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Research Article

The impact of DME treatment on diabetic patients

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Abstract

Background: Both type 1 and type 2 diabetics can potentially develop nephropathy, neuropathy, and retinopathy. Diabetic macular edema(DME) is associated with the severity of diabetic retinopathy (DR). DME results from chronic damage to the microvascular structures of the retina, and together with HbA1C is a clinically proven risk factor for the progression of retinopathy. The duration of diabetes in patients affects both the prevalence and incidence of macular edema, progression of retinopathy, and other complications of the disease. Patients with type 2 diabetes may exhibit signs of diabetes at a significantly late stage of the disease, most often in the presence of macular edema. It is even possible to report no presence of reduced vision. Screening diabetic patients for early detection of retinal abnormalities is essential to prevent the development of DR/DME and avoid vision loss.

Aims: To find and analyze treatment options for DME for diabetic patients.

Methods: This literature review was based on an extensive search of medical databases, including PubMed, Web of Science, and Scopus, by keywords: „diabetic retinopathy", „visual loss", „treatment". The publication time span included articles that appeared between December 01, 2015 and January 01. 2023. Forty-four original works selected for inclusion in the review . It had two main goals:

(1) To examine systematically, in the context of DR, existing therapies for DME.
(2) To work towards improved therapeutic outcomes for DME among individuals with DR.

Results: Traditional diabetes therapy involves photocoagulation or laser treatment. Recently developed pharmacotherapies use anti-VEGF products or corticosteroids. They are designed to attack specific molecular pathways associated with the development of DR. Gene therapies could be a prospective treatment option for some patients. They target those genes that appear involved in generating vascular abnormalities or trigger an inflammatory response and attempt to neutralize their activity.

Conclusion: This literature review examines the advantages and disadvantages of all treatment options for diabetic retinopathy patients'. It could provide all practitioners with important and in-depth information on the current aspects of diabetic retinopathy treatment.

Keywords

diabetic retinopathy, diabetic macular edema, vision loss, treatment

Introduction

DME is a major complication of diabetic retinopathy, the commonest condition in diabetics. With the rapid spread of diabetes worldwide, DME is also on an upswing (Morales-Brown 2023). A person with DR has an increased chance of developing DME, according to Im et al. (2022). All forms of DR represent a major burden to individuals and healthcare systems in terms of both economic and social impacts. Scientific researchers are investigating suitable and effective treatment strategies for this disease that threatens vision. The connection between DME and DR stresses the significance of a thorough scholarly and practical study of effective treatments. With the progression of DR, the risk for macular edema increases (Morales-Brown 2023). This underscores that all currently employed modes of treatment need to be carefully scrutinized and possibly improved. This exploration aims to identify the problematic areas of current interventions for DME fitting within interventions for DR and look for more effective, side-effect, or beneficial answers.

Methods

Inclusion and exclusion criteria

This literature review rests on an extensive search of databases, including PubMed, Web of Science, and Scopus for the timeframe between December 01, 2015 and January 01. 2023.

The inclusion criteria in this review evaluate studies that compare anti-VEGF, corticosteroids or photocoagulation treatment of diabetic retinopathy patients published between 2015 and -2023.

The exclusion criteria concern all studies, published before 2014 and in a language other than English.

DME is a complication of diabetic retinopathy. It involves the swelling or leaking from abnormal new vessels growing above the macula due to damage to the retina by high blood sugar levels (Morales-Brown 2023). According to research, 5.5 per cent of people with diabetes develop DME (Im et al. 2022). Teo et al. (2021) estimated the global preference for DME in 2021 to be 27%.

One study reported that in 2019, there were 463 million diabetes mellitus patients, while the International Diabetes Federation estimated this figure would increase to a staggering level of 700 million across the globe by the year 2045. According to the National Eye Institute (2022), in the USA, about 30 million people are said to have diabetes. Prolonged contact with high blood sugar levels affects the walls of retinal vessels, especially in serious diabetic cases (F. Morales-Brown 2023). DME is accompanied by a buildup of fluid in the macula, which impairs its normal functions and causes vision loss. In short, DME sufferers may have blurred or distorted central vision and reading faces is exhausting (Prevent Blindness 2016; Morales-Brown 2023). DME is a progressive disease, which, if left untreated, can lead to a severe vision loss.

Epidemiological context and prevalence

DME is a common complication of diabetes, especially in people with long-standing diabetes. For example, a cross-sectional study by Lundeen et al. (2022) indicated that the prevalence of DME incidents among diabetic patients increased from 2.8 percent to 4.3 percent between 2009 and 2018. The annual prevalence of anti-vascular endothelial growth factor injections doubled among those with DME, from 15.7 percent to 35.2 percent. The disease prevalently affects people aged 18 to 64 in America (American Academy of Ophthalmology 2021). Because DME becomes more common with longer durations of diabetes, we can say that the condition is chronic. In addition, poor glycemic control and hypertension make patients more susceptible to developing DME. It is becoming ever more significant as the prevalence of diabetes rises throughout the world (Thomas et al. 2019). As a result, DME has become one of the major causes of visual impairment and blindness in working-age adults.

Influence on vision and quality of life

Beyond the physical aspects of DME, vision capabilities and overall quality of life are greatly compromised. This means that DME directly affects activities that require clear sight, such as reading, driving, and facial recognition. DME's relentless blurriness and distortion can cause aggravation, anxiety, and a loss of focus on everyday chores (Shrestha et al. 2022).

Definition and etiology of DR

DR involves damage to the vasculature of the retina. It is one of many complications caused by diabetes. This is because long-term high blood sugar damages the tiny vessels in the retina. Individuals with both vision-threatening diabetic retinopathy and its most common complication, DME, increased from 20.3% to 47.6% (Lundeen et al. 2022). According to the statistics, DR affects 27.0 percent of all diabetics globally and causes blindness in about 480 thousand people around the world every year (Thomas et al. 2019). DR goes through several stages and the retinal blood vessels change differently at each stage. As DR progresses, the effect on retinal blood vessels means these may later suffer fluid leakage or even bleeding. (Morales-Brown 2023). An estimated 4.8 percent of the world's total population with blindness (37 million cases) is attributable to DR, according to a study by the WHO (Shrestha et al. 2022). This is important because it shows vividly why both conditions cannot be treated in isolation, but rather require a more comprehensive approach to prevent losing sight completely. That is the purpose this literature review has set to investigate. As a disease, diabetes causes hyperglycemia due to insufficient insulin action or secretion. Both type 1 and type

2 diabetics can develop complications such as nephropathy, neuropathy, and retinopathy (Suzuki et al. 2023).

According to a review article by Mariya Kalinkova (Kalinkova et al. 2023) the early treatment and prevention of type 2 diabetes can decrease complications. In this way, diabetic macular edema could be avoided. Normally it results from chronic damage to the microvascular structures of the retina (Cohen and Gardner 2016). DME is „retinal thickening within one disk diameter of the center of the macula or definite hard exudates in this region" (Suzuki et al. 2023).

Patients with type 1 diabetes are unlikely to develop macular edema or advanced retinopathy before five years of diagnosis (Musat et al. 2015). Patients with type 1 diabetes have a 75% risk of developing retinopathy, while patients with type 2 diabetes have a 50% risk of developing retinopathy. Patients with type 2 diabetes have a 25% risk of developing DME. The symptoms that appear in patients with diabetes and DME are extensive, depending on the chronicity of the edema and the degree of impairment of the fovea. Patients with DME may also show no symptoms in cases where the macula's centre is unaffected. Gradual progressive vision loss begins to be experienced by patients within weeks or months of central macular involvement. Clinical manifestations can be loss of color vision, poor vision in dark rooms or at night, and a complex adaptation from light to dark and vice versa. Often, patients with DME and central macular involvement complain of fluctuations in vision during the day, with vision improving on one day and worsening on another. These fluctuations in vision are associated with both environmental factors and the presence of hyper or hypoglycemia (Yanoff et al. 2014).

According to Musat (2015), diffuse DME is complicated to diagnose because of the lack of reference points in cases where the retina is of uniform thickness. The height of blood vessels above the retina, cystoid spaces, and loss of foveal depression are used for clinical identification. Scattered patches of hard exudates and intraretinal hemorrhages can be identified as other features that are sometimes seen in diffuse DME (Musat et al. 2015). In diabetic patients, retinal dysfunction begins before microvascular lesions appear. DME in diabetic patients is diagnosed based on signs such as visible hemorrhages, lipid deposits, microaneurysms, and neovascularization. Advances in technology allow modern imaging methods to study retinal diseases, allowing the creation of macular thickness maps and OCT images. Factors that increase the risk of DME are associated with (Musat et al. 2015):

- Duration of diabetes – in patients who have been diagnosed with diabetes for a longer time, there is a higher risk of diabetic retinopathy.
- Blood sugar – controlling blood sugar within certain limits reduces the risk of developing diabetic retinopathy, as glycosylated hemoglobin (HbA1c) should be within 7%.
- The presence of nephropathy – proteinuria is a marker associated with the development of diabetic retinopathy. Therefore, patients with diabetes and nephropathy should be monitored for the development of DME. Patients with hypertension – hypertension increases the risk of diabetic retinopathy.
- Dyslipidemia – control is required to normalize lipid levels, thereby limiting the risk of DME.
- Pregnancy – DME can progress rapidly in pregnant women, especially those with pre-existing diabetic retinopathy.

Cataracts and diabetic nephropathy are among the most significant impairments in patients with diabetes, increasing the risk of visual blindness in adults under 70. Visual impairment in patients with diabetes significantly impacts patients' ability to control the disease, including reflecting on overall life expectancy and the manifestation of various diabetic complications (Wiliams et al. 2004). DME can occur in patients at any stage of diabetes, affecting central visual acuity.

Mechanisms for diagnosis of DME in DR

DME is a critical complication of DR, necessitating an accurate diagnosis for effective management (Schmidt-Erfurth et al. 2017). This article explores the diagnostic aspects of DR in DME, focusing on angiographic manifestations and features revealed by optical coherence tomography (OCT) based on various sources.

Angiographic manifestations in DME

Fluorescein angiography (FA) has long been a staple in DR diagnostics, aiding in severity assessment and guiding laser therapy. While there is an ongoing debate on its role in DME management, FA remains essential for distinguishing leaking microaneurysms (MA), identifying intraretinal microvascular abnormalities (IRMA), and outlining areas of capillary nonperfusion and foveal avascular zone (FAZ) widening (Kylstra et al. 1999). Emerging OCT angiography (OCT-A) offers promise, but FA provides a more comprehensive evaluation of morphological damage before treatment initiation.

Optical coherence tomography

OCT has revolutionized ophthalmic diagnostics, providing high-resolution images for retinal diseases, including DME (Gerendas et al. 2015). Recent OCT advancements, like swept-source (SS) technology, offer superior imaging capabilities (Schmidt-Erfurth et al. 2014). Qualitative features, such as subretinal fluid (SRF), intraretinal cystoid fluid (IRC), and vitreomacular interface status, contribute to disease characterization. While FA remains the gold standard, OCT is crucial in screening, classifying, and monitoring DME (Shin et al. 2011). On OCT, morphological signs like DRIL, changes in retinal layers, and hard

exudates are visible (Sun et al. 2014). Recent trials highlight the importance of individualized treatment regimens based on OCT biomarkers.

Implications for treatment strategies

The existence of DR has a big effect on the selection of treatments for DME. For treatment strategies, implications highlight the importance of involving ophthalmologists with experts in endocrinology and primary care physicians (Takamura et al. 2018; Tatsumi 2023). Everett and Paulus (2021), being closely related, warn that all parties must work together to treat both DR and DME.

Current treatment modalities

Photocoagulation and laser therapy

Traditionally, treatment for DME and DR involves photocoagulation or laser therapy. In this technique, the retina is burned with a laser, and distributed. Leaking blood vessels are cauterized to reduce fluid accumulation in the eye. This is particularly effective if abnormal blood vessels exist, as sealing them can prevent further loss (Everett and Paulus 2018). Laser therapy certainly has proven efficacy, but it does have drawbacks, too. One reason for adopting laser treatment is that it can damage healthy retinal tissue. This may result in losing the visual field (Tatsumi 2023).

Intravitreal injections of anti-VEGF agents

Intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents have become the standard first-line therapy for patients with DME (Tatsumi 2023). These include ranibizumab, aflibercept, bevacizumab, faricimab, and brolucizumab. Obstructing the VEGF pathway in eye tissue reduces blood vessel permeability that slow the filtering of fluids into the macula (Takamura et al. 2018; Tatsumi 2023). Ranibizumab is the Fab fragment of a humanized monoclonal antibody against VEGF (Chen et al. 2023). Aflibercept is a recombinant protein comprising human IgG and VEGF-R1 and – R2 fragments. Bevacizumab is a recombinant humanized monoclonal IgG antibody with two antigen-binding domains. Faricimab is an anti-VEGF/anti-Ang two-humanized bispecific monoclonal antibody. Brolucizumab is a humanized anti-VEGF monoclonal antibody with a single-chain FV fragment. It can block the binding of all VEGF-A isoforms to their receptors (American Academy of Ophthalmology 2021; Chen et al. 2023; Tatsumi 2023). The efficacy of anti-VEGF injections has been proven, with enhanced visual acuity and reduced central macular thickness (Takamura et al. 2018). However, the injections are frequent, and the potential side effects of raised intraocular pressure must be carefully considered.

Corticosteroid treatments

Corticosteroids have anti-inflammatory effects on processes linked with macular edema (Wu et al. 2019). Corticosteroids can be given via intravitreal injection or by sustained-release implant. Corticosteroids include dexamethasone (DEX), fluocinolone acetonide (FA), and triamcinolone acetonide (TA) (Tatsumi 2018). Corticosteroids can reduce the edema, but steroid use inevitably has adverse effects such as increased intraocular tension and cataract formation. Such treatment decisions involve weighing benefits against possible complications and tailoring the application method to an individual patient. Due to their poorer safety profile, corticosteroids are used as a second-line treatment for DME (Wu et al. 2019). The study by Wu et al. (2019) points out that using an intravitreal corticosteroid implant has many benefits, including reducing treatment burden. It ensures reliable pharmacokinetics, even in vitrectomized eyes.

The efficacy and limitations of treatment

The prevalence of DME has increased, with a concomitant increase in diabetic eye disorders. As to effectiveness, Khalil et al. (2023) published a study asserting that DME is best treated with anti-vascular endothelial growth factor (anti-VEGF) agents as the gold standard for treating this condition. In Tatsumi (2023), several studies showed that anti-VEGF intravitreal therapies fared much better than laser monotherapy in BCVA. But despite recent progress in medical science, there are still some obstacles to treating DME resulting from DR. The evaluation process for DME treatment is uncertain and complex, especially in consideration of visual acuity, macula thickness, or retinal changes (L. Morales-Brown 2023). Therefore, it is necessary to monitor the condition regularly to observe its development and decide on the relevance of any measure taken.

However, any approach has its limitations. Laser treatment is very effective, but impairs peripheral vision (Cambridge University Hospitals, n.d.) and must, therefore, be weighed carefully. Though anti-VEGF injections have been highly successful, they must be administered regularly, and some patients develop dampening responses over time. In addition, corticosteroid injections can treat macular edema. However, there are side effects to consider. Underscoring these differences justifies the requirement for a flexible management plan tailored to each patient's needs and responses.

Diabetic retinopathy interventions

Emerging pharmacotherapies

The last few years have seen important steps in developing DR pharmacotherapies, with several promising new drugs set to join current treatment options (Mayo Clinic 2023). Recently developed pharmacotherapies are designed to attack specific molecular pathways associated with the development of DR. These agents include integrin inhibitors and advanced glycation end-product (AGE) inhibitors,

all of which are able to prevent or ameliorate the vascular changes characteristic of diabetics. However, these therapies benefit from a heightened insight into retinal damage. Clinical trials are now being conducted to determine the safety and efficacy of these new pharmacotherapies, and early results look promising (Honasoge et al. 2019).

Gene therapies and individualized medicine

Gene therapies have brought a new era in DR treatment. It may change the concept of personalized medicine completely. All gene therapies aim to intervene at the level of genetics (Narayanan et al. 2021). They target those genes that appear involved in generating vascular abnormalities or start an inflammatory response and attempt to neutralize their activity by modifying these genetic elements responsible for retinal damage specifically caused by diabetes (Drag et al. 2023). In the DR setting, personalized medicine involves treatment strategies based on an individual's genetic profile to achieve better therapeutic results (Kumaran et al. 2018). With advancing genetic research, it is possible to recognize patients at higher risk for DR or poor treatment responses.

Nanotechnology applications

Nanotechnology promises to be an important part of all new approaches to Diabetic Retinopathy. The nano-sized drug delivery systems, including nanoparticles and their stealth counterparts, have novel properties that improve the stability of medicine and its bioavailability for treatment; they also allow targeted control on the administration of drugs precisely in desired retinal tissues (Liu and Wu 2021). These nanotechnological approaches attempt to improve the pharmacokinetics of therapeutic agents, making them released gradually and retained for longer periods within the eye. Making drug delivery more precise and controllable, nanoparticles can cover all drugs, including anti-inflammatory agents and angiogenesis inhibitors (Lemmerman et al. 2020).

In older patients, DME may be complicated by comorbidities, geriatric and socioeconomic syndromes. Sentaro Kusuhara et al. (2022) demonstrated that in comparison to younger patients, DME patients older than 75 years showed less improvement from treatment with anti-VEGF drugs, lower increase in BCVA and less reduction in CMT. Results in clinical practice are often unsatisfactory.

Conclusion

Generally, this literature review thoroughly examined the complex relationships between DR and its associated condition DME. Exploration exposed the rising global burden of diabetes and the impact of DME on patients' vision and quality of life. The stages and development of DR were dissected and diabetic complications are interrelated. This set the scene for an in-depth examination of existing therapeutic modalities, including laser therapy, anti-VEGF agents, and corticosteroids, and their effects. This integration of knowledge can serve as an important basis for objective decision-making and further diabetic complications research in a rapidly changing medical field.

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