMO and found that Hispanics (18%; OR 2.30) and African-Americans (15.6%; OR 2.30) have a greater prevalence and risk of DMO than non-Hispanic whites (6.3%), even after adjusting for confounding risk factors.[38] These ethnic risk factors can be explained by predisposition to conventional risk factors, insulin resistance, and difference in anthropometric measurements truncal obesity, difference in health service facilities, genetic predisposition, and epigenetic changes. There is no difference among both sexes for DMO.[37,38]

There are several other systemic risk factors mentioned in other studies, including high blood pressure, nephropathy, hyperlipidaemia, anaemia, cardiovascular disorders, and high basal metabolic index.[24,39] Asensio-Sanchez et al.[40] reported age, high HbA1c, high blood pressure, smoking, high-density lipoprotein (HDL) cholesterol levels and low-density lipoprotein (LDL)-cholesterol levels, proteinuria, and microalbuminuria as the significant systemic risk factors for DMO. The Veterans Affairs Diabetes Trial[26] claimed young age, early-onset DM, long duration of disease severity of DR, and high HbA1c as high risk factors in addition to urine albumin/creatinine ratio and amputation as associated risk factors.[38] Congestive heart failure, renal failure, and hypoalbuminaemia are among the situations where DMO increased due to either increased hydrostatic pressure or decreased osmotic pressure.[41]

High blood pressure increases have been demonstrated to increase DMO incidence 3-fold. The majority of the studies found high systolic blood pressure more risky. There are also some others claiming high diastolic blood pressure is more risky.[5,7,42,43] This effect is proposed to be related to impaired retinal autoregulation, accelerated endothelial damage and VEGF, and VEGF receptor increase due to vascular tension in retinal endothelium.[44] According to Stefánsson,[32] arterial hypertension raises the hydrostatic pressure in the capillaries which, in turn, increases the fluid leakage. Improvement of DMO has been reported after successful treatment of hypertension.[19] Nephropathy also showed a close relationship with DMO - especially gross proteinuria in the late-onset, insulin-dependent group - increasing the risk severely.[7,23,45] The study of Romero et al.[46] also showed a decrease in diffuse macular oedema after dialysis. No correlation could be assessed between microalbuminuria and DMO. Dyslipidaemia is known to be an important risk factor for DMO.[47] Hyperlipidaemia has been reported as a risk factor first by Dornan in 1982.[48] This has a special importance in DMO cases, as further progression of exudates to the foveal centre resulted in subretinal fibrosis and associated visual loss. Several studies demonstrated a strong relationship with lipid exudates and serum cholesterol and LDL levels.[49-51] Miljanovic et al.,[52] in a prospective study, showed an increase in serum lipids, especially total/HDL cholesterol ratio and triglyceride, to be independent risk factors for both clinically significant DMO and retinal hard exudates. However, CSMO was not found to be correlated with the lipid profile in a recent study by Kamoi et al.[53] A more detailed study comparing the influence of serum lipids on clinically significant versus non-CSMO revealed high serum LDL, non-HDL cholesterol, and cholesterol ratios related to non-CSMO and total cholesterol related to CSMO. The body mass index was also found to have a negative effect on DMO.[51]

The increase in blood viscosity and changes in the fibrinolytic system in hyperlipidaemia are proposed to cause hard exudates.[54] The influx of triglycerides into the cell membrane gives rise to fluidity change and leakage of the plasma content into the retina.[55] Additionally, high lipid levels cause endothelial dysfunction leading to blood retinal barrier impairment as proved by animal studies.[56] The lipid lowering drugs, atorvastatin, have been shown to decrease DMO in two small studies, which also confirm that statins may be an adjunctive medication for the management of DMO. The recently published FIELD[57] (Fenofibrate Intervention and Event Lowering in Diabetes) and ACCORD[58] (Action to Control Cardiovascular Risk in Diabetes) studies indicate that use of fenofibrate for 5 years - which increases the HDL cholesterol, apolipoprotein (Apo) A1 levels, and decreases triglyceride and Apo B levels - lowers the need for laser treatment both in DR and DMO.[59] Owing to this, the management plan for DMO warrants evaluation and inclusion of all risk factors. In addition to these modifiable risk factors, one can

also have unmodifiable risk factors like genetic predisposition. For example, endothelial nitric oxide synthase gene polymorphism may give rise to a change in enzyme expression which may play a role in blood-retinal impairment; therefore, it is assumed to be a risk factor for DMO.[60] The C634-G polymorphism of VEGF, which is the major cytokine responsible for increased permeability, is also thought to be a risk for DR and DMO. Individuals carrying the 634-C allele present more transcription compared to those carrying 634-G allele.[61]

Among ocular risk factors for DMO, severity of DR is the major one. DMO can accompany every stage of DR. The incidence is 3% for mild non-proliferative DR, 38% for moderate non-proliferative DR, and 71% for proliferative DR.[7] In a recent study, increased activity of microvascular disease in the macular region has also been demonstrated to increase the rates of MA turnover and is associated with higher risk for development of CSMO.[62] Retinal arteriolar haemodynamic changes related to blood pressure, age, and duration for DM may also be associated with DMO.[63] Guan et al.[63] noted an increase of arterial circulation and vascular rigidity, especially in the maximum-minimum velocity. Klein et al.[64] reported association of DR progression risk with retinal vein thickness in a recent study.

Besides microvascular complications of DM, vitreous also plays a role in vascular permeability increase under the effect of various factors. Nasrallah et al.[65] declared that DMO is detected in 20% of DR patients with posterior vitreous detachment and in 55% of DR patients with attached hyaloid. These findings supported the role of vitreous traction in DMO pathogenesis. Hikichi et al.[66] detected spontaneous resolution of DMO in 55% of patients with vitreomacular detachment and 25% of patients with vitreomacular attachment longer than 25%. The promising results of vitrectomy as a treatment for DMO is further proof for the role of the vitreous in DMO pathogenesis. Stefánsson[18] suggested that vitrectomy clears VEGF and other cytokines from vitreous, and replacement of vitreous gel with saline facilitates oxygen transport to ischaemic retina. He further explained the effect of traction on retinal oedema by Newton's third law: a force is always met by an equal and opposite force in the retina and this tends to pull the tissue apart and lowers the tissue pressure in the retina. The lowered tissue pressure increases the difference between the hydrostatic pressure in the blood vessels and tissue, and this contributes to oedema formation. However, it is still a matter of debate whether DMO forms a rich environment due to cellular proliferation or vitreoschisis exacerbates DMO.

The wide field angiogram enabled the identification of another risk factor for DMO: the peripheral retinal ischaemia. The RaScal study[67] clearly demonstrated that DMO patients receiving peripheral laser plus ranibizumab treatment showed less recurrence and a decrease in central foveal thickness compared to patients who received macular laser plus intravitreal triamcinolone acetonide. Intraocular surgeries, such as for cataracts, may also have an exacerbating effect on DMO; this is presumed to be related to an exacerbation of the existing chronic inflammation in DMO.[68,69] There are also some protective ocular factors for DMO, such as axial length. Man et al.[70] reported that long axial length is protective for both DR and DMO.

CONCLUSION

Regarding its negative impact on vision and thus QoL, the prevention and treatment of DMO is an important issue that warrants proper and on-time management. Various treatment modalities have to work in synergy and supplement each other for ideal treatment. Intraocular injection of anti-VEGF antibodies can remove VEGF from the retina, and steroids may reduce permeability.

Laser and vitrectomy can increase retinal oxygen tension and thereby reduce VEGF production. Posterior vitreous detachment and vitrectomy can increase diffusion and convection in the vitreous and increase clearance of VEGF and other cytokines from the retina. The hydrostatic gradient between microcirculation and tissue may be reduced by either decreasing the hydrostatic pressure in microcirculation by reducing the arterial blood pressure or by releasing vitreoretinal traction; thus, increasing the tissue pressure. Improved retinal oxygenation through laser treatment or vitrectomy also constricts the retinal arterioles, increases their resistance, and reduces hydrostatic pressure in microcirculation. The Diabetic Macular Edema Treatment Guideline Working Group suggested the use of anti-VEGF therapy for a centre involving patients with a visual acuity <20/32 and laser photocoagulation for patients with a visual acuity >20/32 or DMO not involving the centre. Additional treatment modalities are usually applied in an individualised algorithm; however, close follow-up and control of the modifiable risk factors are of the utmost importance in the treatment of each individual with DMO.

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