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New Advances in the Pathogenesis and Treatment of Dry Eye after Diabetic Cataract Surgery

Wenjing Cai[1,2,a], Zhiqin Wu[1,b,*]

[1]Department of Ophthalmology, Jingzhou Hospital Affiliated to Yangtze University, Jingzhou, Hubei, China
[2]Medical School, Yangtze University, Jingzhou, Hubei, China
[a]1443326767@qq.com,[b] yts121@126.com
[*]Corresponding author

Abstract: *Diabetic cataract is a common complication in diabetic patients. As the diabetic population continues to expand, the number of patients with diabetic cataract is also increasing. Currently, the primary treatment is cataract ultrasound emulsification hand combined with IOL implantation. However, it has been clinically found that these patients have a high incidence of postoperative dry eye, and in severe cases, corneal epithelial defects and ulcers may also occur, which affects the patient's postoperative comfort and visual function. In order to further improve the understanding of postoperative dry eye in diabetic cataract and enhance the postoperative situation, this paper reviews and analyzes the pathogenesis and new advances in the treatment of postoperative dry eye in diabetic cataract.*

Keywords: *Diabetic cataract, Dry eye syndrome, Phacoemulsification*

1. Introduction

It was demonstrated that diabetes mellitus (DM), as a metabolic disease, can not only cause various ocular complications such as diabetic retinopathy and diabetic cataract, but also damage to the corneal epithelium, corneal nerve, lacrimal gland and lid gland, which can lead to dry eye (DES) [1]. Meanwhile, Sahu PK et al. pointed out that preoperative cataract anesthesia, intraoperative incision, mechanical manipulation, ultrasound energy, and postoperative medication can cause dry eye symptoms associated with decreased tear film stability, blurred vision, refractive changes, burning sensation, and foreign body sensation [2]. Therefore, under this dual mechanism of action, clinical studies have found that the incidence of dry eye in diabetic patients undergoing cataract ultrasound emulsion surgery is greatly increased, which seriously affects patients' postoperative comfort, satisfaction, and even their visual function. In this paper, we mainly review the pathogenesis of dry eye after diabetic cataract surgery and the clinical comprehensive treatment.

2. Pathogenesis of Dry Eye after Diabetic Cataract Surgery

The incidence of dry eye after cataract extraction is 9.8%—72.6%. Compared with patients with simple age-related cataract, patients with diabetic cataract combined with dry eye have more severe postoperative symptoms, longer recovery time, slower recovery of tear film function, more reduced tear secretion function and more severe corneal damage [3-4]. The pathogenesis of dry eye after diabetic cataract surgery includes the following aspects.

2.1 Decreased tear film stability

Altered tear film stability is thought to be a central mechanism in the development of dry eye. Epithelial cells of the lid gland and conjunctival cupped cells may be damaged in diabetic patients due to a high glucose environment and insulin resistance/deficiency, and there is lid margin irregularity and lid gland obstruction, resulting in reduced tear film lipid and mucin secretion and thinning of the tear film lipid layer, leading to a significant decrease in tear film stability [5]. At the same time, increased glucose content in tears and increased glycosylation end products (AGEs) in tears cause oxidative stress in the corneal epithelium, resulting in the destruction of lipids, proteins and nucleic acids and other compounds important in the metabolic process, which can also lead to changes in tear composition[6-7].

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In diabetic patients, tear secretion is reduced due to inflammation and fibrosis of the lacrimal gland, autonomic neuropathy, and corneal neuropathy. Therefore, intraoperative surgical incisions should be chosen reasonably and nasal and temporal margin surgical incisions should be avoided as much as possible. Compared with traditional cataract ultrasound emulsification, small incision cataract extraction surgery has less impact on patients' tear film function and the incidence of corneal edema and lens surface pigmentation is significantly reduced[8].

In diabetic patients, lipid metabolism disorders and long-term hyperglycemia lead to a decrease in tear film stability, resulting in dry eye, while the decrease in tear film stability will further aggravate the inflammatory response and further promote the occurrence of dry eye, thus forming a vicious circle.

2.2 Altered corneal function

Diabetic peripheral neuropathy (DPN) is a common clinical complication of diabetes, with a prevalence of up to 60%. While the cornea is rich in nerve endings, the chronic high glucose environment in diabetic patients can lead to damage to peripheral nerves including the corneal nerve, which can be found by confocal microscopic examination including corneal nerve fiber density (CNFD), corneal nerve fiber branch density (CNBD) and corneal nerve fiber length (CNFL), and corneal nerve sensitivity are altered, leading to decreased perception, tear abnormal reflexes, reduced blinking, reduced tear secretion, and leads to significantly delayed wound healing, causing inadequate secretion of tears[9-10]. Therefore, clinical signs increase with the severity of peripheral neuropathy in diabetic patients compared to healthy individuals. However, subjective symptoms are decreased due to loss of perception caused by peripheral neuropathy, so the clinical presentation is a separation of symptoms and signs[11]. In addition, the corneal nerve is severed by the cataract surgical incision, further leading to altered corneal perception, which is thought to depend on the extent of the corneal incision, with smaller incisions associated with localized reduction in corneal sensitivity, faster recovery (1 month) and minimal impact on tear film stability, possibly due to fewer transected nerve fibers[12]. Miric DJ et al. found that diabetic Patients with poor glycemic control had an upregulation of systemic and ocular xanthine oxidase (XOD) compared to patients with age-related cataracts, allowing the lens to undergo oxidative stress earlier and with a harder nucleus, thus requiring higher hyper emulsion energy and causing more damage to the cornea[13]. In addition, Magno MS et al. found that intraoperative use of a corneal protectant (hydroxypropyl methylcellulose [HPMC2%]) protected the fragile ocular surface of patients with dry eye from surgical damage. It reduced the incidence of DES, improved patient postoperative cataract satisfaction, effectively maintained corneal hydration, significantly reduced the frequency of intraoperative BSS application, and improved patient comfort[14].

Therefore, diabetic patients should be closely monitored for tear film function after cataract surgery and use artificial tear supplements for a long time. In addition, active control of blood glucose before and early after surgery can improve the patient's postoperative discomfort such as dry eye surface and irritated tearing[15].

2.3 Immunoinflammatory response and apoptosis

Chronic high glucose environment in diabetic patients decreases tear film stability and enhances the expression of inflammation-related proteins, promoting increased inflammatory response and apoptosis, leading to dry eye[16]. Negre-Salvayre A et al. found that the process of glycosylation affects tear-related proteins, leading to oxidative stress and promoting inflammatory signaling. This leads to a decrease in lipid layer secretion and too strong tear evaporation, which increases tear osmolarity[17]. Recent studies have shown that hyperosmotic stress stimulates the production of the inflammatory factor IL-36α with the inhibited antagonists IL-36RA and IL-38 as a novel mechanism to induce inflammation in dry eye, and IL-36RA and IL-38 may have therapeutic potential for dry eye with hyperosmolarity[18]. Meanwhile, the corneal epithelial barrier is formed by four connections, of which TJ is the main intercellular crossover structure and ZO-1 and Occludin are essential protein components. Corneal epithelial cells are mediated by the TNF-α/MMP pathway in the hyperosmolar state, stimulating both TNF-α and MMPs due to increased mRNA and protein, leading to the destruction of TJ protein, causing the inter tight junctions are disrupted, compromising the integrity of the ocular surface[19]. However, a recent study showed no difference in IL-17A, IL-1β and TNF-α in tears between patients with diabetic dry eye and those with non-diabetic dry eye, suggesting a different pathogenesis of diabetic DE than non-diabetic DE[20]. In addition, the surgical incision of cataract, instrument manipulation during surgery, surgery time, light intensity and water close to the mouth at the end of surgery can all contribute to the development of postoperative inflammatory reactions. It leads to the aggregation of neutrophils and

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macrophages and the production of inflammatory mediators such as free radicals, protein hydrolases and cyclooxygenases, leading to the development of dry eye[21].

Furthermore, Zhang K et al. found that prolonged duration of diabetes was an important factor affecting the lipid layer of the tear film and ocular surface health after cataract surgery[22]. Several studies have shown that disease duration, elevated glycosylated hemoglobin and severe diabetic retinopathy are important factors for reduced corneal sensitivity[23].

3. Treatment of Dry Eye after Diabetic Cataract Surgery

3.1 General treatment

Control of blood glucose, lipids, uric acid, smoking cessation, alcohol cessation, adequate sleep, and improvement of living environment, etc. For diabetic patients, oral aldose reductase inhibitors can reduce nerve damage and promote corneal epithelial growth by attenuating the activation of the sorbitol-aldose reductase pathway[24]. Moreover, Fujishima H et al. showed that topical application of naltrexone (an opioid antagonist) blocking the OGF-OGFr pathway promoted corneal wound healing in a rat model of type 1 diabetes[25].

3.2 Physical therapy

Because the clinical presentation of diabetic patients is a separation of symptoms and signs, it is more important to focus on the evaluation of the preoperative ocular surface condition, the main examination methods are slit lamp microscopy and tear film rupture time examination, and grading the degree of dry eye; mild patients can use artificial tears in the perioperative period, and patients with mild lid gland dysfunction (MGD) can maintain a clean lid margin before surgery, supplemented with lid gland heat compresses For patients with moderate or severe dry eye or MGD, steroid pulse therapy can be used if the ocular surface inflammation is not sufficiently reduced. Cyclosporine A and Lifitegrast Eye Drops can also be used for dry eye treatment, and surgery can be performed after the corneal epithelial defect has largely recovered[26-27]. In addition, intense pulsed light therapy can be effective in improving dry eye in the form of lid gland dysfunction, while most diabetic patients have unhealthy lid margins[28-29].

Yokoi N et al. found that the clinical efficacy of 3% sodium digluconate eye drops to improve the signs and symptoms of severe dry eye in type II diabetes was superior to that of 0.1% Sodium vitrate eye drops[30]. A nasal spray called OC-01 (varenicline solution), a small-molecule nicotinic acetylcholine receptor agonist that binds to cholinergic receptors and activates the intranasal trigeminal parasympathetic pathway to stimulate tear production, may be effective in improving dry eye symptoms and probably is a potential treatment modality for the future[31],However, its use in clinical practice is not yet widespread because of side effects such as mild rhinorrhea, sore throat and self-limiting nasal discomfort. furthermore, recombinant growth factor (cenegermin) eye drops are also thought to have the ability to address neuropathic defects and are a specific therapy for neurotrophic keratopathy (NK)[32]. Therapeutic corneal contact lens glasses: The use of therapeutic bandage lenses after cataract surgery stabilizes the ocular surface and tear film, promotes corneal healing, and reduces the inflammatory response[33].Moreover, Alvarez-Rivera F et al. found that the use of silicone hydrogel contact lenses containing epalrestat in animal eyes can prevent and treat diabetes through corneal accumulation and diffusion, reversible inhibition of polyol metabolic pathways, and inhibition of protein glycosylation related eye disease, which may be one of the treatments for diabetic dry eye disease in the future[34].

3.3 Surgical treatment

There has been evidence that amniotic membrane transplantation can effectively treat dry eye disease, neurotrophic keratoconus (NK) and promote corneal wound recovery, accelerate the restoration of corneal epithelial health and epithelialization, and improve patients' postoperative vision and quality of life[35]. In addition, submandibular gland transplantation can be used to treat end-stage refractory DES with significant improvement in ocular surface and tear film stability, and minor salivary gland transplantation is indicated for non-end-stage refractory DES with less surgical damage than submandibular gland transplantation[36], But, it is only suitable for people with normal or partially impaired gland function, and does not produce the normal lacrimal reflex phenomenon and affects the amount of oral saliva production.

In summary, patients with diabetic cataract surgery can be stabilized and modified by controlling

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blood glucose, designing cataract surgery and perioperative treatment plans by combining the etiology, type and severity of dry eye, and providing mental health education to patients, so as to maintain the stability of the microenvironment of the patient's ocular surface, reduce the inflammatory response, promote the recovery of the disease and improve the quality of vision.

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