Endogenous endophthalmitis among people with diabetes; a review

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ABSTRACT

Although endogenous endophthalmitis (EE) among diabetic individuals (DEE) is uncommon, the prevalence of the condition has recently increased due to better intensive healthcare services available and increased longevity of critically ill patients with systemic infections. The existing literature was critically reviewed on DEE and its present incidence, risk factors, causative organisms, management, outcomes, and proposed measures to improve its public health approach. This review is of critical importance, as the COVID-19 pandemic has increased the risk of EE for diabetic patients as a result of a systemic infection. Aggressive glycemic control is concurrent with patient care for DEE management, which requires lifelong maintenance. Early detection and standard management are crucial for patients’ visual recovery. Still, a guarded prognosis is given to patients and relatives as outcomes are not always predictable. There is a need for the teamwork of ophthalmologists with other health professionals and patients throughout the management. The causative organisms, early pharmacotherapy suitable for the identified organisms, and pars plana vitrectomy are predictors of visual outcomes. DEE patients need lifelong eye care.

Keywords: Endogenous endophthalmitis, diabetic endogenous endophthalmitis, diabetes, COVID-19.

Introduction

Inflammation of the contents of intraocular cavities-including intraocular fluids, the vitreous body, and the aqueous humor-is called endophthalmitis, an emergency opthalmic condition that requires urgent treatment to avoid irreversible damage to the anatomy and functions of the visual apparatus. This damage could result in permanent blindness, a disorganized eyeball, and orbital cellulitis if the condition spreads, posing a potentially fatal risk to immunocompromised patients [1].

Dependent on the transmission mode of the causative agents, endophthalmitis could be either exogenous or endogenous. Exogenous endophthalmitis could occur after a surgery, an intraocular injection, or another form of intraocular trauma. The endogenous transmission of organisms occurs from other organs, primarily via a hematogenous route [2].

Because patients are increasingly surviving septicemia, the incidence of endogenous endophthalmitis (EE) is rising [3]. EE rarely occurs in healthy individuals, but it remains common among intravenous drug abusers, diabetic patients, individuals taking immunosuppressive medication for systemic diseases and malignancies, and those who have recently undergone a major surgical procedure [4].

The issue of EE is once again in focus as the incidence is reported during the COVID-19 pandemic [5,6]. Several articles have reviewed EE [7,8-10]. However, the evidence on the magnitude and management outcomes of EE among diabetic patients in isolation are limited. The focus on diabetic endogenous endophthalmitis (DEE) is essential for caregivers of patients in countries with a high incidence of diabetes. Of the 537 million adults with diabetes worldwide, 73 million live in the Middle East and North African regions, and this number is projected to rise to 95 million people by 2030 [11].

In this review article, the magnitude, risk factors, diagnosis, management outcomes, public health issues, and recommended clinical care were analyzed to address DEE.

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Endogenous endophthalmitis in diabetics

Subjects and Methods

The review was held between December 2021 and January 2022. In this review, research publications in the indexed journals from 2010 to 2021 were included. The existing evidence from the literature was used, and direct interaction with patients was not involved.

Two investigator ophthalmologists were involved in this review. A data search was done and a template was developed, pilot, and implemented. All review articles on EE and those regarding DEE in the final interpretation were included. Review articles written in non-English languages were excluded.

The MEDLINE/PubMed search was conducted using the following terms: endogen (all variations), endophthalmitis, diabetes mellitus (DM), humans, and English.

In addition to MEDLINE/PubMed, research articles were also reviewed and assembled using Google Scholar, Embase, Cochrane Library, and Scopus search engines.

All articles were collected using Zotero software; duplicate articles were identified and removed manually. The abstracts of the collected articles were then studied to ensure the relevance of the content. Two investigators independently studied these articles for shortlisting and collected full articles of those articles that fulfilled the inclusion criteria. Additionally, the level of evidence on the topic was reviewed for each article provided; the quality of evidence present in several articles was also reviewed wherein grading of evidence was not available.

However, a meta-analysis was not conducted because most of the studies were case series and case reports, and thus methods of reporting varied widely. The results were graphically prepared and described along with discussions as per the preplanned presentation framework.

Discussion

Although diabetes was a present comorbidity in many patients with EE, few articles focused specifically on DEE (Figure 1).

Magnitude of EE and DEE

In the United States, the incidence of EE among patients hospitalized with hematogenous infections is 0.05% to 0.04% and 0.04% to 0.5% among patients with sepsis [2,12]. The risk of EE among the diabetic population is high, but the incidence remains unknown. In a study of 120 patients with EE in Malaysia, 60% of patients were diabetic [13]. In a similar study conducted in Taiwan with 70 EE patients, 63.9% of patients were diabetic [14]. Thus, the odds of diabetes with ophthalmic manifestations including endophthalmitis among hospitalized patients with hematogenous infection is 7.02. The overall incidence of EE is low but increases dramatically among those with diabetes.

Factors related to DM and DEE

Type 2 DM is the most common predisposing medical illness for EE [14]. Diabetes patients who were treated and maintained their condition with medication were 47% less likely to have EE compared to those not treated with medication [15]. Those treated with a single drug regimen-including insulin or an oral medication-had a lesser risk of EE compared to those treated with a combination of insulin and oral therapy (adjusted hazard ratio 0.257-0.544). The risk difference of DEE was significantly more if a single treatment medication for diabetes was in a patient with liver abscess [15].

Sources of infection

The spread of endogenous infection to the vitreous and retina resulting in endophthalmitis is through the hematogenous route. Septicemia followed by a thromboembolic lesion that reaches the eye is the main mechanism by which organisms from other parts of the body—including the liver [15,16], urinary tract [17], heart [18], skin [19] and thyroid [20]-reach the eye. It is possible due to the breakage of oral, gastric, and intestinal mucosa after an invasive procedure such as endoscopy leading to transient bacteremia [21,22]. During the COVID-19 pandemic, DEE was reported from the prostate [23].

Organisms

Gram-positive bacteria are among the most commonly identifiable causative organisms of DEE [24]. These organisms include Staphylococcus, Streptococcus, Klebsiella, Candida, and Aspergillus species [1]. Among the Gram-positive isolates, Staphylococcus aureus is the leading cause of DEE in the United States and Europe, primarily reaching the eye via endocarditis [25]. In East Asia, Gram-negative bacteria are the more common culprits of DEE [15]. Klebsiella pneumoniae, a prominent cause of DEE in Southeast Asia [26], usually originates from a liver abscess, reaches the eyes, and results in poor visual outcomes for patients [27].

One study in Taiwan reported the presence of DEE from a renal or perinephric abscess caused by K. pneumoniae. The organism entered the intraocular space by crossing the blood-ocular barrier and caused endogenous K. pneumoniae endophthalmitis (EKE) [14]. Another study of EKE suggested that more than half of the patients had DM and most had a simultaneous liver abscess [28]. Poly-microbial infections such as Escherichia coli and K. pneumoniae were also reported [29]. Other rare causes of DEE include Citrobacter koseri, a Gram-negative anaerobic bacilli, Candida glabrata, Leucysphora, and Aeromonas hydrophila [30,31].

Endophthalmitis, as a result of fungus, is usually noted in patients with uncontrolled diabetes and systemic comorbidities including immune deficiencies, intravenous drug abuse, and recent surgical procedures [32]. There are two main types of fungi that cause DEE...
Endogenous endophthalmitis in diabetics

including Candida and Aspergillus. Candida species are the leading cause of fungal EE, especially in patients with chronic immuno-deficiency [33]. The main manifestation occurs when the vitreous is inflamed [18]. DEE by Aspergillus causes retinitis, vasculitis, and inflammation of the pigment epithelium. The prognosis of DEE with a simultaneous aspergillus infection is poor and often requires the evisceration of the affected eye. Rare types of fungi like Fonsecaea, Fusarium, Paecilomyces, Pseudallescheria, Colletotrichum, Cryptococcus, and Trichosporon are also noted in these cases [34]. In DEE cases, the first line of treatment often fails, and drug resistance to antifungal medication presents a major challenge. The prevalence of fungal DEE is rising and requires the periodic revision of management protocols for affected patients and long-term follow-up [35].

Ocular manifestations

DEE patients usually experience a critical systemic condition and remain under intensive care for septicemia. Therefore, ocular complaints in the initial stages of the condition are not common. DEE patients most often present with a painful or painless decrease in vision, visual acuity reduced hand motions or less, red eyes, and discharge. Upon examination, conjunctival injection, chemosis, fine keratic precipitates, hypopyon, fibrin exudates, and scleral suppurations are also present [36]. Additionally, a posterior segment examination might reveal the absence of a red reflex. Further, a retinal evaluation is often difficult to achieve due to the opacity of the vitreous [37]. However, the retina might show nonspecific signs of VITRITIS, retinal hemorrhage, nerve fiber layer infarction, retinitis, perivasculitis, and sub-retinal exudates [38].

Optical coherence tomography (OCT) is useful in the diagnosis of DEE. The lesions are of four types depending on location and extent of retinal involvement. OCT findings in the diagnosis and management of DEE help to predict visual impairments and management prognoses [33].

B scan ultrasound investigation is usually carried out to support the clinical diagnosis of DEE [25,36]. Computerized tomography and Magnetic Resonance Imaging are helpful to detect the primary source and extension of the infection. However, X-rays and ultrasound of orbit have a limited role in the diagnosis and management of DEE [2].

Despite the history and ocular assessment suggestive of DEE, systemic investigations are crucial to confirm its diagnosis. The most reliable investigative methods for this diagnosis include blood cultures and aqueous and vitreous sampling [39]. The culture-positive rate is often low when the diagnosis is made later during hospitalization and after the administration of empirical therapy [2]. A polymerase chain reaction of the aqueous and vitreous samples might be used to increase the diagnostic yield [40].

Further, a positron emission tomography is helpful in the systemic assessment of DEE cases following a COVID-19 infection [41].

Figure 1. The algorithm for research paper collection and generating secondary evidence using PUBMED and Google Scholar.
Endogenous endophthalmitis in diabetics

Management of DEE

Pharmacotherapy, used especially via an intravitreal route, and technological advancements in surgical procedures are key for the successful management of DEE [1]. These protocols must be implemented in addition to the systemic treatment required to address septicemia. The selection of antibiotics depends on the blood culture reports of each individual patient.

In view of this rare condition but rising trend in recent years, standard management guidelines were recommended [3,42]. Intravitreal antibiotics for clinically suspected bacterial DEE were initiated after the sample was collected for the culture and sensitivity test. For clinically suspected bacterial DEE, intravitreal antibiotics are initiated after the sample is collected for the culture and sensitivity test. Vancomycin 1 mg/0.1 ml and cefazolin 2.25 mg/0.1 ml is used for Gram-positive bacteria, and 2.25 mg/0.1 ml ceftazidime or 0.4 mg/0.1 ml amikacin are preferred for Gram-negative bacteria. For the Vancomycin-resistant strain of bacteria, daptomycin 200 µg/0.1 ml and quinupristin/dalfopristin 0.4 mg/0.1 ml are preferred. Fluoroquinolones are also used to cover both gram-positive and negative bacterial infections. Once reports of culture and sensitivity are available, therapy needs to be targeted to treat organisms found for rapid response [36].

For cases of DEE with a simultaneous Candida fungal infection, the American Academy of Ophthalmology has recently described a screening protocol [43]. The treatment of Candida DEE includes Amphotericin B (AMB) (5 to 10 µg/0.1 ml of saline or voriconazole (100-200 µg/0.1 ml of saline) injected intravitreally. The Infectious Disease Society of America recommends using fluconazole (400-800 mg per day) as a treatment instead of AMB due to its lesser side effects [44] To treat other fungal DEE, voriconazole, AMB, and Fluconazole are effective. These treatments could be administered intravitreally in conjunction with a surgical procedure like pars plana vitrectomy. However, in severely immunocompromised patients, antifungal therapy is administered systemically [45].

In addition to patients with type 1 DM, exogenous insulin therapy in patients with type 2 DM is recommended during acute illness or prior to a surgery, and therefore patients with DEE must control their diabetes using insulin [46] and strictly monitor the condition to avoid hypoglycemia and an electrolyte imbalance [47]. Systemic therapy to address septicemia is essential because the infection emerges from other organs in patients with DEE.

A vitreous tap and an intravitreal injection of broad-spectrum antibiotic and antifungal medication within 24 hours of DEE diagnosis is the currently expected procedure and has been shown to be a predictor of better visual outcomes [27,36]. Pars plana vitrectomy (PPV) is recommended to remove the infected vitreous, and earlier intervention provides a better prognosis for DEE [15,36,48]. PPV also enables care providers to address intraocular complications of EE such as epiretinal membrane and retinal detachment [49]. In endophthalmitis, with fungal etiology and virulent bacterial infection often present in addition to PPV, a lensectomy and an anterior chamber wash are carried out [50]. Based on a cutaneous refractory fungal infection treatment, thermal therapy was reported to be successful in EE by Sporothrix schenckii [50].

The removal of the eyeball by evisceration or enucleation to prevent the spread of infection to intracranial organs was common in the past but is currently rare due to the advancement of DEE pharmacotherapy. However, 12% of patients’ eyes had to be removed in a study conducted in Denmark over 16 years [36]. In cases of DEE due to K. pneumoniae, the rate of enucleation was as high as 25% [39]. Unfortunately, the mortality of DEE patients is high, especially among the late presenters and with organisms’ refractory to conventional treatment [39]. The mortality is reported to be higher in culture-positive patients than in culture-negative EE patients [50].

Visual outcomes and predictors

Poor visual outcomes and high mortality are noted in DEE [12]. Fungal infections are purported to have better visual outcomes than bacterial DEE [19]. Early detection and prompt and aggressive medical and surgical management are the key to better visual outcomes in these patients [36]. Initial visual acuity at presentation and the type of organisms causing DEE are predictors of visual outcomes [38,49], though baseline visual acuity in the affected eye is often the only predictor of visual outcomes in DEE with fungal and Gram-negative bacterial organisms. DEE with a yeast type of fungi has a better visual prognosis and the eye removal rate is less than in patients with DEE caused by mold types of fungi [50].

Prevention and rehabilitation of DEE

The prevention of DEE requires vigilance from family physicians, endocrinologists, and emergency physicians who manage diabetic patients with septicaemia and other comorbidities such as intravenous drug abuse, malignancies, or COVID-19 infections. Although challenging for patients in intensive care who often do not communicate, routine screenings for vision impairments, ocular pain, and early changes in the retina by an ophthalmologist are suggested as preventative measures [39]. Once an ophthalmologist detects a case of DEE, a team of health professionals should focus on a thorough systemic evaluation of the patient to find the source of the infection. Once discharged from the hospital, patients with DEE have a high rate of loss to follow-up [12]. This could be due to more pressing systemic health issues than eye care or a higher overall mortality risk among these patients than the general population. The successful management of DEE requires proactive follow-ups and
Endogenous endophthalmitis in diabetics

338 life-long reminders for periodic ophthalmic checks.
339 After recovering from DEE and accompanying systemic infections, these patients would often require support in learning to use their residual vision; some patients might qualify as candidates for low-vision rehabilitation.

340 Conclusion

341 Improved health services have helped to prolong the lives of critically ill patients. In these patients, the risk of EE, particularly among patients with diabetes, would continue to increase. Since 2020, DEE has risen significantly because of the COVID-19 pandemic. Ophthalmologists and other healthcare providers should work as a team to conduct surgical treatments and administer appropriate pharmacotherapy to patients in need. Patients and relatives should be counseled for points of recurrence, complications, and long-term eye care maintenance.

342 List of Abbreviations

343 AMB Amphotericin B
344 DEE Diabetic endogenous endophthalmitis
345 DM Diabetes mellitus
346 EE Endogenous endophthalmitis
347 KPE Klebsiella pneumoniae endophthalmitis
348 OCT Optical coherence tomography
349 PPV Pars plana vitrectomy

350 Conflict of interest

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Endogenous endophthalmitis in diabetics


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