Introduction

Glaucoma is one of the leading causes of blindness worldwide. High intraocular pressure (IOP) contributes to the development and progression of the condition. Although the specific mechanism underlying IOP increase in glaucoma remains elusive, it is clear that the Schlemm's Canal (SC) is a crucial structure in regulating IOP and a potential therapeutic target. With the advancement of inspection techniques, we can obtain high-quality images of the SC, which facilitates quantitative measurements and improves the understanding of the SC structure. In this review, we summarized the current data about the morphological changes in the SC under physiological, pathological, and post-treatment states.

Anatomy and Function of the SC

In 1830, the Schlemm’s Canal (SC) was first described and named by Schlemm, a German anatomist Hamanaka and Ujike [2], and was considered an important pathway in draining aqueous humor into the circulation system and an important structure of the blood–aqueous barrier. SC is a ring-shaped vessel located at the inner part of the corneoscleral junction, where it links the trabecular meshwork (TM) and collector duct. The SC area estimated via histological staining was 1709 µm². However, the in vivo, non-invasive optical coherence tomography (OCT) showed that the SC areas vary from 4064 to 7164 µm² Dautriche et al. [3]. Due to the difference in microenvironment, the endothelium of the SC is not equal. The endothelial cells near the TM comprise the inner wall, and the remaining is referred to as the outer wall. The inner wall has been extensively explored as the increase in IOP in primary open-angle glaucoma (POAG) was found to be mainly correlated to the increased resistance of the inner wall and juxtacanalicular tissue Overby et al. [4]. Under the electron microscope, the inner wall is characterized by a smooth nucleus projected into the SC, and numerous giant vacuoles and pores could be observed in the inner wall cells. Giant vacuoles were considered to be linked cell processes, or invaginated juxtacanalicular cytoplasm, whereas the pores were the inner wall structures, which regulated aqueous flow into the SC. Moreover, unlike normal vascular endothelial cells, the basement membrane beneath the inner wall is incomplete and the direction of pressure on the endothelial cells is different. The stress direction of normal vascular endothelial cells is from the top to the bottom, whereas that of the SC endothelial cells is opposite. Thus, the SC is more at a risk of deformation and collapse Ramos et al. [6]; Raviola and Raviola [7]. In addition, to maintain the function of the blood–aqueous humor barriers, the SC maintains a relatively closer connection between the endothelial cells, indicating that it has greater pressure difference when facing the same volume of reflux liquid Bhatt et al. [8]; Ramos et al. [6].

Measurement and Evaluation of the SC

Because of the small size and hidden location of the SC, the early observation of the SC was based on the histopathology of in vitro
tissue. Although the position and morphology of the SC could be investigated with an optical microscope, the original structure might be affected in the processing of sections Ten Hulzen and Johnson [9]. With the development of laser scanning confocal microscope, the physiological structure could be better preserved because tissues need not be fixed, embedded, and cut into sections for microscopic examination. Furthermore, when the microscope is used in combination with fluorochrome, we could observe the drainage pathway of the aqueous humor Battista et al. [10]. The use of electron microscopy helps obtain an in-depth understanding of the SC at the cytological and sub-cytological levels, particularly the vacuole and pore of the SC. Ultrasound biomicroscope (UBM) was first introduced in the early 1990s by Foster and Pavlin. As a method used to obtain the cross-sections of the SC, the diameter of the SC was measured with high-resolution image using higher-frequency acoustic waves Pavlin et al. [11]. With near-infrared ray and optical interference, OCT was used to obtain the intraocular imaging of biological tissues. UBM and OCT are imaging techniques used to obtain the structure of the anterior chamber. The main advantage of the UBM is its capability to visualize structures behind the iris, which include the ciliary body and lens. OCT has a significantly higher resolution (>10 μm) than other imaging modalities, and it has been widely used in measuring the structure of the SC Kumar et al. [12].

**Morphological Change in the SC**

The SC is an important structure of the anterior chamber angle that regulates the flow of aqueous humor and IOP. The morphological changes and size of the SC will become potential therapeutic targets. The morphological changes in the SC include physiological, pathological, and post-treatment presentation of the SC.

**Changes in the SC during Physiological or Pathological States**

Fernandez et al. assessed Caucasian children aged 3–18 years and found that SC size increased with age. Meanwhile, morphological changes, such as the underdevelopment of outflow pathway or a smaller SC area, could not be detected Fernandez Vigo et al. [13]. It was reported that the SC has regulation capability that temporarily decreases the IOP in a younger population Jenssen and Krohn [14]. To figure out the precision of the relationship, Daniel et al. measured the size of the SC of healthy children aged 4–16 years during accommodative effort, and concluded that the radial diameter and cross-sections of the SC significantly increased 0.011 mm and 0.507 mm² respectively, and the diameter of the SC has a significant negative association with age Daniel et al. [15]. Results indicated that accommodation, which affected the SC diameter and area, may affect IOP regulation in children and young individuals. Moreover, they found no correlation between SC size and gender, refractive error, TM thickness, or anterior chamber angle. The latest research has shown that the size of the SC significantly decreased with age, and several speculative reasons were used to explain the alteration.

First, the degeneration of the SC and the decreased density of giant vacuoles and pore populations were correlated to the increase in age. Second, motor impairment of the ciliary muscle and change in limbal corneoscleral contour were observed in the aged group. Third, the SC size may decrease with the lower production of aqueous humor, which significantly decreased with age Chen et al. [16]. Yan et al. measured the changes in the SC and lens after exercise and concluded that the lens vault decrease caused SC expansion by the connecting fibrils between the SC and ciliary body Yan et al. [17]. Hann et al. examined the anatomical change in the SC under 10 or 20 mmHg perfusion pressure within 2 hours and concluded that the SC volume was 3.3 times greater at 10 mmHg than 20 mmHg in healthy participants. However, the SC volume expanded only two times in individuals with POAG. Meanwhile, the SC volume was smaller in patients with POAG than healthy participants Hann et al. [18].

From the pathological perspective, Kagemann et al. identified the relationship between SC area and acute IOP elevation (30 mmHg) *in vivo*. The mean IOP increased by 189%, and the mean SC area decreased by 32% compared with the baseline. The change in the SC area was 66.6 μm²/mmHg Kagemann et al. [19]. In line with this conclusion, Hong et al. found that the mean SC area was significantly different between patients with POAG and healthy participants (11332 ± 2015 vs 13991 ± 1357 mm²). In addition, although the mean IOP showed a correlation with the SC area, the severity of glaucoma damage with the SC area was challenging to estimate Hong et al. [20]. A recent research revealed that eyes with high myopia had a larger SC area and thinner TM, and this information helped us understand the increase in the prevalence of open-angle glaucoma in high myopia. Furthermore, the change was attributed to three factors: longer axial length, a series of collagen fiber alteration, and lesions or obstruction of collector channels caused by the first two changes Chen et al. [21].

**Morphology of the SC after Treatment**

The first-line treatment for glaucoma is the use of conventional medications, which include α-adrenergic receptor agonist, β-adrenergic receptor blockers, carbonic anhydrase inhibitors, and prostaglandin analogs. Pilocarpine, a nonselective muscarinic receptor agonist, has been commonly used in the treatment of glaucoma because of its capability to expand the juxtacanalicular portion and SC area. Skaat et al. have scanned the SC before and one hour after the administration of 1% pilocarpine in healthy eyes and 2% pilocarpine in POAG eyes. Results showed that the mean SC areas increased by 21% and 24% in the healthy group and that with POAG, respectively. In addition, the mean SC volume increased from 8,004,000 to 9,685,000 μm³ in the healthy group and from 6,468,000 to 7,970,000 μm³ in the group with POAG Skaat et al. [22]. Meanwhile, cyclopentolate, a parasympatholytic antimuscarinic agent, could relax the iris sphincter muscle and result in a decrease...
in the mean SC area by 17%, and in the mean SC volume from 6,163,061 to 5,119,462 µm³ Rosman et al. [23]. Travoprost is widely used due to its capability to increase uveoscleral outflow. However, there are limited studies of whether travoprost also increased conventional outflow. To identify the mechanism, Chen et al. included 12 healthy participants who received 0.004% travoprost and found that the mean SC areas increased by 90.30% and 90.20% in the nasal and temporal sides, respectively, and the drug effects lasted for 48 and 60 hours, respectively Chen et al. [24]. Except the abovementioned traditional drug for glaucoma, emerging evidence has indicated that Rho kinase inhibitor and nitric oxide expanded TM and SC. Moreover, NO modulates IOP by directly regulating TM and SC, which eventually increased the conventional outflow facility. Rho kinase inhibitor is the downstream of NO/cGMP, which may shed more light on clinical drug therapy for glaucoma Cavet et al. [25]; Yang et al. [26].

Morphology of the SC After Glaucoma Surgery

When IOP was uncontrollable despite the use of the maximum tolerated medication, surgery is considered Xin et al. [27]. Hong et al. validated the expansion of SC morphology in primary angle-closure glaucoma eyes within a month after trabeculectomy compared to the baseline value (SC diameter: 34.2 ± 28.4 µm; SC area: 8117 vs. 5200 µm²), and the extent of SC expansion and IOP decrease were found to be correlated Hong et al. [28]. In accordance with the results, a report has shown that selective laser trabeculoplasty, a first-line therapy for POAG, led to 8% SC expansion Skaaet al. [29]. In addition, a research explored the morphology of SC in individuals with acute primary angle closure (APAC) before and one week after laser iridotomy. Results showed that the SC area of APAC expanded (10,600 ± 2691 µm²) at presentation, and no difference was observed between normal controls (7192 ± 1022 µm²) and individuals with APAC eyes (6499 ± 1754 µm²) after surgery Manssoori et al. [30].

The conventional penetrating surgery creates a direct communication between the anterior chamber and sub-conjunctival space, which is accompanied by a series of complications. Therefore, non-penetrating surgeries, such as canaloplasty, are recommended. Canaloplasty is a burgeoning non-penetrating glaucoma surgery that aims to re-establish the natural trabeculo-canalicular outflow by 360° circumferential catheterization and insertion of tensioning sutures. Some studies have shown that canaloplasty significantly decreased IOP and had fewer surgical complications than trabeculectomy, and it is currently considered the gold standard for glaucoma surgery. A study evaluated the early anatomical changes in the SC after canaloplasty, and results showed that the SC expanded significantly and was detectable on OCT and UBM three months postoperatively. Moreover, the increase in the SC height was more pronounced than in the SC width (height: +369%, width: +152%) Fuest et al. [31]. To validate long-term anatomical changes after canaloplasty, Kuerten et al. examined patients who underwent successful surgery over a mean follow-up of 20 months, and results have shown that the height and width of the SC increased by 351% and 144%, respectively, and the dilation of the SC was persistent and stable Kuerten et al. [32].

Canaloplasty can re-establish the natural trabeculo-canalicular outflow by the dilation of the SC and stretching of the inner wall and TM. Canaloplasty can prevent some of the disadvantages of invasive surgeries, which include the use of antimetabolic drugs, removal of the stiches, bleb leakage, and infection. However, conventional canaloplasty still has some disadvantages. First, it is not suitable for patients with angle-closure glaucoma or POAG with a disrupted SC. Second, physicians find it challenging to perform a Descemet’s window. Third, the conjunctiva is injured during canaloplasty; therefore, conducting another surgery will be difficult. Xin et al. have used a special trocar to make canaloplasty suitable for participants with a disrupted SC Xin et al. [33]. Wang et al. simplified the procedure for canaloplasty and named it reconstruction of aqueous outflow drainage, thereby omitting the two steps of conventional canaloplasty (scleral lake and Descemet’s membrane window) Wang et al. [34]. In addition, a minimally invasive glaucoma surgery, namely, ab interno canaloplasty (ABiC), has been developed. The SC is only expanded by viscoelastic agents without suture into the SC compared to conventional surgery. A clinical study has shown that ABiC lowered IOP, which lasted for at least one year, even though the SC was only transiently dilated by microcatheter and viscoelastic agent Korber [35]. Therefore, the veritable mechanism of non-penetrating surgery is still being debated.

Summary

Glaucoma is the leading cause of blindness worldwide. Currently, we have identified several risk factors of glaucoma, which include genes, environment, IOP, and trans-lamina cribrosa pressure gradient Huang et al. [36]; Sang et al. [37]. IOP plays a key role in the development and progression of glaucoma, but the precise mechanism underlying the increase in IOP still needs to be investigated. The SC is an endothelial-lined, circular channel, and it bridges the anterior chamber and bloodstream, which plays a vital role in maintaining a normal IOP. According to the function of SC, the SC is a potential therapeutic target for glaucoma. With the development of instruments, we obtained a high-resolution image of the chamber angle, which helped us understand the morphological change in the SC and investigate new therapy paradigm for glaucoma. In the future, based on the parameters provided using imaging and biomechanics instruments, we can assess for medications, gene therapy, and surgical procedures, which aim to expand the SC and increase conventional outflow pathway, to identify the most suitable size and delivery mechanism of microcatheter, and to maximize the therapeutic effect of canaloplasty and decrease the rate of surgery-related complications.
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