• Review Article •

Effect of rigid gas permeable contact lens on keratoconus progression: a review

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Abstract

● The prevalence of keratoconus is 1/2000 in the general population and is high in adolescents. Keratoconus is a progressive disease, which has a great impact on patients' quality of life and mental health. It can be managed by surgical and non-surgical means, rigid gas permeable (RGP) contact lens as its main non-surgical method is widely used in clinic. The efficacy of wearing RGP contact lens has been confirmed to some extent, but some studies have found that wearing RGP contact lens has adverse effects, which may promote disease progression. In this paper, the advantages and disadvantages of RGP contact lens in controlling keratoconus were reviewed to provide more suggestions and references for the clinical application of RGP contact lens.

● **KEYWORDS:** rigid gas permeable; keratoconus; contact lens

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INTRODUCTION

Keratoconus is a chronic progressive disease characterized by thinning and expansion of the cornea. The central part of the cornea protrudes forward in a conical shape, resulting in highly irregular myopic astigmatism and visual impairment[1]. At present, there is no cure for keratoconus, improving the visual acuity and delaying the development of the disease are the main clinical intervention purposes. The use of contact lens is an important non-operative management measure for keratoconus. There are a variety of contact lenses available for keratoconus management, such as rigid gas permeable (RGP) contact lens, soft and soft toric contact lens, piggy back contact lens, hybrid contact lens, scleral and corneoscleral contact lens[2]. According to the total diameter, RGP contact lens can be classified as corneal contact lens, intralimbal contact lens and scleral contact lens[3]. Among them, corneal RGP contact lenses are the first choice for patients with keratoconus and are widely used, which is often referred to as RGP contact lens. In this paper, we mainly discuss this type.

The mechanism of keratoconus has been studied for a long time, and it is generally believed that keratoconus is the result of multi-factor and multi-pathologic process. Suspected factors include genetic and environmental factors (eye friction, contact lens wear, ultraviolet exposure), allergic diseases, specific diseases and inflammation[4]. RGP contact lens is designed from a special rigid hydrophobic material. Patients wear RGP contact lens to form a "contact lens-tear-cornea" system to correct irregular astigmatism, reduce aberrations, provide good visual quality, and control the development of the disease through mild "shaping" effect[2,5]. Although the benefits of RGP contact lens are widely recognized, knowledge of complications is now evolving with increased numbers of wearers[2]. The mechanical friction and inflammation caused by direct contact between RGP contact lens and anterior corneal surface, poor follow-up compliance of patients, and the improper management of RGP contact lens will cause damage to the morphological and biological characteristics of each layer of eye structure, and further affect the visual quality and disease control of keratoconus patients[6].

This article will review the effect of RGP contact lens on keratoconus progress, and provide reference for clinical application of RGP contact lens.

THERAPEUTIC EFFECT OF RGP ON KERATOCONUS

Visual Quality Improvement RGP contact lens has long been used to correct refractive errors and astigmatism caused by irregular corneal surface. The contact lens acts on the tear film layer of the patient to create a new regular anterior surface in front of the optical system, and the irregular cornea is

covered, so as to correct the aberration caused by the irregular surface, improve the patient's vision and contrast sensitivity, and significantly improve the visual quality[7]. Bilgin *et al*[8] observed 518 patients with keratoconus who wore contact lens over a 30-year period, indicating that wearing contact lens is the most common and successful management measure for keratoconus, it can provide patients with good vision and control keratoconus progression, and wearing contact lens delayed the need for surgery in 98.9% of cases. Lim and Vogt[9] evaluated the efficacy of wearing contact lens in 130 keratoconus patients, most of whom had good corrected vision, and a few of whom underwent surgery for contact lens intolerance. However, some studies have shown that the vision and contrast sensitivity of patients with moderate and severe keratoconus are rarely improved to normal level due to the existence of neural defects and residual aberrations. This suggests that more thorough correction of corneal aberrations may improve the patient's visual performance[10-12].

Ultraviolet Protection Ultraviolet radiation is the most energetic radiation in the solar spectrum reaching the human eye and is mainly absorbed by the cornea and the lens cortex. Since high-energy photon radiation has a strong potential for biological damage to absorbing tissues, exposure to ultraviolet radiation is harmful to health and can cause damage to corneal cells, which is thought to be related to the development of keratoconus[3,13]. Ultraviolet exposure can make the level of reactive oxygen species in cells higher than the antioxidant buffer capacity, thus destroying the oxidation-reduction homeostasis. The damage to the cornea is mainly caused by oxidative stress, which affects the corneal epithelial cells, and the endothelial cells are more sensitive to ultraviolet-induced oxidative toxicity[14]. Long-term exposure to ultraviolet light is a risk factor for keratoconus. Wearing RGP contact lens may reduce the absorption of ultraviolet light in corneal tissue and protect the cornea of patients, but there is no direct research related to it.

At different stages of keratoconus development, wearing appropriate RGP contact lens is helpful for keratoconus patients to obtain good visual quality. But when the corneal diopter exceeds 52 D, the cornea will become thinner and more irregular, and the patients' corrected visual quality will be reduced. Moreover, inappropriate lens can aggravate the friction on the top of the keratoconus, changes in the type of contact lens or surgical treatment are required[15]. Besides, some individuals are in a static state during the early stages of the disease and do not need to wear the RGP contact lens prematurely to control the disease. Wu *et al*[15] investigated the effect of RGP contact lens on visual acuity-related quality of life in keratoconus patients of different severity, the results of confocal microscopy and the experience of patients with long-term wear of RGP contact lens were collected. It was concluded that patients under 20 years of age with keratoconus have poor corneal toughness, wearing RGP contact lens will aggravate corneal irregularities, make the central cornea cloudy, and even require corneal transplantation. In order to avoid these problems, patients under 20 years of age with keratoconus should be corrected with glasses as far as possible when visual impairment occurs[16]. So as to ensure good visual quality, we need to choose appropriate contact lens parameters or other management measures according to patients' age, type of keratoconus, stage of disease and patients' individual needs.

POTENTIAL RISK FACTORS FOR KERATOCONUS PROGRESSION

No agreement has been reached on the pathophysiological basis of the development of keratoconus. In recent years, several clinical evidence and experimental results have shown that the occurrence of keratoconus is related to the chronic injury of corneal surface. Corneal injury leads to excessive release of corneal epithelial inflammatory factors and excessive expression of corneal matrix metalloproteinases, which causes the dysregulation of corneal stromal enzyme metabolism and the initiation of cell apoptosis, and ultimately results in the loss of corneal stromal cells, decreased corneal tensile strength and conical expansion of the cornea[17-19]. As early as 1978, Gasset *et al*[20] suggested that hard contact lens may be an environmental risk factor for keratoconus. McMonnies[21] have shown consistent conclusions and suggest that contaction-induced abnormal friction and injury may lead to keratoconus progression. In recent years, with the wide application of RGP contact lens, its side effects have drawn increasing attention, including the changes of corneal tissue structure, the effects on vascular system, changes in the tear system and the inflammation induction. Further research is needed to determine the relevance of these changes to RGP contact lens wearing and whether it will promote keratoconus progression.

Effects on Vascular System There have been many studies on the injury of soft contact lens to conjunctival microvessels, and it is believed that it is related to mechanical friction, inflammation caused by discomfort of contact lens and chronic hypoxia caused by long-term wearing[22-24]. A case report described the rare complication of intracorneal hemorrhage in patients with keratoconus and high myopia who were wearing rigid contact lens for a long time, which was also attributed to contact lens friction and long-term chronic hypoxic injury[25]. Compared with the previous soft and rigid contact lenses, RGP contact lens has high oxygen permeability, and the improvement of personalized lens matching technology improves patient comfort, which reduces the possibility of mechanical and hypoxic injuries. Currently, there are few

studies on conjunctival reactions directly related to RGP contact lens, and whether long-term wearing of RGP contact lens will cause conjunctival microvascular damage has not been fully demonstrated. However, it is also very important for the clinical application of RGP contact lens, more case investigations and follow-up studies are needed to provide more reference for the management of keratoconus diseases.

Effects on Lacrimal System To study the effect of contact lens wear on ocular surface changes in keratoconus patients, Moom *et al*[26] compared keratoconus patients wearing RGP contact lens with non-wearers, and found that break-up time (BUT) and goblet cell density of the RGP contact lens wearer were significantly reduced. The study by Yuksel Elgin *et al*[27] found that the use of contact lens reduced the BUT, but no effect on goblet cell density and tear osmolarity. At the same time, it has been suggested that cytological changes usually occur in the early weeks of the disease, and differences in the results of imprinted cytology in the study may be due to cellular compensation mechanisms and tolerance to conjunctival changes[28-29]. The diagnostic features of dry eyes syndrome are reduced tear secretion, decreased BUT, decreased conjunctival goblet cell density, increased tear osmotic pressure, decreased lysozyme and lactoferrin content in tears, *etc*[30]. Studies have described that in the process of blinking, due to shear stress, corneal epithelial cells release increased diadenosine polyphosphates. This is especially true in patients with dry eyes, and diadenosine polyphosphates is also considered an objective biomarker for dry eye syndrome[29,31]. Therefore, the above study seems to suggest that wearing RGP contact lens may aggravate the clinical symptoms of dry eyes in keratoconus patients.

Inflammation is a core driving force in the pathogenesis of dry eyes. Experimental dry eyes stimulated IL-1β, TNF-α, MMP-9 expression and production, activated mitogen-activated protein kinase signal pathway, stimulated cellular inflammatory molecules on the surface of the eye[32-33]. In recent years, more and more clinical evidence and experimental results suggest that keratoconus is related to inflammation[34-36]. Fodor *et al*[37] demonstrated a higher concentration of pro-inflammatory factors in the tears of contact lens users and found that 14 inflammatory mediators and other mediators were changed in the tears of keratoconus patients, prompting the occurrence of keratoconus. Previously, Lema *et al*[38] described overexpression of pro-inflammatory cytokine in the tear film of keratoconus patients wearing RGP contact lens in a study of more than 88 subjects, and in severe keratoconus cases, these pro-inflammatory molecules are elevated at higher levels. Therefore, we conclude that, similar to rubbing the eyes, contact lens are associated with mechanical stimulation of the corneal surface, which may increase the number of inflammatory molecules in the tears by activating the mediators, thus aggravating the “vicious circle” of inflammation in the dry eyes, promoting the occurrence and development of keratoconus. On the other hand, increased inflammatory molecules in tears also contribute to the risk factors for the progression of keratoconus.

Effects on Corneal Tissue Structure

Effects on corneal endothelial cells The effect of RGP contact lens on keratoconus patients has been studied in many aspects, such as the changes of cell density, cell area and pleomorphism, and the effects on corneal stroma and corneal nerve. Comparing the keratoconus patients with RGP contact lens and keratoconus patients without contact lens, Dogan *et al*[39] found that there were no statistical differences in the density of corneal endothelium, coefficient of variation and the proportion of hexagonal cells between the two groups. Ghosh *et al*[40] had different results, they suggested that wearing RGP contact lens increased the pleomorphism of corneal cells. Meanwhile, it has been shown that the pleomorphism of endothelial cells is a common consequence of wear of contact lens and correlates with the cumulative wear time of RGP contact lens[41]. Mocan *et al*[42] said that the wearing of contact lens has no effect on the density of corneal endothelial cells, and the number of corneal endothelial cells is related to the occurrence of keratoconus. So, the effect of RGP contact lens on corneal endothelial cells in keratoconus patients is not consistent. But it is certain that prolonged daily contact with contact lens in keratoconus patients, as well as the use of only the tip contact, increases the risk of corneal endothelial changes.

Effects on corneal epithelial cells and stromal cells The effects of RGP contact lens on corneal epithelial cells and stromal cells also have different findings. Some studies have demonstrated that the density of anterior and posterior corneal stromal cells is reduced in patients with keratoconus wearing RGP contact lens, the area of mean corneal stromal cells is significantly changed, the pleomorphism of cells is increased, and turbidity is increased[40]. In another study, RGP contact lens was found to be associated with a further decrease in the density of epithelial cells and anterior corneal stromal cells, but had no effect on the density of posterior corneal stromal cells[43]. While Mocan *et al*[42] reported that the number of corneal epithelial cells and stromal cells was not affected by the use of contact lens. Kallinikos and Efron[23] observed the irregular distribution of stromal cells in the corneal stroma of RGP contact lens wearers. Moreover, Weed *et al*[44] reported that corneal stromal cells and their regular distribution in the matrix, collagen fiber production and regular alignment play an important role in maintaining corneal transparency. The

occurrence of keratoconus is thought to be related to friction-induced epithelial injury[17], whether the changes of corneal stromal cells are related to the injury of corneal epithelial cells, and whether the wearing of RGP contact lens will affect it, more research is needed.

Effects of corneal thickness Corneal stroma thinning is a key clinical feature of keratoconus. In 2002, Pflugfelder *et al*[45] observed that contact lens wearers had significantly lower corneal thickness than non-wearers. However, the results of the Dogan *et al*[39] described that the corneal thickness of patients with keratoconus wearing contact lens was significantly lower than that of the normal control group, and there was no statistical difference compared with the keratoconus patients without contact lens. It is considered that RGP contact lens has no effect on the corneal thickness of patients with keratoconus[39]. McKay *et al*[46] hypothesized that keratoconus-derived corneal fibroblasts were more susceptible to hypoxia-induced oxidative stress than healthy controls, leading to thinning and worsening of keratoconus. Therefore, *in vitro* environment, the effects of hypoxia on extracellular matrix secretion, assembly and matrix metalloproteinase expression in corneal fibroblasts in healthy controls and keratoconus patients were evaluated. After one week of hypoxia, the extracellular matrix thickness decreased in both groups. This suggests that hypoxia affects the expression of collagen and matrix metalloproteinase in human keratoconus cells, which may have an effect on corneal thickness of keratoconus patients[46].

Effects on corneal nerve The corneal nerve plays a vital role in maintaining the normal structure and function of the cornea and is an important factor in determining corneal sensitivity. The central basal nerve density in keratoconus was significantly lower than that in normal corneas[47-48]. Brookes *et al*[49] found that in the early stages of keratoconus, the basal nerve fibers of the cornea play a transmitting role, promoting the interaction between keratinocytes and corneal epithelium, and facilitating the degradation of corneal epithelium and stroma. Patel *et al*[50] showed that there was a significant correlation between the decrease of corneal basal nerve density and the decrease of basal epithelial cell density in keratoconus. They believed that changes in the corneal basal nerve may lead to changes in basal epithelial cell density, which are associated with the occurrence of keratoconus. Keratoconus patients wearing contact lens were compared with non-contact lens wearers, decreased corneal sensitivity was found in contact lens wearers[50-51]. Beyond that, it has been suggested that the decrease of corneal sensitivity is not accompanied by the decrease of nerve fiber density, the contact lens has no effect on the corneal nerve density, distribution or morphology[43,52]. However, Patel *et al*[53] demonstrated by laser *in vivo* confocal microscopy (IVCM) that the basal nerve density of patients with keratoconus wearing contact lens is reduced compared to non-contact lens wearers. Studies have also shown that the use of the orthokeratology (OK) lens can reduce both corneal sensitivity and corneal basal nerve density[54]. Therefore, the effect of contact lens on the corneal nerve may be related to the type of contact lens or other factors, the effect of RGP contact lens on the corneal nerve in keratoconus patients, and the effect of nerve changes on the development of keratoconus need more attention.

Mocan observed the changes of corneal microenvironment in keratoconus patients, found that the density of corneal epithelium, endothelial cells, anterior, middle and posterior corneal stromal cells decreased, and the rate of corneal opacity increased[42]. Prior to this, Weed *et al*[44] evaluated the changes of the corneal microenvironment in keratoconus patients compared to the normal control group , the result showed that the density of corneal endothelial cells was unchanged, the density of corneal epithelial cells was decreased, and the density of both anterior and posterior corneal stromal cells was increased, and these changes were related to the severity of the keratoconus. In addition, Goebels *et al*[55] observed the changes of corneal endothelial cells in 712 keratoconus patients and found that with the increase of keratoconus severity, the density of endothelial cells decreased and the variability of endothelial cells increased significantly. Studies have found that only pleomorphic changes occur in endothelial cells of keratoconus patients, and the number does not change[56]. However, studies have also shown that corneal endothelial cells in patients with keratoconus have higher density than normal controls[57]. These changes may be related to apoptosis during the development of keratoconus. The inconsistency of observation results may be caused by different stages of disease development. The wear of RGP contact lens and the changes of cellular structure in different layers of cornea have no definite conclusion, but the corneal damage associated with contact lens, the changes of inflammatory factors in tear and hypoxia induced by long-term wearing of RGP contact lens are the risk factors of the changes of corneal structure. At present, there is an agreement that the release of RGP-induced inflammatory mediators that stimulate the corneal surface and lead to apoptosis may be the main reason for the decrease in the number of corneal cells. The correlation between RGP contact lens and continued thinning of cornea in patients with keratoconus and the effect on keratoconus progression need to be further studied.

Compliance of Patients and RGP Contact Lens Management Keratoconus is a progressive disease with increased corneal irregularities in the advanced stage of the disease, making it difficult to get an optimal or ideal fit with RGP contact lens, and increased the risk of ocular surface damage[58-59]. Some patients have a hard time putting up with

RGP contact lens, and many wearing RGP contact lens also complain that in dusty environments some debris can get trapped under the lens, causing immediate discomfort[15]. During the wear of RGP contact lens, the patient's adaptability to RGP contact lens changes as the disease progresses, regular visit according to doctor's advice is a guarantee for patients to obtain the best management plan. But in clinical practice, many people stop seeing a doctor. In 2017, Russell *et al*[60] conducted a survey of patients who had lost contact with RGP contact lens in keratoconus. Patients with keratoconus with unilateral symptoms were more likely to stop seeing a doctor, and discomfort was a possible cause of the discontinuation. Patients with easy discontinuation also had shorter wearing times of contact lens, and discontinuation of management generally resulted in discontinuation of the use of RGP contact lens[60]. Different stages of the disease require different management measures, the continued visual state of the discontinued patient is unknown, and clinical intervention loses the opportunity, which is likely to aggravate the progression of the disease.

Moreover, the inappropriate management of the lens by the patient also poses a threat to the development of the disease. Sleeping and swimming with contact lens, using tap water to clean and store contact lens, not following a replacement schedule and reusing disinfectant are all important risk factors for keratitis[61-62]. The replacement and care of the contact lens and lens case are very important, inflammation induced by improper lens care is a risk factor for the development of keratoconus. The patient's immune response and toxic reactions to lens care solution may also lead to eye diseases and even systemic diseases[63-64]. When choosing RGP contact lens for management measure, we should also consider the patient's compliance and the ability to maintain RGP contact lens. In order to minimize the adverse effects of RGP contact lens on patients, it is suggested to combine objective assessment with subjective assessment for comprehensive assessment. Furthermore, specialists also play an important role in the prevention of contact lens wear complications by providing health guidance and follow-up to patients.

DISCUSSION

The cornea is an avascular tissue, and its oxygen source is mainly atmospheric oxygen and dissolved oxygen in body fluid and tear film. The production of ATP is maintained by oxidative phosphorylation, which plays a key role in the function of the corneal tissue structure[65]. Some studies have shown that keratoconus is more susceptible to oxidative stress than normal cornea, hypoxia also induces aggravation of oxidative stress and induces apoptosis[66-67]. Because of its incomplete oxygen permeability, RGP contact lens can reduce the use of oxygen in corneal tissue. Hypoxic damage caused by long-term wear of RGP contact lens can affect the morphological and biological characteristics of the cornea. For example, conjunctival imprinted cytology has a reduced goblet cell density, an increase in the number and pleomorphism of epithelial cells, stromal cells, endothelial cells, and the like.

Ocular surface lesions in keratoconus were characterized by lacrimal deficiency and abnormal results of imprinted cytology[68]. In the sample of 26 keratoconus subjects, compared with normal subjects, the secretion immunoglobulin A in tears was significantly reduced, the anti-inflammatory proteins lactoferritin and lipophilin were reduced, and serum albumin levels were increased, indicating that the inflammatory response was active on the surface of the eye[69]. The earliest structural changes in keratoconus are thought to occur in the epithelium of the cornea. Subsequently, the damaged epithelial cells released cytokines and catabolic enzymes, resulting in the rupture of the bowman layer, apoptosis and death of stromal cells and loss of keratinocytes, which are thought to be associated with corneal thinning and normal corneal structural degeneration[18,57,70]. The synthesis, deposition of corneal stromal cells in the corneal stroma and reconstruction of extracellular matrix are important for the structural rigidity and optical properties of the structure. For keratoconus patients, the thinning of the corneal stroma is more likely to cause biomechanical changes in the cornea, leading to visual defects and progression of the disease.

A previous study reported that contact lens-induced keratinocyte loss may be associated with three factors, such as hypoxia, mechanical stimulation, and inflammation induction[23]. Some researchers believe that changes in the shape and size of corneal endothelial cells are due to hypoxia and mechanical stress caused by wearing contact lens, prolonged contact lens use and decreased oxygen permeability can cause pleomorphic changes in endothelial cells[71-72]. Similar to rubbing eyes, long-term use of RGP contact lens in keratoconus triggers the release of inflammatory cytokines and induces apoptosis[23,73]. Meanwhile, the wear of RGP contact lens can damage normal physiological function of tears and aggravate dry eyes[74]. McMonnies[17] believes that inflammation is the key to keratoconus development and that the contact lens-associated dry eyes inflammatory process may exacerbate other inflammation mechanisms associated with keratoconus. Meanwhile, Efron[75] suggests that chronic, low-grade subclinical inflammation of the ocular surface may have a positive protective effect during contact lens wear.

CONCLUSION

In summary, RGP contact lens are the most suitable non-operative management option for patients with keratoconus, which can provide satisfactory visual quality and improve the regularity of corneal surface. But whether the wear of RGP contact lens on the cornea, the chronic hypoxia stimulation,

the change of tear components, the proinflammatory effect on ocular surface and the induction of apoptosis can promote the progression of keratoconus is still not concluded. Published Studies showed significant differences in the study population, age of participants, severity of keratoconus, clinical outcome measurements, and follow-up time, further research of high quality is required. In the application of RGP contact lens, in addition to the experience and efforts of specialists, patient cooperation is also very important. We should also consider variables, such as the age of keratoconus, the time of disease, corneal topography changes, the wearing time of RGP contact lens, the speed of disease development. These variables make the patient's adaptive contact lens different, and also have a great impact on the patient's prognosis. With the increase of research on RGP contact lens, the optimization of RGP contact lens material properties has greatly improved its oxygen permeability and comfort, and greatly reduced the incidence of side reactions. However, the effect of long-term wearing of RGP contact lens on the development of keratoconus cannot be ignored. There is a difference between the management modalities that provides the best vision and the management measures that provides the best long-term health, clinicians need to give more comprehensive consideration. Simultaneously, the further improvement of RGP contact lens performance will bring better therapeutic effect to keratoconus patients, more research is needed to support the selection of optimal alternatives.

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