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Risk Factors for Diabetic Macular Edema-An Overview

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ABSTRACT

Diabetes mellitus is one of our century's most common general health problems. By determining multiple systemic complications, this disease alters diabetic patient's quality of life, while also increasing the mortality rate. One of the most frequent and life-impacting complications is represented by diabetic macular edema and diabetic retinopathy, as they determine visual impairment and increase the risk of blindness. This review aims to evaluate the most important risk factors associated with the development of these pathologies.

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Introduction

Diabetes Mellitus (DM) has become one of the most serious and common chronic diseases of our time [1]. The global prevalence of DM has reached pandemic proportions. The rising prevalence of diabetes has been attributed principally to the increase in the proportion of people >65 years of age in the general population. However, decreasing mortality among those with diabetes due to improving medical care as well as an increase in diabetes incidence in some countries resulting from a rising occurrence of diabetes risk factors, especially obesity, are also important drivers of the higher prevalence of DM [2,3].

DM is the most common disease causing life-threatening, disabling and costly complications, and reducing life expectancy [4].

Over 90% of patients with diabetes have type 2 DM (T2DM). Diabetic complications can be classified according to organ involvement in cardiopathy, encephalopathy, nephropathy, retinopathy, and peripheral vasculopathy. DM increases the risk of all these complications, and multiple vasculopathy is associated with a poorer general prognosis. Diabetic complications are usually classified into two main categories: macro/microvascular disease, or complications classified by target organs [5]. One of the most life-impacting DM complications are represented by Diabetic Retinopathy (DR) and Diabetic Macular Edema (DME), the latter being considered the most frequent blindness cause among these patients. This review aims to present the main systemic risk factors that are involved both in the occurrence and progression of DME.

Definition of DME

DME represents retinal fluid accumulation, especially in the outer and inner plexiform layers, that determines a subsequent retinal thickening within two-disc diameters of the macular center. It is usually associated with the presence of hard exudates, that can be identified as white-yellow deposits in the macular area. The main mechanism responsible for diffuse edema is represented by Blood-Retinal Barrier (BRB) breakdown, that further determines leakage from arterioles, retinal capillaries and microaneuvrysms. DME is one of the most frequent causes of visual impairment worldwide, therefore prompt diagnosis and treatment are crucial to improve diabetic patients' quality of life, but also the healthcare system economic hardship [6].

Epidemiology of DME

Population-based studies have shown that patients with DM have a higher risk of developing multiple ophthalmic conditions, including DR, DME, cataract, diabetic papillopathy, glaucoma, central retinal vein occlusion, dry eye syndrome, and infectious diseases. These conditions are often associated with progressive visual loss [7-14].

Proliferative Diabetic Retinopathy (PDR) is a vision-threatening ocular complication of DM. Still, DME is responsible for most of the vision loss experienced by diabetic patients [15]. DME can occur in any stage of DR, but it is almost unfailingly present in patients with T2DM that present PDR [16]. Additionally, DR and DME have also been linked to the occurrence of other severe diabetes-related complications such as cardiovascular events, nephropathy and peripheral neuropathy [17,18].

The prevalence of DME is estimated to be between 4.2 and 7.9% among patients with type 1 DM (T1DM) and 1.4 to 12.8% among those with T2DM [19].

Only a few population-based studies worldwide evaluate the incidence of DR, and even less focus only on DME. This lack of systematic medical information is mostly due to the fact that developing countries are not able to sustain the needed medical infrastructure to evaluate diabetic patients long-term. However, in the last half a century there have been a few large cohort studies conducted worldwide that aimed to evaluate DR and DME.

The most elaborate of these studies is the Wisconsin Epidemiologic Study of Diabetic Retinopa-thy (WESDR), which has evaluated T1DM over a period of 25 years, showing a 59% cumulative 4 years incidence of DR, that reached as far as 97% at the final evaluation at 25 years, while the incidence of DME in the same group was of 29 % [20].

Regarding T2DM patients, Europe and USA had a similar incidence of DR, ranging from 26% at 4 years to 72.3% at 14 years, while Asia reported a significantly higher incidence of 47.9% at the 5 years evaluation [20].

Most of long-term cohort population-based studies, especially those involving T1DM patients, have been conducted a while ago, therefore the present incidence of DR and DME is considered to be a lot lower due to the significant development in assessing and managing diabetes and DR risk factors.

Risk Factors Involved in DME

DME is more common among people with T2DM than those with T1DM. Even though increased diabetes duration is a strong risk factor for DME, this association might not be as strong as it is for DR. There are a great number of systemic risk factors that contribute to the development of DR and DME, currently targeted by healthcare professionals worldwide in an attempt to reduce the occurrence of general and ocular DM complications.

Poor Glycemic Control

There is a general consensus that hyperglycemia is the most important factor that increases the risk of both DR and DME. Graue- Hernandez et.al. have found an increasing prevalence of DR ranging from 9.2% at HbA1c lower than 7%, to 24.6% when HbA1c was higher than 9%. Regarding DME, prevalence varied between 3.1% and 9.4 %, when evaluated at the same HbA1c levels [21]. Considering these findings, managing hyperglycemia remains the key factor in avoiding DR and DME occurrence, as only a 1% decrease in HbA1c leads to a 10-25% lower risk of DME development and a 31% decrease of laser therapy necessity according to DCCT/EDIC [22].

Diabetes Type/Duration

A strong correlation exists between DM duration and the incidence and prevalence of ocular complications such as DR and DME. Still, differences should be noted between T1DM and T2DM patients when evaluating the risk of their occurrence. T1DM subjects are prone to develop significant DR and DME usually only after 5 years of diabetes duration, while T2DM patients might have DME at the time of diagnosis [6].

The WESDR has shown a 10-year incidence of DME of 20-25% in T1DM patients, reaching 29% at 25 years, without a linear relation to diabetes duration, perhaps due to increase in medical care in the latter years of the study [20].

Diabetic Retinopathy Severity

DME can virtually occur in any stage of DR, affecting about 5.5% of people with diabetes [23]. Studies have shown that the presence of DME increases with the severity of DR, without any clear correlation between the stage of DR and the severity of DME [24].

According to WESDR, DME was present in 3% of eyes with mild non-proliferative diabetic ret-inopathy, 38% in severe non-proliferative diabetic retinopathy and 71% of the cases with PDR [20].

Insulin Usage

Insulin remains the elected treatment in T1DM, but it is very also important in those with T2DM in whom glycemic control could not be further improved or obtained with oral medication. However, despite the obvious benefits on glycemic control, several studies have found insulin to actually increase the risk of proliferative DR and DME [25].

Genetic Factors

Few studies have evaluated the genetic risk factors that contribute to the development of DME and it's response to treatment, most of them mainly referring to DR. Systemic risk factors in conjunction with poor diabetes management represent only a part of the problem. Given the fact that some diabetic patients develop general and ocular complications only after a short duration of the disease, while others remain complication-free long-term, genetic contribution to this variability becomes of great interest. The most frequent candidate genes studied in relationship with DME are: Apolipoprotein E (APOE), Erythropoietin (EPO), Nitric Oxide Synthase (NOS), Vascular Endothelial Growth Factor A (VEGF A), Vascular Endothelial Growth Factor C (VEGF C), Manganese Superoxide Dismutase (SOD2), Pigment Epithelium-Derived Factor (PEDF), Aldose Reductase (ALR 2) and Micro Rna Genes (mi RNA) [26].

As most of diabetic patients simultaneously present DR and DME, it becomes quite difficult to only evaluate the genetic profile involved in DME. Another significant limitation regarding all the available data is represented by the small number of studies developed in this direction, most of them having relatively small patient groups. Still, since it is known that variability exists not only regarding the occurrence of ocular disease, but also involving the response to intravitreal injections with anti-VEGF, the most frequent and effective treatment in DME, larger studies involving the genetic field should be taken into consideration [27].

Hypertension

Most diabetic patients, especially those with T2DM end up having high blood pressure (values as high as 140/90 mmHg or higher). By the age of 60 years old, 47% of these patients are diagnosed with hypertension (HTA) [28]. Therefore, recent studies have evaluated the association between HTA and diabetic eye disease. Results have shown that even in diabetic patients with normal elevated blood pressure (values above 120/80 mmHg) the prevalence of DR increased with 11.49%, while DME was found mostly in the group with moderate HTA [29].Furthermore, regarding HTA treatment, the risk of diabetic ocular complication was found to be significantly reduced when a tight blood pressure control was applied-only a 10 mmHg decrease of systolic blood pressure leading to a 15% decreased risk of DME development, need for retinal Argon laser photocoagulation and vision loss, according to UKPDS 69 [28].

Dyslipidemia

In addition to glycemic control and hypertension, dyslipidemia

is considered one of the key risk factors associated with DR and DME. The underlying mechanism could be explained by permeability changes of the retinal microvessels, therefore secondary retinal leakage and deposition of exudates [30]. Different studies have evaluated both cholesterol fractions and triglycerides' impact on retinal health in diabetic patients. High LDL-c levels have been associated with an in-creased incidence of DR, while diabetic patients with DME had significantly higher levels of both triglycerides and LDL-c, when compared to diabetic persons without DME [31,32]. Mostly, diabetic patients with dyslipidemia are treated with a combination of statin and fenofibrate but their direct impact on progression of DR and DME are still to be further investigated. Recent data have shown that statins alone have no impact on progression of DR, while in association with fenofibrate, there is a temporary reduced progression of DR, according to ACCORD study [33,34]. The benefits of fenofibrate administration in diabetic patients with dyslipidemia and diabetic ocular disease has also been evidenced by the FIELD study, as it reduced the need for Argon laser retinal photocoagulation for DME by 31% and the occurrence of DME by 64% [35]. Even if data regarding the direct involvement of dyslipidemia on the progression of DR and DME are still somewhat inconclusive, the benefits of lipid-lowering agents are to be taken into consideration [36].

Nephropathy

Diabetic nephropathy, is one of the major microvascular complications of DM and it is mainly characterized by a decreased glomerular filtration rate and albuminuria. The latter it is known to determine vascular injury and endothelial dysfunction, and a similar mechanism also found in the development of DME. Given this aspect it is known that the severity of diabetic neuropathy is both associated with DME development and a possible progression indicator of DR, suggesting that diabetic patients with poor kidney function should undergo an ophthalmologic evaluation as they might have diabetic ocular complications [37-39].

Neuropathy

Diabetic neuropathy with its four subtypes (peripheral, autonomic, proximal and focal) refers to nerve damage caused by poorly controlled diabetes in individuals with long-term disease. According to a US study, patients who end up developing neuropathy are prone also to develop DME (HR=1.41;95% CI 1.50-1.69, $p<0.0001$), while significant correlation between peripheral neuropathy and DME ($p<0.006$) was found in a study conducted by D. Acan et.al [19, 40].

Anemia

Anemia, independent of kidney disease, is more frequent in diabetic patients. When evaluating the correlation between anemia and DR it has been shown that anemia is responsible for the progression and development of diabetic microvascular complications, anemic individuals being 1.8 times more likely to develop DR [41,42]. Furthermore, the risk of developing vision-threatening DR and DME is higher in patients with more severe anemia [43,44].

Sleep Apnea

Obstructive sleep apnea, a more and more concerning health problem, is more frequent in the diabetic population, it's prevalence reaching up to 36% [45]. It is known that patients with DME have a prevalence of obstructive sleep apnea ranging from 70.7% to 80.6% [46].

Obesity

Weight control is one of the most challenging aspects regarding the treatment of diabetes, most of diabetic patients being overweight, especially those with T2DM. As the body mass index elevates, the prevalence of DME increases. Furthermore, concerning treatment results in DME, lowering body mass had a beneficial effect on obtaining a better visual acuity post-treatment [21].

Cataract Surgery

Diabetic patients are 5 times more likely to develop cataract than the general population [47]. The presence of diabetic ocular complications such as DR and DME is one of the main reasons that might determine a poor visual prognosis after cataract surgery. Worsening of DR and DME post-operative might occur due to postsurgical inflammation that is increased in diabetic patients, and might last up to 3 months after cataract surgery, and later start to decrease naturally. On the other hand, diabetic patients have a higher risk of developing macular edema post-cataract surgery even in the absence of retinopathy, a risk that gradually increases with the severity of diabetic retinopathy [48,49].

Pregnancy

Pregnancy is considered to determine a state of general hyperdynamic circulation having as a possible consequence the progression of DR and DME. The presence of DME at conception is considered a direct cause of worse visual outcome, even after adequate treatment [50]. Managing these ocular complications means using retinal laser treatment or anti-VEGF intravitreal injections, but it remains a challenge due to possible side effects, so if the clinical situation allows it, delaying treatment and close monitoring remains a frequent option. Still, improved screening methods for diabetes during pregnancy and better treatment options have led to a good pregnancy outcome in diabetic patients, considering that in the 1970' PDR was an indication to terminate the pregnancy [51].

Lifestyle

Smoking is known to have a negative effect on glycemic control and evolution of diabetes, as nicotine tends to impair insulin activity, therefore determining an increase in blood sugar levels and subsequent risk of diabetic complications. Still, regarding the direct impact of smoking on DR and DME data is inconsistent, ranging from a evidence of progression of DR in T1DM patients, to a lack of relationship in progression over 4 years in the WESDR study, while smaller studies shown that current smokers were less likely to have DME [20,52,53].

When referring to alcohol, studies have shown inconclusive data between alcohol consumption and the progression of DR and DME. Still, chronic heavy usage of alcohol determines an increase in overall inflammation, which has a negative effect on general and eye health [54].

Gender/Ethnicity

Regarding gender, male subjects with diabetes tend to have more frequent ocular complications. Type 1 diabetic males have a greater risk of progression of DR, while type 2 subjects have a more severe degree of DR at the time of diagnosis with DM [55]. DME also remains more prevalent in male subjects [19].

DR and DME are known to be more frequent in black and hispanic diabetic patients. Still, conclusive data regarding the ethnic distribution of vision-threatening DR is yet to be determined, as minorities tend to be underrepresented in large clinical trials [56].

Clinical Assessment and Imaging of DME

Clinically, DME is defined by the presence of hard exudates, microaneuvrysms and blot hemorrhages within one disc diameter

of the center of the macula, determined by intraretinal leakage of fluid, lipids and protein. All these structural alterations leading to progressive thickening of the retina. Since the 1980's, the most used grading system was the one developed by the Early Treatment Diabetic Retinopathy Study (ETDRS), which defines the notion of non-clinically significant macular edema and clinically significant macular edema, the latter implying retinal thickening within 500 μm or less from the center of the macula, or hard exudates with adjacent retinal thickening within 500 μm or less from the center of the macula or at least one disc size area of retinal thickening anywhere within one disc diameter from the center of the macula[57]. Besides the ETDRS, other similar grading systems such as The International Clinical Disease Severity Scale for diabetic retinopathy, might be outdated but still of great importance, leaving space for more up-to-date protocols like the SAVE grading protocol, or the classification proposed by Otani both evaluating tomographic features of retinal changes in diabetic patients [58-60].

From Helmholtz's invention of the ophthalmoscope in the 1850's to artificial intelligence, evaluating and grading DME has come a long way [61,62]. Even with all this progress, first objective in evaluating a diabetic patient remains to assess visual acuity, but mostly as a parameter of following the progression of DME, since in early stages edema might not alter it significantly [63]. The next step is represented by a dilated fundus exam, obtained by a slit lamp biomicroscopy of the posterior pole, in order to evaluate the presence of exudates, retinal hemorrhages, area of retinal thickening and presence of cystoid changes [64]. This method alongside fundus photography remain quite subjective and somewhat time-consuming, as mild or moderate thickening of the macular area might go undetected [65]. A more advanced variant of fundus photography is fundus autofluorescence imaging (FAF), based on mapping fluorophores such as lipofuscin in the retina [66]. Regarding DME, the usage of blue FAF has shown a 80% sensitivity and 89% specificity, while green FAF remains of a more limited value [67]. Due to oxidative stress, macular pigment is diminished in DME, therefore measuring macular pigment optical density (MPOD) has been considered as a tool to diagnose DME, revealing 91% specificity and 80% sensitivity. Both blue FAF and MPOD have limited usage in these areas of diagnosis due to low sensitivity [68].

A more invasive option to asses retinal complications of DM is fluorescein angiography, method that implies intravenous injection of fluorescein dye while assessing patterns of hyper fluorescence in retinal vessels, determined by the disrupted BRB in diabetic eyes [69]. It serves mostly to guide laser photocoagulation in eyes with DR, rather than diagnose DME. Also, side effects ranging from mild ones as slight nausea to risk of anaphylaxis are to be considered [70].

These days, the most frequently performed imaging modality for evaluating retinal diseases is represented by optical coherence tomography (OCT) [71]. Having a similar working principle as the ultrasound, it makes it a repetitive method without implying patient-related risks, therefore being the most useful tool in grading DME, establishing a treatment protocol and a accurate followup [72,73]. OCT offers the possibility to quantify macular thickening as well as detailed cross-sectional imaging of retinal structures in order to identify diabetes related ocular complications such as diffuse retinal thickening, epiretinal membranes, posterior hyaloid traction, serous or tractional retinal detachment [74,75]. In addition, the more recent OCT variant, OCT-angiography offers simultaneous high-resolution images of both retinal and choroidal vasculature, but is still not used on a large scale in clinical practice [76]. Paired with these devices, adaptive optics tools by the usage of wavefront sensors reduce the aberrations' effect on retinal imaging, while also having a future potential in detecting retinal vasculature alterations in diabetic patients [77].

Emerging technologies such as the above-mentioned macular pigment optical density (MPOD) and adaptive optics (AO) have been tested or used alongside already known imaging devices, but their role is yet to be defined in diagnosing and grading DR and DME [77,78]. While all these and the more recent telemedicine development [79] still have a long way to go until daily base usage, OCT remains the most precise clinical assessment tool of DME [80].

General Treatment Approach of DME

Treatment approach of DME depends on the patient's baseline visual acuity, but also on the extend of the retinal disease. Patients that do not have clinically significant macular involvement, are asymptomatic and have a visual acuity >20/25 are usually observed. Once the patient is symptomatic due to DME, central retinal thickness increases beyond 300 microns, or visual acuity lowers under 20/30, treatment must be initiated, meaning choosing between retinal laser photocoagulation or intravitreal injections with either anti-VEGF or corticosteroids [81].

Retinal laser treatment remains the gold standard for treating PDR, but is still of great importance in DME management [82].

Anti- VEGF represent a great innovation regarding the treatment of DME, their use being associated with vision loss reverse, unlike laser therapy[83-85]. Substances like off label bevacizumab or the FDA approved substances ranibizumab, aflibercept or the most recent brolicizumab and faricimab are used in treatment protocols that usually begin with a loading dose of 3-6 monthly injections, that are later continued according to diabetic retinal disease progression [86].

Intravitreal corticosteroids represent the therapeutic algorithm for patients with chronic DME, that no longer benefit from receiving anti-VEGF agents [87]. For these particular cases, intravitreal injection of agents like triamcinolone, or implants with dexametazone or fluocinolone acetonide that have a sustained-release of the therapeutic agent become the treatment of choice [88-90]. Regardless the chosen medical approach, treating DME remains a challenge, considering that each of these therapeutic options imply certain patient-related risks and treatment results depend on the patients' retinal disease individuality and compliance to treatment [91-93].

Conclusion

The main purposes when treating DR and DME refer to maintaining or improving visual acuity in diabetic patients and at the same time preventing any further retinal, especially macular structural damage [86].

In order to achieve these goals, the first step is represented by the systemic management of the above-mentioned risk factors involved in the development and progression of DR and DME [94]. While some factors like gender/ethnicity, genetic factors, diabetes type/duration and pregnancy status are unmodifiable, all others must be taken under strict observation and management. Therefore, a strict glycemic and blood pressure control must be imposed, but also lowering lipid levels, proper management of obesity, sleep apnea, renal impairment and anemia must be

obtained. Last but not least, cessation of smoking and alcohol consumption must be advised in all diabetic patients, regardless of retinal complications degree [86].

A better understanding of the ocular pathology among the general medical profession is essential for an optimal therapeutic approach regarding diabetic population [25]. Patients with uncontrolled diabetes are at risk of developing a variety of ocular pathologies that affect almost every part of the eye. While vision-threatening conditions like DR, DME, and cataracts are more widely recognized, it is important to acknowledge the effects of diabetes on other ocular tissues, as these can also lead to a decline in visual function [95]. Apart from DR and DME, other diabetes-related ocular pathologies, such as cataracts, diabetes-related refractive changes, infections, and optic neuropathies (such as diabetic papillopathy and non-arteritic anterior ischemic optic neuropathy), are also linked to chronic hyperglycemia [96].

Considering the major social impact and economic burden of diabetes-related ocular pathologies, especially DME, a better medical screening of at-risk populations and a more efficient management of the risk factors that contribute to the development of this pathology are the first and maybe the most important steps in improving the diabetic patients' quality of life.

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