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Review

Treatment of diabetic macular edema

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Summary

Diabetic macular edema (DME) is the most common cause of vision loss in individuals with diabetes mellitus, particularly in the working-age population, and its prevalence is increasing due to the global rise in diabetes incidence. The aim of this paper is to review current principles of DME diagnosis and treatment based on available scientific literature. This is a narrative review article, with a search of PubMed and Google Scholar databases. Optical coherence tomography (OCT) is the gold standard in diagnostics, enabling quantitative and qualitative assessment of edema. Anti-VEGF therapy is the first-line treatment for DME involving the center of the macula, demonstrating significant improvement in visual acuity. Corticosteroids represent a valuable alternative in patients who do not respond to anti-VEGF or have a prominent inflammatory component. Laser photocoagulation, although historically the gold standard, now plays a secondary role. Timely diagnosis and an individualized therapeutic approach are crucial for preserving visual function.

Key words: diabetic macular edema, diabetic retinopathy, anti-VEGF therapy, corticosteroids, laser photocoagulation

Introduction

Diabetic macular edema (DME) is defined as retinal thickening that involves or approaches the center of the macula and is the most common cause of vision decline in patients with diabetes mellitus [1]. Diabetic macular edema represents the accumulation of fluid within the central retina, resulting from breakdown of the blood-retinal barrier. DME is the leading cause of vision loss in the working-age population, and its frequency is increasing due to the significant rise in the incidence of diabetes mellitus worldwide [4]. The aim of this paper is to present, through a review of available professional and scientific literature, the current principles of

diagnosis and treatment of diabetic macular edema.

Methods

This paper is conceived as a narrative review. PubMed and Google Scholar databases were searched using the keywords: diabetic macular edema, anti-VEGF, laser photocoagulation, corticosteroids. Articles published between 2010 and 2024, as well as relevant clinical guidelines, were included.

Pathogenesis and classification

The pathogenesis of DME is complex and multifactorial, primarily involving breakdown of the blood-retinal barrier, which leads to accumulation of fluid and macromolecules from serum into intracellular spaces. Accelerated apoptosis of pericytes and endothelial cells, acellular capillaries, thickened basement membrane, and capillary occlusion result in endothelial damage and disruption of the inner blood-retinal barrier. DME can occur at any stage of diabetic retinopathy (DR), but is most commonly associated with longer duration and greater severity of DR [2].

The nature of DME is characterized by slow progression of retinal thickening until it involves the center of the macula, causing impairment of visual acuity. Spontaneous resolution of DME is rare and usually occurs secondary to improvement in systemic risk factors such as glycemic control, hypertension, and hypercholesterolemia [1].

DME can be classified as focal or diffuse. Focal macular edema manifests as a localized area of retinal thickening resulting from focal leakage from a microaneurysm or a cluster of microaneurysms. The area of focal leakage is usually clearly demarcated by a partial or complete ring of hard exudates in a circinate pattern.

Diffuse macular edema results from extensive damage to capillaries, microaneurysms, and arterioles, and manifests as more widespread macular thickening due to generalized abnormal leakage from the retinal capillary network. Diffuse macular edema tends to be symmetric and without significant exudation. Ocular and systemic risk factors for the development and progression of diffuse DME include increased number of microaneurysms, advanced retinopathy, vitreomacular traction, adult-onset diabetes, renal disease, and severe hypertension.

Cystoid macular edema, often associated with diffuse macular edema, results from generalized breakdown of the blood-retinal barrier with accumulation of fluid in a flower-petal pattern, primarily in the outer plexiform and inner nuclear layers. The presence or absence of cystic changes does not directly affect the prognosis or treatment of DME. In clinical practice, the distinction between focal and diffuse edema is not always clear, and mixed forms are frequently encountered [5].

Diagnosis

Diagnosis of DME is based on clinical examination, optical coherence tomography, fluorescein angiography, and OCT angiography. OCT can be used for screening, classification, monitoring, and assessment of DME treatment. It provides information on central macular thickness as well as various morphological characteristics of edema and can show morphological changes after DME treatment.

Fluorescein angiography (FA) can detect various signs of DR, such as microaneurysms, proliferative DR, and ischemic maculopathy. FA has been an important diagnostic tool in DR for decades and is formally recognized as a key component in assessing the severity of pathology and the precise location of retinal changes, enabling appropriate targeted laser therapy. FA is not required for diagnosing

DME, but it provides a qualitative assessment of vascular leakage, aiding in the detection of treatable changes, and is also important for assessing enlargement of the foveal avascular zone (FAZ), which may be associated with poor visual prognosis. The main advantage of OCT angiography over FA is the ability to focus on different retinal layers and to highlight changes at the level of the deep capillary plexus [6].

Treatment options

In addition to control of systemic disease, numerous ophthalmological treatment methods for DME exist: anti-VEGF agents, corticosteroids, laser photocoagulation, and pars plana vitrectomy.

Laser photocoagulation

Laser photocoagulation was the standard of care for DME before the advent of intravitreal injections [6]. Laser photocoagulation techniques for DME can be divided into focal or grid [8]. In clinical practice, mixed forms of DME are commonly encountered, where focal and diffuse leakage are combined, clearly visible on fluorescein angiography. In these cases, a modified grid laser technique is applied. This technique primarily consists of grid treatment of the area of diffuse leakage and focal treatment of localized leakages within or outside the area of diffuse edema [1].

A newer laser modality for DME is the micropulse laser, in which the laser beam is not continuous as in conventional laser, but is divided into multiple short, repetitive micro-pulses. A significant advantage of this laser is that there is currently no evidence of adverse effects or complications resulting from its use [4].

Clinical changes associated with worse visual acuity after DME laser photocoagulation include diffuse macular edema involving the center of the macula, macular ischemia, hard exudates in the fovea, diffuse fluorescein leakage, and pronounced cystoid macular edema [3].

Although historically the gold standard, laser photocoagulation today has a secondary role. Its use is recommended for focal DME without foveal center involvement or as adjunctive therapy to anti-VEGF.

Anti-VEGF therapy

Currently, drugs targeting excessive vascular endothelial growth factor (VEGF) in the eye are the most popular approach for treating DME. Their use requires numerous decisions, including choice of agent, treatment regimen, and combination with other options such as laser or corticosteroids [9]. Angiogenesis inhibitors block VEGF and other angiogenic factors influencing the development and progression of DME [4]. The most commonly used anti-VEGF agents are bevacizumab, ranibizumab, aflibercept, and faricimab.

Bevacizumab is a recombinant full-length monoclonal antibody that binds all VEGF isoforms [3, 6]. Ranibizumab is a recombinant humanized Fab fragment of a monoclonal antibody with high affinity for VEGF-A [5]. Aflibercept is a recombinant decoy receptor inhibitor for VEGF-A, VEGF-B, and placental growth factor, demonstrating efficacy and safety for DME treatment [7]. Faricimab is a monoclonal antibody that acts by inhibiting key mediators such as vascular endothelial growth factor-A (VEGF-A) and angiopoietin-2 (Ang-2) [10].

Table 1 compares the most commonly used anti-VEGF agents in the treatment of DME, showing their molecular structure and the standard intravitreal dose for each drug.

Anti-VEGF therapy is currently the most effective modality for treating DME involving the center of the macula, with level I evidence from randomized controlled trials.

Table 1. Comparison of anti-VEGF agents in the treatment of DME

Agent	Molecule type	Dose (intravitreal)
Bevacizumab	full-length monoclonal antibody	1.25 mg
Ranibizumab	Fab fragment	0.5 mg
Aflibercept	receptor-IgG fusion protein	2 mg
Faricimab	bispecific antibody (VEGF-A + Ang-2)	6 mg

Corticosteroids

Intravitreal corticosteroids have been used for a long time in the treatment of DME due to their anti-inflammatory and antiangiogenic effects. Corticosteroids reduce vascular permeability, fibrin accumulation, leukocyte migration, and help preserve the blood-retinal barrier. The use of corticosteroids in DME is indicated in cases where inflammation plays a key mechanism in the pathogenesis of the disease. The corticosteroids most commonly used in DME treatment can be administered intravitreally or parabulbarly [4]. Commercially available corticosteroids for intravitreal administration include triamcinolone acetonide, dexamethasone implant (Ozurdex), and fluocinolone (Iluvien) [9].

Corticosteroids (particularly the dexamethasone implant) represent a valuable alternative in patients who do not respond to anti-VEGF therapy, in those with pseudophakia (without risk of cataract), or in whom inflammation plays a key role. However, caution is needed due to possible elevation of intraocular pressure.

Individualized clinical choice

The clinical choice of therapy should be individualized, taking into account the morphological type of edema, OCT findings, the patient's systemic condition, and response to prior therapy.

Limitations

This paper represents a narrative literature review, not a systematic review or meta-analysis. No formal criteria for assessing the quality of included studies (e.g., PRISMA) were applied. The paper does not contain original clinical data, so the conclusions are based solely on the available literature. Therapeutic algorithms have not been validated in the local population of Bosnia and Herzegovina.

Conclusion

Diabetic macular edema (DME) is a major cause of vision loss in patients with diabetes. Diabetic macular edema progresses with the duration of diabetes and diabetic retinopathy. The development of various diagnostic methods and therapeutic options has increased the success rate of treatment and control of diabetic macular edema. Contemporary treatment of DME requires an individualized approach based on the morphological type of edema, OCT findings, and response to therapy, with anti-VEGF agents representing the current gold standard.

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Liječenje dijabetičkog makularnog edema

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Dijabetični makularni edem (DME) predstavlja najčešći uzrok gubitka vida kod osoba sa dijabetes melitusom, naročito u populaciji radno sposobnog uzrasta, a njegova prevalencija raste usljed globalnog porasta učestalosti dijabetesa. Cilj ovog rada jeste prikaz savremenih principa dijagnostike i liječenja DME na osnovu dostupne naučne literature. Rad predstavlja narativni pregled literature uz pretragu baza podataka PubMed i Google Scholar. Optička koherentna tomografija (OCT) predstavlja zlatni standard u dijagnostici, omogućavajući kvantitativnu i kvalitativnu procjenu edema. Anti-VEGF terapija predstavlja terapiju prvog izbora kod DME koji zahvata centar makule i pokazuje značajno poboljšanje vidne oštrine. Kortikosteroidi predstavljaju značajnu terapijsku alternativu kod pacijenata koji ne odgovaraju na anti-VEGF terapiju ili imaju izraženu inflamatornu komponentu. Laserska fotokoagulacija, iako istorijski zlatni standard, danas ima sekundarnu ulogu. Pravovremena dijagnoza i individualizovan terapijski pristup od ključnog su značaja za očuvanje vidne funkcije.

Ključne riječi: dijabetični makularni edem, dijabetična retinopatija, anti-VEGF terapija, kortikosteroidi, laserska fotokoagulacija