Journal of Clinical and Nursing Research, 2024, Volume 8, Issue 7
http://ojs.bbwpublisher.com/index.php/JCNR
Online ISSN: 2208-3693
Print ISSN: 2208-3685

Advances in the Pathogenesis and Pharmacologic Treatment of Diabetic Cataracts

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Abstract: Diabetic cataract (DC) is a common complication prior to diabetes mellitus, which is a metabolic disease with pathogenesis including abnormal metabolism of polyphenol pathway (PP) and non-enzymatic glycosylation (NEG) of proteins, etc. The therapeutic drugs are mainly aldose reductase inhibitors (ARIs) and glycosylation inhibitors. The therapeutic regimens for DC are becoming more and more diversified due to the development of biological testing and clinical research technology, thus improving its clinical efficacy. With the development of biological testing and clinical research technology, the treatment options for DC have become increasingly diversified and the treatment specificity has been improved, improving its clinical efficacy. In order to comprehensively analyze the pathogenesis and pharmacological treatment of this disease, the following review is made.

Keywords: Diabetic cataract; Pathogenesis; Drug therapy

Online publication: August 12, 2024

1. Introduction

Local nutritional disorders, genetic factors, immune system disorders and toxicity can lead to damage to the lens capsule, which in turn increases osmotic pressure, reduces the barrier function of the lens, and induces abnormalities in lens metabolism, resulting in clouding of the lens and ultimately leading to cataract [1]. Diabetes mellitus is a systemic disease, the prolonged course of the disease will involve the lens, destroying the structure of the lens and then losing its transparency, resulting in DC. In the early stage of the disease, the patient can see the anterior subcapsular water cracks or blisters, accompanied by snowflakes and dot-like turbidity in the superficial cortical layer, which may lead to vision loss or even blindness, and the long-term prognosis is poor. The pathogenesis of DC is complex, and there are various treatment options which can be studied in depth to improve the effectiveness of the treatment.

2. Analysis of the pathogenesis of DC

2.1. Abnormal polyol pathway (PP) metabolism

In a healthy physiological state, the lens' internal glucose metabolism and clearance process, with the help of

an anaglycolytic pathway, a small amount of glucose is metabolized using the catalytic reaction of hexokinase or PP. In contrast, after diffusion of glucose occurs, it can continue to enter the interior of the lens through the process of allosteric transport. Therefore, the function of glucose metabolism affects lens transparency. Based on the above theoretical basis, the aldose reductase (AR) receptor within the PP will be involved in the pathogenesis of DC, and its receptor activation can be used as a promoter to accelerate the progression of DC. AR has a complementary role to the existing metabolic pathway of glucose, and after the elevation of glucose, the glucose can enter into the inner lens in large quantities through the atrial fluid, which then saturates the hexokinase and activates the AR within the PP, so that glucose is converted to sorbitol and will accelerate the conversion of galactose to galactitol. Based on this, sorbitol as well as galactitol accumulate excessively inside the lens, causing a significant increase in cellular osmotic pressure. Fluid extravasation occurs to compensate for the cellular osmotic gradient, leading to lens disintegration or fibrous edema, which ultimately induces DC. Li X *et al.* (2023) concluded that serum 1,5-D-sorbitol (1,5-AG) inhibits the progression of pre-diabetes mellitus (p-T2DM) to T2DM, suggesting that sorbitol has an involved role in diabetes mellitus pathogenesis [2]. Thus, AR has a key role in the pathogenesis of DC, and the mediation of AR receptor will increase polyol aggregation and generate high osmotic pressure, which will aggravate the swelling of cortical fibers inside the lens and accelerate the apoptosis of epithelial cells, generating a large number of vacuoles, which will lead to the induction of acute cataract. Han Z *et al.* (2023) concluded that enhanced PP metabolism increases the accumulation of sorbitol in tissue cells and activates oxidative stress, which in turn induces diabetic complications [3]. the positive correlation between the increase in AR content and the subsequent increase in cataract incidence suggests that the activation of the AR receptor within PP will be directly involved in the disease development process of DC.

2.2. NEG theory

Persistent, excessive production of glycosylation products (AGE) accelerates the progression of DC. The reaction process of glycosylation occurs with the help of non-enzymatic catalysis. It is the internal protein of glucose as well as the free carbonyl group highly combined with the free amino group that generates Schiff bases, which are highly unstable. The Schiff bases undergo a slow process of chemical rearrangement that results in the formation of glycoprotein complexes, the Amadori product. This product reacts strongly with the free amino group, which in turn produces AGEs (non-disulfide bonded cross-links) [4]. In a healthy physiological state, the amount of AGE present in the lens is low and consists of substances such as N-carboxyethyl lysine and arginine pyrimidine. The AGE content inside the lens gradually increases with age, and its content increases rapidly under hyperglycemic prerequisites. According to Liu Y *et al.* (2020), the AGE generated by diabetic patients is faster than its removal rate, so AGE interferes with the function of lens proteins, affects their charge distribution characteristics, and thus changes the conformation of the internal proteins, which leads to the rapid and continuous glycosylation reaction of heat shock proteins [5]. Based on the above process, the existing activity of heat shock protein molecules decreases significantly, which reduces the amount of thermal aggregation of proteins and decreases the antioxidant damage capacity of the lens, thus leading to lens clouding. In addition, AGE and its receptor have a strong activation effect on the receptor for the glycosylation end products (RAGE) signaling pathway, which can alter the structure of tissue cells and cause turbid changes in the lens.

2.3. Oxidative stress damage theory

The lens is chronically in a low oxygen environment, utilizing the vitreous time-regulator oxygen partial pressure, which consumes less oxygen. Prolonged hyperglycemia increases reactive oxygen species and oxygen

radical content and, in this way, damages the lens. Common oxygen radicals within the lens include H_2O_2 and O_2 and contain antioxidant enzymes such as superoxide dismutase and antioxidant substances such as vitamin E, and the levels of each substance are in dynamic balance. After elevated blood glucose, AR is activated and combined with abnormalities in the antioxidant defense system, resulting in DC due to oxidative stress damage. Li Q *et al.* (2023) pointed out that free radicals accelerate the development of DC because the abnormal PP metabolism due to elevated blood glucose, the auto-oxidative state, and the protein glycosylation reaction all elevate the generation of oxygen free radicals, which activate the nuclear transcription factor-κβ pathway and have a stimulating effect on the existing expression level of apoptosis-inducing genes, and in turn, stimulate the expression level of apoptotic genes [6]. This activates the nuclear transcription factor-κβ pathway, which stimulates the current expression level of apoptosis-inducing genes. This increases gene transcription and expression, generates excess nitric oxide, and aggravates oxidative stress damage, leading to lens clouding.

3. Advances in the pharmacologic treatment of DC

3.1. Aldose reductase inhibitors (ARI)

ARI inhibits the AR activity of the PP metabolic pathway, which can delay the progression of DC. Jiang F *et al.* (2020) performed ARI fidaxomicin treatment for patients with diabetic peripheral neuropathy (DPN), and the results confirmed that fidaxomicin could regulate the expression of NLRP3 inflammasomes in patients with this disease, which in turn delayed the disease process [7]. Chen L (2021) performed conventional treatment for DPN patients: oral hypoglycemic drugs and insulin intramuscular injection, which was the control group; and ARI treatment, i.e., oral epalrestat tablets at a dose of 50 mg before each meal, three times a day for 12 weeks, which was the experimental group [8]. The results showed that the experimental group's fasting blood glucose and glycosylated hemoglobin were lower than the control group ($P < 0.05$). It can be seen that epalrestat can control the blood glucose level of diabetic patients and then inhibit the development of cataracts. Wang J *et al.* (2020) performed surgical treatment for DC patients, the control group was treated with taurine eye drops after surgery, and the observation group was treated with epalrestat, the results showed that the levels of malondialdehyde (MDA) and total antioxidant capacity (TAC) of the observation group were better than those of the control group, and the quality of life score was higher than that of the control group ($P < 0.05$) [9]. It indicates that epalrestat can regulate intraocular osmotic pressure and inhibit stress injury, which can improve the surgical prognosis of DC patients.

3.2. Glycosylation inhibitors

Pimagedine is derived from nucleophilic hydrazide, which is inhibitory to the glycosylation process of lens proteins, can reduce the amount of AGE production, block the protein cross-linking process, and can reduce the activity of AR, avoiding the large number of fluorescent products of advanced glycosylation end-products (AGEs) in the lens, and thus slowing down the development of DC. For patients with severe DC, pimagedine can intervene in the early glycosylation process and delay the chemical rearrangement process of Schiff bases, thus reducing the severity of the disease. Zheng J *et al.* (2021) divided diabetic nephropathy rats into model group, Notoginseng triterpenes group, pimagedine group, and combined group, and the results showed that the levels of blood glucose, 24h urinary protein, as well as tumor necrosis factor-alpha, and C-reactive protein in Notoginseng triterpenes, pimagedine, and combined groups were lower than those in the model group ($P < 0.05$) [10]. It indicates that pimagedine combined with Notoginseng triterpenes can improve glomerular function and correct the pathological state in diabetic nephropathy, and it can reduce the level of inflammation and inhibit oxidative

stress. Free lysine inside the lens is susceptible to glycosylation to remove glucose and maintain the lens's healthy state. Based on this, lysine treatment for DC patients can improve the high-glucose environment, inhibit cataract formation, and has antidiabetic, nontoxic, and anticataract effects [11].

3.3. Antioxidants

Taurine has a high content inside the lens and its antioxidant properties can protect tissues and cells and inhibit oxidative damage. Cataract progression decreases the taurine content inside the lens, so exogenous supplementation of taurine can inhibit the continuous secretion of small-molecule proteins inside the lens and avoid multiple enzyme leakage. It also reduces the extent of oxidative damage and significantly scavenges oxygen free radicals to maintain lens function [12]. Vitamin C, vitamin E and other vitamin analogs have antioxidant effects, their absorption rate is high, and they can be utilized to improve cataract symptoms by using a specificity transport mechanism, which can significantly reduce the MDA content within the lens and exert antioxidant effects. At the same time, it can remove superoxide and reactive hydroxyl groups inside the eye tissue, and its physiological effect is similar to that of endogenous insulin, which can improve the glucose transport mechanism. Yin L *et al.* (2023) implemented vitamin A palmitate and diclofosol sodium eye drops for cataract ultrasonic emulsification patients, and the results showed that the clinical efficacy grade of the observation group was better than that of the control group, and the level of inflammatory factor and tear immersion length and other indexes were better than that of the control group ($P < 0.05$) [13]. It can be seen that vitamins can enhance the therapeutic effect of patients after cataract surgery and facilitate the regression of the disease.

4. Recent advances in drug therapy

Dandelion flavonoids, quercetin and other wood ginger camellia extracts can prevent the rupture and swelling reaction of lens fiber cells; rhodopsin can reduce the amount of sorbitol aggregation inside the lens and reduce the number of cortical vacuoles [14]. Moreover, dendrobium extract: butyric acid can reduce the AR activity inside the lens and decrease the galactitol content, reducing the high osmotic pressure of the lens and protecting the lens function. Among the glycosylation inhibitors, rutin contains substances such as rutin disaccharide glycoside and quercetin, which can combine with $CuCl_2$ to generate a redundant compound, thereby reducing the specific amount of autoxidized material generated, blocking the lens glycosylation reaction, and in this way, inhibiting the progression of DC. Cinnamon extract: Proanthocyanidin-β2 belongs to the carbonyl scavengers, which can inhibit the NEG reaction of glucose carbonyl on lens proteins, reduce the amount of AGE generation, and avoid the large number of insoluble proteins generated in the lens. Mucuna pruriens - leaf extracts can reduce AR enzyme activity and inhibit AGE production, so the antioxidant capacity is high. Based on this, DC can be actively treated with traditional Chinese medicine (TCM), and a combination of Chinese and Western medicine can be chosen to utilize fully its therapeutic advantages.

5. Future prospects

The pathogenesis of DC is complex, and commonly used drug therapies are ARI, glycosylation inhibitors and antioxidants. In the future, gene editing technology and stem cell technology can improve the function of lens cells, and advanced electronic devices such as smart glasses or optical technology can treat the disease, thus providing new ideas for the clinical treatment of cataracts.

Disclosure statement

The author declares no conflict of interest.

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