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Review

Development and material characteristics of glaucoma surgical implants

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ABSTRACT

Background: Glaucoma is the leading cause of irreversible blindness worldwide. The reduction of intraocular pressure has proved to be the only factor which can be modified in the treatment, and surgical management is one of the important methods for the treatment of glaucoma patients.

Main text: In order to increase aqueous humor outflow and further reduce intraocular pressure, various drainage implants have been designed and applied in clinical practice. From initial Molteno, Baerveldt and Ahmed glaucoma implants to the Ahmed ClearPath device, Paul glaucoma implant, EX-PRESS and the eyeWatch implant, to iStent, Hydrus, XEN, PreserFlo, Cypass, SOLX Gold Shunt, etc., glaucoma surgical implants are currently undergoing a massive transformation on their structures and performances. Multitudinous materials have been used to produce these implants, from original silicone and porous polyethylene, to gelatin, stainless steel, SIBS, titanium, nitinol and even 24-carat gold. Moreover, the material geometry, size, rigidity, biocompatibility and mechanism (valved versus nonvalved) among these implants are markedly different. In this review, we discussed the development and material characteristics of both conventional glaucoma drainage devices and more recent implants, such as the eyeWatch and the new minimally invasive glaucoma surgery (MIGS) devices.

Conclusions: Although different in design and materials, these delicate glaucoma surgical implants have widely expanded the glaucoma surgical methods, and improved the success rate and safety of glaucoma surgery significantly. However, all of these glaucoma surgical implants have various limitations and should be used for different glaucoma patients at different conditions.

1. Introduction

Glaucoma, characterized by progressive degeneration of the optic nerve, is the leading cause of global irreparable blindness.[1] The prevalence of glaucoma in 2013 is 3.54% for people aged 40–80, and in 2040, it is estimated to increase to 111.8 million, with people living in Africa and Asia being more significantly affected. The huge patient base stresses the importance of taking better guidance and more support in prevention, early detection, treatment and relevant public health initiatives for glaucoma.[2]

Traditionally, the reduction of intraocular pressure (IOP) and the protection of optic nerve are thought to be the main therapeutic principle for glaucoma.[3] At present, lowering the IOP has been proven to be the best characterized and most modifiable method for effective glaucoma treatment, yet neuroprotection is still confronted with great challenges.[4] Lowering IOP could be achieved by eye drops, oral drugs, laser or surgery procedures. However, in certain cases, pharmacotherapy or laser treatment cannot control IOP effectively or patients are intolerant of related side effects or have poor compliance, surgical management shown as the only and ultimate choice.[5]

Traditional glaucoma filtration surgery, commonly termed as trabeculectomy, has been considered the “gold standard” for glaucoma

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surgical treatment. In practice, trabeculectomy creates a guarded-filtration fistula between the subconjunctival space and the anterior chamber. Therefore, the aqueous could egress from the scleral flap, to form a subconjunctival bleb. Amounting evidence from clinical trials concluded that trabeculectomy has an excellent lowering effect on IOP that prevents further vision loss. However, the complicated surgical procedure, along with its tissue invasiveness, leading to numerous complications, such as subconjunctival fibrosis and hypotony.[6,7] Encouragingly, the latest materials and manufacturing techniques surpass the initial conception, with more convenient glaucoma drainage devices (GDDs) becoming popular and showing remarkable effect for the reduction of IOP.[8] Furthermore, the unveiling of more delicate, safer and minimally invasive glaucoma surgery (MIGS), leads the surgical management of glaucoma to enter a new era.[5] From initial Molteno, Baerveldt and Ahmed glaucoma implants to the Ahmed ClearPath device, Paul glaucoma implant, EX-PRESS and the eyeWatch implant, to iStent, Hydrus, XEN, PreserFlo, Cypass, SOLX Gold Shunt, etc., both of these GDDs and MIGS devices differ markedly in their property, such as material type, geometry, size, rigidity, biocompatibility and mechanism (valved versus nonvalved). And all of these discrepancies could lead to different clinical prognoses. This article aims to discuss the progress of glaucoma surgical implants with a focus fell on its material characteristics and is intended to bring new inspiration for future products design.

2. GDDs

2.1. Conventional GDDs

In the early 20th century, ophthalmologists started to explore the materials that could be inserted into the anterior chamber to create an artificial drainage pathway. Begun in 1906, Rollet threaded horsehair through the corneal punctures to enhance aqeous humor outflow in painful absolute glaucoma patients that just had anterior chamber penetration.[9] Then, materials like tantalum wire, silk thread, autologous canaliculus, gold foil, glass, platinum, teflon and gelatin film have been tested as intraocular implants to increase aqueous outflow. Disappointingly, these devices performed badly with severe foreign body reactions and extensive intraocular inflammation.[10]

Until 1969, Molteno described his implant. By attaching a thin silicone tube to the upper surface of a circular acrylic plate, Molteno implant could act like a functional filter-bubble that diverts the aqueous humor from the anterior chamber to an equatorial collecting reservoir (Fig. 1A; Table 1).[11] As the place site of Molteno plate is the sclera surface, the device is concave to better fit the curvature of the eye. Beyond this, the multi-hole edge rim (0.7 mm thick) of Molteno implant allows the sutures to fix it to the sclera to prevent its dislocation. In 1981, in order to promote the aqueous absorption, Molteno implant was modified to a

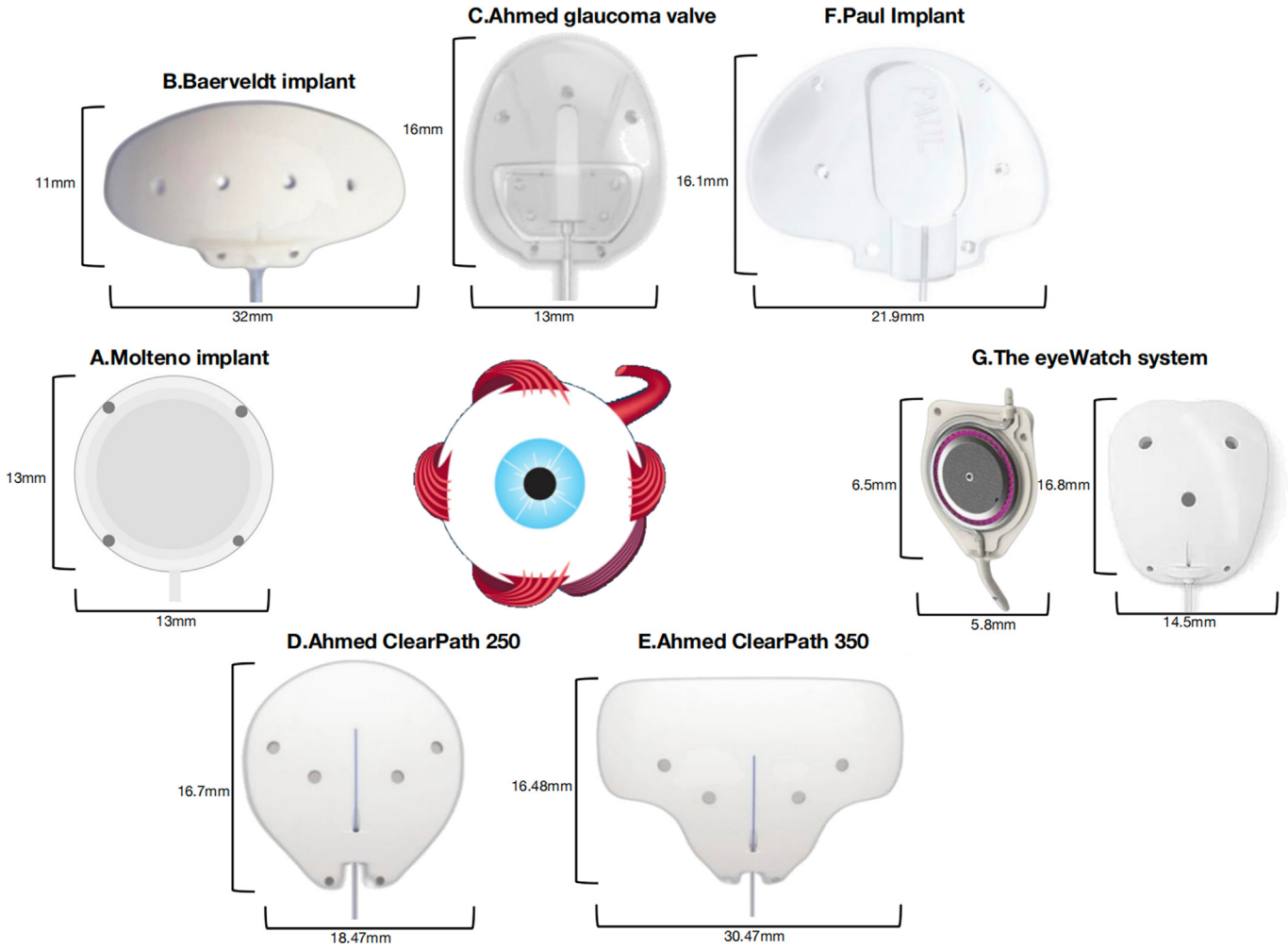

Fig. 1. Various GDDs.

Table 1
Summary of various GDDs.

Devices		Molteno implant	Baerveldt glaucoma implant	Ahmed glaucoma valve	Ahmed ClearPath	Paul glaucoma implant	The eyeWatch implant
Regulatory status		CE mark, FDA approval	CE mark, FDA approval	CE mark, FDA approval	CE mark, FDA approved since 2019	CE mark granted in 2018	CE mark granted in 2017
Manufacturer, Country		Molteno Ophthalmic Limited, Dunedin, New Zealand	Abbot Medical Optics Inc., Santa Ana, CA, USA	New World Medical Inc., Rancho Cucamonga, CA, USA	New World Medical Inc., Rancho Cucamonga, CA, USA	Advanced ophthalmic innovations PTE. LTD. Singapore	Rheon Medical, Lausanne, Switzerland
Material	**Tube**	Silicone	Silicone	Silicone	Silicone	Silicone	Silicone
	Plate	Polypropylene	Silicone	Silicone; Polypropylene; Porous polyethylene	Silicone	Silicone	Silicone (eyePlate)
Tube Diameter	**external**	0.60 mm	0.64 mm	0.635 mm	0.635 mm	0.467 mm	0.30 mm (implant) 0.63 mm (eyePlate)
	internal	0.30 mm	0.32 mm	0.305 mm	0.305 mm	0.127 mm	0.20 mm/0.30 mm (Plate)
Tube Length		/	32 mm (BG101-3 50; 103–250) 7 mm (Pars Plana; BG 102–350)	25.00 mm	32.00 mm	Around 29.00 mm	/
Plate size	**Thickness**	0.70 mm (edge rim)	0.50–2.00 mm	0.90 mm (Valve)	0.86 mm (Max)	0.95 mm (Max)	0.80 mm
	Long × wide	13.00 mm in diameter (circle)	22.00 mm in length (250) 32.00 mm in length (350)	13.0 mm*16.0 mm (FP7)	16.70 mm *18.47 mm or 16.48 mm *30.47 mm	21.9 mm *16.1 mm	6.5 mm*5.8 mm (implant) 14.5 mm*16.8 mm (eyePlate-200) 18.5 mm*18.9 mm (eyePlate-300)
	Surface area	135 mm^2	250–350 mm^2	96–364 mm^2	250 or 350 mm^2	342 mm^2	200 or 300 mm^2
Mechanism		Non-valvular	Non-valvular	Pressure-sensitive valvular	Non-valvular	Non-valvular	Adjustable device

double-plate model, which was composed of two plates (13 mm in diameter) and a connecting tube.[12] Compared with single-plate Molteno, the surgical process of double-plate version is more tricky and complicated. And the randomized clinical trial showed that although double-plate Molteno achieved more drainage of the aqueous than single one, it was related with greater risks of corneal decompensation and choroidal hemorrhages or effusions.[13]

Silicone is a synthetic polymer with a polysiloxane structure.[14] It exhibits many useful characteristics with good safety to support its numerous applications. The chain entanglement and high intermolecular interaction constitute the macromolecular structure of silicone and provide silicone with enough strength and stability.[15] Besides, the inorganic property, low-chemical reactivity, hydrophobicity, and low-surface energy impart silicone with biocompatibility. Silicone is also featured with flexibility, high thermal stability and elastomeric property.[16] Thus, it has the potential suitability to be used as glaucoma drainage tube. Polypropylene is a transparent, colorless-to-yellow solid, polymerized from propylene. It has three different stereoisomeric forms, with the isotactic polypropylene as the only commercially available isomeride in clinical applications. The melting point of polypropylene is approximately 165 °C, with a heat distortion temperature of around 104 °C at 66 PSI. Besides, it has a tensile strength of 5000 PSI and a flexural strength of 6000 PSI at yield. Due to its thermostability, high tensile strength, flexibility and more importantly, relative biological inertness, polypropylene has been proved to be successful as an intraocular implant.[17] Apart from suitable materials, ingenuity in the design of Molteno implant also leads to several functional advantages: First, the reservoir (plate) of Molteno implant makes full use of posterior conjunctival space to effectively promote the drainage of aqueous humor. Second, as the plate is placed posterior to the Tenon's capsule, it gets more protection from abnormal exposure. Third, instead of being directly exposed to subconjunctival tissue, the back end of silicone tube is connected to the collecting reservoir, so the incidence of tube fibrotic obstruction is greatly reduced.[10] These delicate features entail Molteno implant being the first successful GDD in clinical application and the main example for basically all following invented devices, and the revised model is still in use today by some glaucoma surgeons.[18,19]

In early 1990, the Baerveldt implant and Ahmed glaucoma valve (AGC) were introduced. Both of them have similar features with the Molteno, but different in size, shape, composition, and the IOP regulation mechanism.[20] The Baerveldt glaucoma implant (BGI) is composed of a non-valved silicone tube with one end implanted to the anterior chamber through a scleral flap, and another being opening at raised ridge of the outer surface of a carrier plate (surface area: 250–350 mm^2; Fig. 1B). The larger surface area of Baerveldt plate could lead to a lower and longer control of IOP.[21] Different from Molteno implant, the plate of BGI is made of soft medical-grade silicone elastomer that impregnated with barium sulfate. Medical grade silicone meets higher standards of manufacture, biocompatibility and safety. Compared with acrylic plate, soft silicone elastomer poses less irritation and damage to surrounding tissues and makes the implantation process much simpler. The radiopaque property enables devices to be easily viewed by X-ray, thereby allowing better patient progress monitoring.[22] In addition, except for two reserved suture holes in the edge for scleral fixation, the central area of the plate is also perforated to facilitate a tethered bleb formation with limited size. More specifically, the scar tissue will grow through the hole, forming a tether that attaches the device to the sclera and pulls the filtering bleb towards the eye. Although the scar tissue and drainage bleb are necessary for GDDs to control the outflow of the aqueous humor, in patients with extremely high IOP or small orbit, the drainage bleb with an excessive size could cause much pressure to the eyeball and the occurrence of protrusion problems and vision distortions. The decreased size of formed drainage bleb following Baerveldt implantation could reduce the incidence of these complications.[23]

Both Molteno and Baerveldt implants themselves have no resistance to aqueous outflow and thus are saddled with complications, like shallow

anterior chamber, hypotony, choroidal detachment.[12] Ahmed glaucoma drainage device was designed with a pressure-sensitive valve (7 mm wide and 8 mm long) to restrict the over-filtration (Fig. 1C). The Ahmed glaucoma valve (AGV) implant has various models with differences in their plate materials (polypropylene, medical-grade silicone, or porous polyethylene), type (single plate, double plate, or Pars plana), size (96–364 mm^2), providing surgeons and patients with more choices. The plate of M4 AGV model is made of porous high-density polyethylene.[24] Previous biomaterials research found that inertness was not always the most important attribute to alleviate foreign body response, especially at host sites where movement occurs. The micromovement of ploymer at the implantation site could significantly aggravate these adverse reactions.[25] Porous polyethylene is a tissue friendly, stable and infection-resistant thermoplastic synthetic material and has a pore size of 100–400 μm.[26] The porosity of M4 AGV model eases the ingrowth of vascular and fibrotic tissue to allow the integration of the device with host tissue, thereby improving resistance to mechanical deformation, abnormal exposure and inflammatory response. Moreover, the pretensioned silicone membranes of AGV implant valve help to reduce the incidence of hypotony by closing when IOP has returned to normal level again.[27] So far, BGI and AGV are still two of the most used GDDs with significant success rates for treating glaucoma.

2.2. The Ahmed ClearPath device

Ahmed ClearPath (New World Medical Inc., Rancho Cucamonga, CA, USA) is a novel valveless GDD. It was approved in 2019 by the US Food and Drug Administration (FDA) and considered as a promising new GDD with a significant success rate. There are two available sizes for different demands: 250 mm^2 and 350 mm^2 (Fig. 1D and E).[28] Both the tube and plate of Ahmed ClearPath are made of barium impregnated medical-grade silicone for better compliance to eye curvature and easier insertion.

The design of Ahmed ClearPath device has a lot in common with BGI, but is superior to BGI in the following aspects: First, without a front plate ridge, Ahmed ClearPath presents with a thinner profile, resulting in a lower and more diffuse bleb postoperatively. The benefits of this design include the accomplishment of long-term and lower IOP control, less inflammatory infiltration and reduced diplopia occurrence. Second, the 350 mm^2 model features with winged design and a positioned plate to avoid rectus muscle insertions and allow more stability, and the smaller 250 mm^2 model is designed to fit between rectus muscles without the need for muscle isolation. Limited muscle manipulation eases the surgery procedures with better safety. Third, the more anterior position of suture fixation eyelets eliminates the need for extensive posterior dissection and incision, which helps to reduce the operative time but also promotes faster recovery. Finally, the preloaded polypropylene ripcord in the lumen of the tube could reduce early hypotony.[29] In 2022, the first study with 24-month follow-up proved the safety and effectiveness of Ahmed ClearPath in reducing both IOP and medication burdens in patients with refractory primary open-angle glaucoma, and demonstrated that only a few short-term complications were noted after implantation.[30]

2.3. The Paul glaucoma implant

Clinical comparison researches have reported that compared with the AGV, BGI has a lower failure rate but a significantly higher risk of postoperative hypotony.[31] Thus, the team of clinical scientists was committed to developing a GDD with similar efficacy to the BGI but with a reduced complication rate, and then the Paul glaucoma implant (PGI; Advanced ophthalmic innovations PTE. LTD. Singapore) was invented. The PGI is a nonvalved aqueous shunt made of implantable medical-grade silicone (Fig. 1F). As the superior efficacy of the BGI is thought to be related to its larger plate size, this character is preserved for PGI. The winged end plate of the PGI possesses a large surface area for aqueous absorption. In particular, the tube size of the PGI is smaller compared to the Baerveldt and Ahmed tubes, with an internal diameter of 0.127 mm and external diameter of 0.467 mm. Thus, rather than a 3-0 polypropylene ripcord used for occluding BGI lumen, a 6-0 size is enough for blocking the tube and allowing less egress of aqueous, which negates the necessity of a Vicryl ligature. These design features of PGI are likely to decrease the incidence of tube exposure, hypotony and endothelial cell loss, and meanwhile enhance postoperative IOP reduction.[29,32,33] The recent two-year clinical outcomes proved that the PGI could reduce IOP continuously with a low incidence of hypotony in patients with advanced glaucoma.[34] So far, PGI has received Conformite Europeenne (CE) mark in Europe, but has not been granted by FDA.

2.4. The eyeWatch system

The lack of proper IOP control postoperatively is the main problem for all filtering procedures and could lead to several complications, such as hypotony and shallow anterior chamber.[35] The eyeWatch (Rheon Medical, Lausanne, Switzerland) is the world's first adjustable device for treating glaucoma. Briefly, it is composed of an implant and its control unit, the eyeWatch Pen. The implant is 6.5 mm long and 5.8 mm in width with a thickness of 0.8 mm (Fig. 1G). It is featured with a rotating magnetic disk, which could compress or decompress a deformable drainage tube. The drainage tube is made of silicone (MED-4830; NuSil, Carpinteria, CA) with a 0.3 mm outer diameter and 0.2 mm internal diameter. This implant should be always linked to an eyePlate or a Baerveldt glaucoma implant. It is not recommended to use the eyeWatch device as a stand-alone device.[36] The eyePlate implant is made out of medical grade silicone. It can be used either as a stand-alone device or in conjunction with the eyeWatch device. The plate features two fixation holes for scleral attachment and three fenestrations for limiting the bleb's volume.

By using the eyeWatch Pen, the magnetic disk around the shaft can be controlled non-invasively during operation or post-operation. One end of the eyeWatch pen is a flat compass to measure the angular position of the magnetic disk, and another end is a permanent magnet to perform the adjustment. The magnetic field of the pen could interact with internal magnetic disk of the implant. By precisely orienting the axis of the magnet from the pen, the magnetic disk within the implant could rotate around an eccentric axis and then push or retract the outside ring of the ball bearing mechanism.[37] The radial motion of the outside ring results in a variable compression and cross-sectional area change of drainage tube, followed by the alteration of fluidic resistance in aqueous outflow. Meanwhile, the angular position of the magnetic disk controls the compressed tube length and the degree of radial compression.[36]

The initial clinical study of the eyeWatch in refractory glaucoma patients showed that the postoperative complication rate was low, and the IOP could be sufficiently controlled.[38] In 2021, the FDA has granted Breakthrough Device Designation to Rheon Medical's eyeWatch technology. Currently, the device is available in European and Asian markets, and is now undergoing the US-based clinical trial (NCT04323930).

3. MIGS

With the arrival of MIGS, the algorithm of glaucoma treatment witnesses a dramatic evolution. The term MIGS refers to a type of surgical procedures sharing the common theme of micro-incision, small device geometry, short operating time, easy instrumentation and fast postoperative recovery. The safety and effectiveness of MIGS have made them an attractive option for early and moderate glaucoma. Based commonly on the drainage site of aqueous humor, MIGS can be separated into three groups: Subconjunctival MIGS (XEN, Ex-PRESS, PreserFlo); Trabecular MIGS (iStent, iStent Inject, Hydrus); Suprachoroidal MIGS (Cypass, SOLX Gold Shunt, iStent Supra).[39]

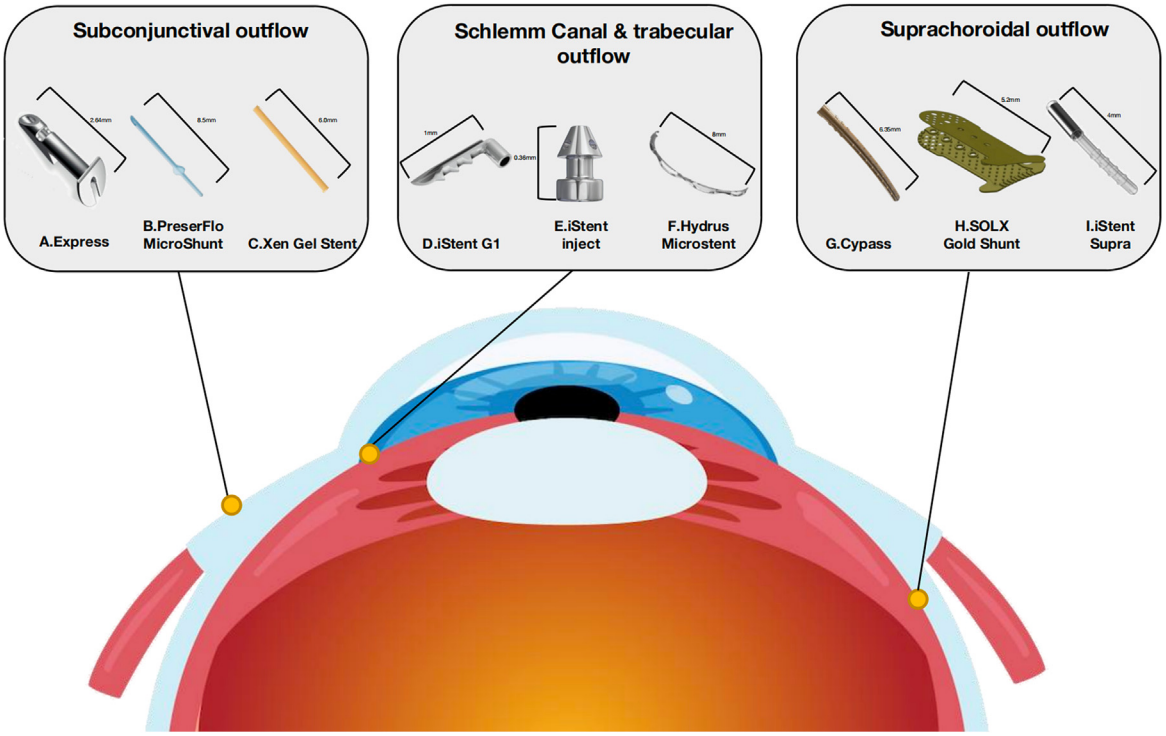

Fig. 2. Various MIGS.

Table 2
Summary of various MIGS devices.

Mechanism	Increase subconjunctival outflow			Increase Schlemm Canal and trabecular outflow			Increase suprachoroidal outflow		
Device	EX-PRESS	PreserFlo MicroShunt	XEN gel stent	iStent G1	iStent inject	Hydrus Microstent	Cypass Microstent	SOLX Gold Shunt	iStent Supra
Regulatory status	CE mark, FDA approved since 2002	CE mark granted in 2012	CE mark granted in 2013, FDA approved since 2016	CE mark granted in 2004, FDA approved since 2012	CE mark granted in 2010	CE mark granted in 2011, FDA approved since 2018	Withdrawn from the global market in 2018	CE mark granted, approved in Canada	CE mark granted in 2010
Manufacturer, Country	Alcon Laboratories , Fort Worth, TX, USA	Santen Pharmaceutical Co. Ltd., Osaka, Japan	Allergan Inc., Dupont Dr, Irvine, CA, USA	Glaukos Corporation, Laguna Hills, CA, USA		Ivantis, Irvine, CA, USA	Alcon Laboratories, Fort Worth, TX, USA	SOLX, Waltham, MA, USA	Glaukos Corporation, Laguna Hills, CA, USA
Material	Stainless steel (316L)	Poly(styrene-block-isobutylene-block-styrene); SIBS	Porcine gelatin cross-linked with glutaraldehyde	Heparin-coated non-ferromagnetic titanium (Ti6AI4V ELI)		Nitinol (55% nickel-45% titanium alloy)	Polyamide	24-carat gold(99.95% pure)	Polyether sulfone (PES)
Size	2.64 mm in length with a 50 or 200 μm internal lumen size	8.5 mm long with a 350 μm outer diameter and a 70 μm lumen.	6 mm long with lumen sizes of 45, 63 and 140 μm	1 mm in length and 0.3 mm in height	360 μm in height with a central lumen of 80 μm	8 mm long	6.35 mm long cylinder with a 510 μm external diameter and 310 μm lumen	5.2 mm in length; Plus:5.5 mm in length	4 mm tube with a lumen of 0.16 mm

3.1. Subconjunctival MIGS

3.1.1. EX-PRESS

The EX-PRESS Glaucoma Filtration Device (Alcon Laboratories, Fort Worth, TX, USA) was FDA authorized in 2002. EX-PRESS looks like a nail and is made of biomedical stainless steel (316L) with strong stability and MRI compatibility. Metallic materials are extensively used as biomaterials and account for around 70% of all medical implants and devices. Metals usually have larger Young's model. Therefore they possess better biomechanical strength and are also easy to process. Additionally, metallic implants can be sterilized by the traditional sterilization procedure, which simplifies their manufacture and handling.[40] Among them, 316L stainless steel and Ti6AI4V are the most common biomaterials used, due to the excellent mechanical strength and tissue compatibility.[41] 316L stainless steel is an austenitic chromium-nickel alloy with molybdenum endowed corrosion resistance. This is especially advantageous in avoiding pitting and crevice corrosion in chloride environments. 316L stainless steel has a density of 8 g/cm^3 and its modulus of elasticity is 29 × 10^6 PSI (200 GPa) with a melting point of 1370 °C. Besides, the manufacturing costs of 316L stainless steel are much cheaper than titanium and cobalt-based alloys, and the manufacturing technique for 316L stainless steel is relatively simple.[42]

These material attributes give 316L stainless steel great advantage to be used as intraocular implants. And the biocompatibility test of EX-PRESS showed no active inflammatory reaction or tissue irritation around the implant position.[43]

EX-PRESS is 2.64 mm in length with either a 50 or 200 μm internal lumen size, and can be divided into three parts: drainage tube, wing collar, and short protuberant (Fig. 2A; Table 2). The distal end of drainage tube that near the anterior chamber is tipped to facilitate precise and controlled insertion. Besides, three orifices are opening up at the distal end to form an alternative passage to drain aqueous when the main tube is blocked by the iris. The short protuberant in the proximal end of the tube is for preventing device extrusion, whilst the angled wing collar is used to ensure a predetermined implantation depth and avoid the slide of the device into the eye.[44]

The EX-PRESS was initially designed to be positioned under conjunctival via *ab externo* approach. However, a higher risk of erosion, extrusion and hypotony was noticed following surgery. Therefore, the operation was revised as placing the device underneath the partial thickness scleral flap.[45] The EX-PRESS has enhanced filtering surgery by standardizing the "hole" with a simpler, quicker, and less traumatic surgery procedure. As it requires making scleral and conjunctival flap, some people suggest that it should not be listed as MIGS. The randomized prospective clinical trial showed that mean IOP after implantation and success rates at 3 years of EX-PRESS were comparable to trabeculectomy.[46]

3.1.2. The PreserFlo MicroShunt

The PreserFlo MicroShunt (Santen Pharmaceutical Co. Ltd., Osaka, Japan) was approved byCE mark in 2012 and is currently being tested in a Phase 3 clinical study granted by the FDA.[47] It is a tubular device with the distal end resting in the anterior chamber while the proximal end laying in the subconjunctiva space (Fig. 2B). The device is made of a new synthetic thermoplastic elastomeric biomaterial (poly(styrene-block--isobutylene-block-styrene); SIBS). SIBS is a triblock copolymer, in which hard glassy polystyrene domains hold the soft polyisobutylene (PIB) rubbery chains. SIBS is thermoformable and has good solubility in various nonpolar solvent. These properties make it easier to be extruded, injected or compressed into different shapes.[47] SIBS has the advantages to resist bio-degradation in the body, as well as good biocompatibility. It is soft and flexible, and can be easily shaped in line with the curvature of the eye. It was reported that SIBS implants induced less collagen deposition and fibroblast proliferation *in vivo*, therefore mitigating the scar formation and encapsulation of filtering bleb. When first tested in the rabbit eye, SIBS was extremely well tolerated both in the stroma of the cornea and under the conjunctiva and Tenon's capsule.[48]

The PreserFlo MicroShunt is 8.5 mm long with an outer diameter of 350 μm and a lumen size of 70 μm. It is placed through an *ab externo* route. The unique lateral "fins" design 4.5 mm far from the distal end helps to fix the position and direction of the device, and meanwhile, prevents the peritubular leakage to reduce the happening of hypotony. The validity and utility of PreserFlo MicroShunt have been proved over time, with the research showing that the one-year results of postoperative mean IOP reduction, peak IOP, and IOP fluctuations were not statistically significantly different between trabeculectomy and PreserFlo MicroShunt.[49] Another study compared the effect of PreserFlo MicroShunt, Xen Gel Stent, and trabeculectomy with MMC, and demonstrated a comparable surgical success rate in all three groups after 6 months.[50] But, the PreserFlo implant was presented with a lower risk of hypotony when compared with traditional glaucoma surgery, but also with other MIGS approaches such as XEN.[51]

3.1.3. XEN gel stent

In 2016, the XEN gel stent (Allergan Inc., Dupont Dr, Irvine, CA, USA) was approved by FDA for the treatment of refractory open-angle glaucoma. It is a hydrophilic tubular implant made out of porcine gelatin cross-linked with glutaraldehyde.[52] Gelatin is a natural origin protein derived from chemical, physical or enzymatic hydrolysis of collagen type I with features of good biocompatibility and safety, non-toxicity and low immunogenicity. The greatest disadvantage of pure gelatin for its use in medical applications is thermal instability at physiological temperature. Therefore, glutaraldehyde is introduced as a crosslinking agent, allowing XEN to be a stable and permanent implant.[53]

The XEN gel stent is 6 mm long with lumen (Fig. 2C). When hydrated, the state of the implant can change from hard to soft and flexible. It only takes 1–2 min for this transformation when applying XEN to the eye. Thus, the tube can be much easier to implant in its rigid and straight state, but becomes tissue-conforming after insertion to improve patient comfort.[54] When aqueous humor flows in, the XEN gel stent expands to its final size, which could prevent the potential migration and erosion. The Hagen-Poiseuille equation $Q = \pi \times r^4 \times \Delta p/(8\eta L)$ is used to calculate the laminar flow in the tube, where Δp is the pressure gradient, L is tube length, r is tube radius, Q is the volumetric flow rate, η is dynamic fluid viscosity. The formula describes the basic fluid mechanic principles on which XEN's design is based. According to this equation, the company offers three different models with lumen sizes of 45, 63 and 140 μm (XEN 45, 63 and 140). Postoperative hypotony was reported to be related with XEN 63 and 140, but not with XEN 45.[55]

The flexible tube is preloaded into a 27-gauge needle, which penetrates the anterior trabecular and sclera to the subconjunctiva, guiding the tube to run through the trabecular mesh to subconjunctival space via an *ab interno* way. Therefore, a drainage channel formed without any external cutting or suturing.[54] The clinical study of Kaweh Mansouri et al. reported that 2 years after surgery, XEN gel stent significantly reduced IOP and the number of anti-glaucoma medications.[6] But the encapsulation or twine of XEN tube within Tenon's capsule may happen, and further needling and adjustment may be required.[56] Thus, the modification of its design is needed to avoid these problems.

3.2. Trabecular MIGS

3.2.1. iStent and iStent inject

iStent (Glaukos Corporation, Laguna Hills, CA, USA) is the smallest human medical implant to date, and is the first MIGS device approved by the FDA in 2012. The device connects the anterior chamber to Schlemm's canal in an *ab interno* approach, allowing more and quicker drainage of aqueous by traversing congested trabecular meshwork. It is a trabecular microbypass stent that is composed of heparin-coated non-ferromagnetic titanium (Ti6AI4V ELI).[57]

Alpha-beta alloy containing 6% AI and 4% V, referred to as Ti6AI–4V, is one of the most commonly used titanium alloys. This alloy has very high tensile strength and toughness. It is lightweight and is able to resist extreme temperatures. Titanium has a high affinity with oxygen atoms, thus a very thin dense oxide layer (TiO_2) can be formed on its surface at room temperature, which is also the reason for its excellent corrosion resistance. As for medical applications, strict user specifications require controlled microstructures and freedom from melt imperfections. Controlled interstitial element levels are designated ELI (extra low interstitials). The essential difference between Ti6AI4V ELI (grade 23) and Ti6AI4V (grade 5) is that the oxygen content is reduced to 0.13% (maximum) at grade 23. Reduced interstitial elements oxygen and iron improve plasticity and fracture toughness. Thus, Ti6AI4V ELI is the first choice for any situation where a combination of high strength, light weight, good corrosion resistance and toughness is required. And because of its low modulus, biocompatibility, good fatigue strength, non-magnetism and avirulence, Ti6AI4V ELI is a good choice for implant materials.[58,59] The coated heparin of iStent helps to prevent thrombosis and reduces adhesion of blood components on the device.

The iStent G1 (first-generation model) is 1 mm in length and 0.3 mm in height, and has a snorkel with 250 μm length and a snorkel bore with 120 μm diameter (Fig. 2D). The open half-pipe has three paralleled retention arches that protrude from tube wall to secure its position in the Schlemm's canal.[18,60] The proximal end of the iStent G1 is a

self-trephining tip for easier insertion, and the half-cylinder profile of the open posterior wall will inhibit blockage or fibrosis over the tip.[60,61] After penetrating the cornea, the iStent can be released from the inserter in a side-sliding way, and is then located in the trabecular meshwork by simple promotion of the extensions.

The second-generation implant is iStent inject, sharing the same material and working mechanism with iStent G1, but with different appearances. The iStent is 360 μm in height with a central lumen of 80 μm and is loaded with 2 stents (Fig. 2E). The apical stent is 230 μm in diameter with four side flow outlets of 50 μm each to increase aqueous drainage. Another stent is a flange that faces the anterior chamber to secure the position of the device. The highlight of the iStent inject is the single-piece design without a snorkel, thus the surgical procedure can be much easier without the positioning requirement of sideways sliding. Additionally, one inserter is preloaded with up to two devices, through which the surgeon can deliver two iStents while only entering the eye once.[62] A retrospective study compared the effectiveness of iStent vs. iStent inject implantation combined with phacoemulsification, and found that both groups had similar success rate, but iStent inject resulted in a lower IOP at 6 months and more patients had an IOP $\leq$15 mmHg at 6/12 months.[63]

3.2.2. The Hydrus Microstent

The Hydrus Microstent (Ivantis, Irvine, CA, USA) is approved by CE mark in 2011 and FDA in 2018. It is an 8 mm long Nitinol (55% nickel-45% titanium alloy) scaffold with a similar radium with the Schlemm's canal and is implanted in an *ab interno* technique (Fig. 2F). Nitinol is a metal alloy of nickel (Ni) and titanium (Ti). So far, it has been used widely in various implantable devices for its flexibility, non-cytotoxic, high damping, non-mutagenic and biocompatibility. Nitinol is a shape memory alloy. It has super-elasticity properties, and therefore can be used as a structural supporter in Schlemm's canal.[64–67] Nitinol has been used in a subretinal drug delivery system.[68] Besides, it was reported that the nitinol clip prototype on the iris surface was well tolerated and innoxious in Yucatan mini-pigs, further demonstrating its intraocular biocompatibility.[69] The implant of Hydrus is laser cut from nitinol tubing to a patented profile with alternating "spines" for structural support and "windows" to enhance outflow of aqueous humor.[70] After that, the scaffold is heat-set to a curvature that similar with the Schlemm's canal and is then electro-polished to produce a smooth biocompatible surface.

The scaffold has a non-luminal open structure 290 μm in diameter. The rounded proximal tip is for a smooth passage into Schlemm's canal and the 1–2 mm inlet facilitates the aqueous flow. Unlike the iStent inject, which is inserted into the trabecular meshwork perpendicularly, the Hydrus Microstent is placed parallel with the natural circular anterior chamber angle with a 90° occupation to augment the Schlemm's canal around 4–5 times its anatomical cross-sectional area (241 μm). The Hydrus-loaded injector is used to make the micro-incision of the cornea and incise the trabecular meshwork tissue firstly. Then, the microstent is promoted to span the Schlemm's canal, with an inlet staying in the anterior chamber.[70] A prospective randomized trial with a follow-up of 12-month found that compared with the iStent, Hydrus had a higher surgical success rate with fewer medications, but both of them had good security.[71]

3.3. Suprachoroidal MIGS

3.3.1. Cypass

In 2016, the Cypass Microstent (Alcon Laboratories, Fort Worth, TX, USA) was approved by FDA following the COMPASS pivotal trial. It is a biocompatible, non-biodegradable and flexible polyamide implant that is positioned in the suprachoroidal area to improve the flow of the aqueous humor via the uveoscleral pathway. Polyamide is synthetic polymer and widely used by manufacturers in both industrial and medical field. It has biotolerable and inert properties, resulting in less histological reactions and adhesion formation. Apart from that, production of polyamide has lower cost than polypropylene. Polyamide has been successfully used in diverse tissue sutures and is suitable to make catheters that require stability and high precision for its capability to resist crushes, cracking, tears, and punctures.[72,73]

Cypass is a 6.35 mm cylinder with a 510 μm external diameter and 310 μm lumen (Fig. 2G). There are three retention rings located in the distal end of the tube for its fixation. And the optimal position depth is one retention ring being seen in the anterior chamber. The proximal end of the microstent is fenestrated with pores (76 μm in diameter) to promote circumferential egress of aqueous, and the lumen allows longitudinal egress of fluid.[8] Although the Cypass Microstent was proved to be effective as Hydrus Microstent and iStent, Cypass was voluntarily withdrawn by Alcon from the global market for the significant corneal endothelial cells loss that caused by the greater number of retention rings residing in the anterior chamber.[74,75]

3.3.2. SOLX Gold Shunt

The SOLX Gold Shunt (SOLX, Waltham, MA, USA) is a suprachoroidal shunt placed via *ab externo* approach. 24-carat (99.95% pure) gold is used to produce the device as it is inert as a foreign body in the eye without causing inflammation and scarring.[76] The first generation of Gold Shunt is 5.2 mm in length with a weight of 6.2 mg, and the newer Gold Shunt Plus is 0.3 mm longer and 3.0 mg heavier than the old one with larger microchannels to increase outflow. The shunt looks like a tiny chip welded by the upper and lower two golden plates (Fig. 2H). The end positioned in the anterior chamber has 60 holes each with a diameter of 100 μm to allow the aqueous flow into the device, while the other end placed in suprachoroidal space has 117 holes arranged regularly to promote the outflow of aqueous. The two ends of the shunt are connected by posts that form 10 closed tubules and 9 open tubules (24 μm wide and 50 μm tall) to drain aqueous directionally. The highlight of this device is that the closed tubules can be opened by a titanium-sapphire laser to re-modulate the aqueous outflow postoperatively.[77] A CE mark has been granted to the SOLX Gold MicroShunt in Europe, however FDA approval has not yet been obtained. Available studies reported a high failure rate after SOLX Gold Shunt implantation, which may be significantly related to obstruction of fenestration and fibrous encapsulation.[78–80] Given this, it is less promising that SOLX Gold Shunt becomes a commercially available implant for glaucoma surgery.

3.3.3. iStent supra

The iStent Supra (Glaukos Corporation, Laguna Hills, CA, USA) is a 4 mm tubular implant with a 0.16 mm lumen. It is composed of heparin-coated polyether sulfone (PES) with a titanium sleeve. PES is chemically derived from bisphenol A and dichlorodiphenylsulfone through condensation reaction via aromatic nucleophilic replacement. It is a favorable candidate in medical applications and waste-treatment films due to its outstanding temperature tolerance, stable chemical properties, resistance to oxidation, and good mechanical strength and film-forming abilities.[81,82]

iStent Supra has curved design, allowing it to follow the supraciliary contour. There are 4 retention ridges to improve retention in its desired location (Fig. 2I). But different from Cypass, the retention ridge is positioned far away from the anterior chamber angle to avoid its adverse effect on corneal endothelial cells. The stent is implanted via a preloaded inserter through a clear corneal incision under gonioscopic guidance by *ab interno* approach. Early reports showed that combined with the postoperative travoprost, the implantation of iStent Supra demonstrated with success.[74] Adverse events that occur most frequently are early hypotony and self-limited choroidal effusions.[83] At present, the iStent Supra is already authorized for marketing in the European Union. And it is currently being studied under an Investigational Device Exemption clinical trial (NCT01461278) in support of U.S. FDA approval.[84]

4. Conclusions

Over the years, improvements in design and biomaterial promote a simpler, safer, faster, and minimally invasive implantation technique for glaucoma surgery. Choosing the right biomaterials for implant is essential for its long-term success. A number of factors need to be taken into consideration to achieve the best effect in long-term placement, including mechanical strength, wear and corrosion resistance, price, complexity of manufacture, biocompatibility, etc. From original silicone and porous polyethylene, to gelatin, stainless steel, SIBS, titanium, nitinol and even 24-carat gold, more and more biocompatible materials with unique features continue to emerge for the preparation of glaucoma devices. The smart designs for sclera suturing, plate perforation, position fixation and aqueous outflow of these glaucoma surgical implants greatly facilitate the surgical operation with benefits for both surgeons and patients. However, there are still some "Good in design but less to execution" devices, which remind us that the inadequate consideration of small design details could lead to a failure of the product during clinical application. Richard M.H. et al. first proposed the 10-10-10 aspiration goal for glaucoma devices, namely, controlling IOP to 10 mmHg, staying functioning for 10 years and being implanted in 10 min with nearly no complication.[5] There is a strong possibility that the first two targets will be achieved within the next few years, but the operation time of 10 min poses a great challenge to the device design. Here, we hope the intelligent design details from material and shape to structure and function of various glaucoma implants discussed here could bring inspirations for future investigators to make more advanced products.

Study approval

Not Applicable.

Author contribution

Conception and design of study: MC, KJW; Manuscript preparation QYQ, CSZ; Manuscript revision NJY, FJ; Figure preparation: QYQ, XL and QZ. All authors reviewed the results and approved the final version of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

1. Wu X, Konieczka K, Liu X, et al. Role of ocular blood flow in normal tension glaucoma. *Adv Ophthalmol Pract Res*. 2022;2(1):100036. https://doi.org/10.1016/j.aopr.2022.100036.
2. Tham YC, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology*. 2014;121(11):2081–2090. https://doi.org/10.1016/j.ophtha.2014.05.013.
3. Vernazza S, Oddone F, Tirendi S, et al. Risk factors for retinal ganglion cell distress in glaucoma and neuroprotective potential intervention. *Int J Mol Sci*. 2021;22(15). https://doi.org/10.3390/ijms22157994.
4. B S, Ö A, A YG, et al. Retinal tissue bioengineering, materials and methods for the treatment of glaucoma. *Tissue engineering and regenerative medicine*. 2020;17(3):253–269. https://doi.org/10.1007/s13770-020-00254-8.
5. Rmh L, B Y, E I, et al. Translating minimally invasive glaucoma surgery devices. *Clinical and translational science*. 2020;13(1):14–25. https://doi.org/10.1111/cts.12660.
6. L R. The surgical management of glaucoma: a review. *Clin Exp Ophthalmol*. 2022;50(2):213–231. https://doi.org/10.1111/ceo.14028.
7. Schlunck G, Meyer-ter-Vehn T, Klink T, et al. Conjunctival fibrosis following filtering glaucoma surgery. *Exp Eye Res*. 2016;142:76–82. https://doi.org/10.1016/j.exer.2015.03.021.
8. Koike KJ, Chang PT. Trabeculectomy: a brief history and review of current trends. *Int Ophthalmol Clin*. 2018;58(3):117–133. https://doi.org/10.1097/iio.0000000000000231.
9. Thomas R, Gieser SC, Billson F. Molteno implant surgery for advanced glaucoma. *Aust N Z J Ophthalmol*. 1995;23(1):9–15. https://doi.org/10.1111/j.1442-9071.1995.tb01639.x.
10. Melamed S, Fiore PM. Molteno implant surgery in refractory glaucoma. *Surv Ophthalmol*. 1990;34(6):441–448. https://doi.org/10.1016/0039-6257(90)90124-e.
11. Molteno AC. The optimal design of drainage implants for glaucoma. *Trans Ophthalmol Soc N Z*. 1981;33:39–41.
12. Patel S, Pasquale LR. Glaucoma drainage devices: a review of the past, present, and future. *Semin Ophthalmol*. 2010;25(5-6):265–270. https://doi.org/10.3109/08820538.2010.518840.
13. Heuer DK, Lloyd MA, Abrams DA, et al. Which is better? One or two? A randomized clinical trial of single-plate versus double-plate Molteno implantation for glaucomas in aphakia and pseudophakia. *Ophthalmology*. 1992;99(10):1512–1519. https://doi.org/10.1016/s0161-6420(92)31772-5.
14. C JJ. Modifications of textile materials with functional silanes, liquid silicone softeners, and silicone rubbers-A review. *Polymers*. 2022;14(20). https://doi.org/10.3390/polym14204382.
15. B W, D C MF, et al. Intraocular silicone implant to treat chronic ocular hypotony-preliminary feasibility data. *Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie*. 2016;254(11):2131–2139. https://doi.org/10.1007/s00417-016-3364-4.
16. Allen Jr LV. Compounding with silicones. *Int J Pharm Compd*. 2015;19(3):223–230.
17. Hm C. Polypropylene. *Ophthalmology*. 1981;88(9):959–964. https://doi.org/10.1016/s0161-6420(81)80012-7.
18. Razeghinejad MR, Spaeth GL. A history of the surgical management of glaucoma. *Optom Vis Sci*. 2011;88(1):E39–E47. https://doi.org/10.1097/OPX.0b013e3181fe2226.
19. Välimäki JO, Ylilehto AP. Molteno3 implantation as primary glaucoma surgery. *J Ophthalmol*. 2014;2014:167564. https://doi.org/10.1155/2014/167564.
20. Vl T, AL C, My C, et al. Aqueous shunts for glaucoma. *Cochrane Database Syst Rev*. 2017;7. https://doi.org/10.1002/14651858.CD004918.pub3. CD004918.
21. P B PA. Glaucoma drainage implants. *Int J Ophthalmol*. 2020;13(8):1318–1328. https://doi.org/10.18240/ijo.2020.08.20.
22. Rittenbach TL. Proptosis from a Baerveldt tube shunt implant. *Optom Vis Sci*. 2014;91(6):e145–e148. https://doi.org/10.1097/opx.0000000000000278.
23. Smith MF, Doyle JW, Sherwood MB. Comparison of the Baerveldt glaucoma implant with the double-plate Molteno drainage implant. *Arch Ophthalmol*. 1995;113(4):444–447. https://doi.org/10.1001/archopht.1995.01100040060027.
24. Riva I, Roberti G, Katsanos A, et al. A review of the ahmed glaucoma valve implant and comparison with other surgical operations. *Adv Ther*. 2017;34(4):834–847. https://doi.org/10.1007/s12325-017-0503-1.
25. Jacob JT, Burgoyne CF, McKinnon SJ, et al. Biocompatibility response to modified Baerveldt glaucoma drains. *J Biomed Mater Res*. 1998;43(2):99–107. https://doi.org/10.1002/(sici)1097-4636(199822)43:2<99::aid-jbm3>3.0.co;2-g.
26. Berghaus A, Stelter K, Naumann A, et al. Ear reconstruction with porous polyethylene implants. *Adv Oto-Rhino-Laryngol*. 2010;68:53–64. https://doi.org/10.1159/000314562.
27. Riva I, Roberti G, Oddone F, et al. Ahmed glaucoma valve implant: surgical technique and complications. *Clin Ophthalmol*. 2017;11:357–367. https://doi.org/10.2147/opth.S104220.
28. Grover DS, Kahook MY, Seibold LK, et al. Clinical outcomes of ahmed ClearPath implantation in glaucomatous eyes: a novel valveless glaucoma drainage device. *J Glaucoma*. 2022;31(5):335–339. https://doi.org/10.1097/ijg.0000000000002013.
29. K M, Ms S. New glaucoma drainage implants available to glaucoma surgeons. *Curr Opin Ophthalmol*. 2023;34(2):176–180. https://doi.org/10.1097/icu.0000000000000936.
30. Dorairaj S, Checo LA, Wagner IV, et al. 24-Month outcomes of ahmed ClearPath(®) glaucoma drainage device for refractory glaucoma. *Clin Ophthalmol*. 2022;16:2255–2262. https://doi.org/10.2147/opth.S368634.
31. Budenz DL, Barton K, Gedde SJ, et al. Five-year treatment outcomes in the Ahmed Baerveldt comparison study. *Ophthalmology*. 2015;122(2):308–316. https://doi.org/10.1016/j.ophtha.2014.08.043.
32. Vallabh NA, Mohindra R, Drysdale E, et al. The Paul® glaucoma implant: 1-year results of a novel glaucoma drainage device in a paediatric cohort. *Graefes Arch Clin Exp Ophthalmol*. 2023;261(8):2351–2358. https://doi.org/10.1007/s00417-023-06000-9.
33. M K. [Comparison of glaucoma drainage implants]. *Die Ophthalmologie*. 2023;120(4):372–377. https://doi.org/10.1007/s00347-023-01846-0.
34. Tan MCJ, Choy HYC, Koh Teck, Chang V, et al. Two-year outcomes of the Paul glaucoma implant for treatment of glaucoma. *J Glaucoma*. 2022;31(6):449–455. https://doi.org/10.1097/ijg.0000000000001998.

35. Lim KS. Control and optimisation of fluid flow in glaucoma drainage device surgery. *Eye*. 2018;32(2):230–234. https://doi.org/10.1038/eye.2017.316.
36. Villamarin A, Roy S, Bigler S, et al. A new adjustable glaucoma drainage device. *Investigative Ophthalmology & Visual Science*. 2014;55(3):1848–1852. https://doi.org/10.1167/iovs.13-12626.
37. Roy S, Villamarin A, Stergiopulos N, et al. MRI after successful eyeWatch(TM) implantation. *Eur J Ophthalmol*. 2022;32(1):Np79–np82. https://doi.org/10.1177/1120672120973617.
38. Roy S, Villamarin A, Stergiopulos C, et al. Initial clinical results of the eyeWatch: a new adjustable glaucoma drainage device used in refractory glaucoma surgery. *J Glaucoma*. 2019;28(5):452–458. https://doi.org/10.1097/ijg.0000000000001209.
39. Saheb H, Ahmed II. Micro-invasive glaucoma surgery: current perspectives and future directions. *Curr Opin Ophthalmol*. 2012;23(2):96–104. https://doi.org/10.1097/ICU.0b013e32834ff1e7.
40. Motallebzadeh A, Peighambardoust NS, Sheikh S, et al. Microstructural, mechanical and electrochemical characterization of TiZrTaHfNb and Ti1.5ZrTa0.5Hf0.5Nb0.5 refractory high-entropy alloys for biomedical applications. *Intermetallics*. 2019;113:106572. https://doi.org/10.1016/j.intermet.2019.106572.
41. Saini M, Singh Y, Arora P, et al. Implant biomaterials: a comprehensive review. *World J Clin Cases*. 2015;3(1):52–57. https://doi.org/10.12998/wjcc.v3.i1.52.
42. Ali S, Irfan M, Niazi UM, et al. Microstructure and mechanical properties of modified 316L stainless steel alloy for biomedical applications using powder metallurgy. *Materials*. 2022;15(8). https://doi.org/10.3390/ma15082822.
43. Nyska A, Glovinsky Y, Belkin M, et al. Biocompatibility of the Ex-PRESS miniature glaucoma drainage implant. *J Glaucoma*. 2003;12(3):275–280. https://doi.org/10.1097/00061198-200306000-00017.
44. Rouse JM, Sarkisian Jr SR. Mini-drainage devices: the ex-PRESS mini-glaucoma device. *Dev Ophthalmol*. 2012;50:90–95. https://doi.org/10.1159/000334780.
45. Chan JE, Netland PA. EX-PRESS Glaucoma Filtration Device: efficacy, safety, and predictability. *Med Devices (Auckl)*. 2015;8:381–388. https://doi.org/10.2147/mder.S63350.
46. Gonzalez-Rodriguez JM, Trope GE, Drori-Wagschal L, et al. Comparison of trabeculectomy versus Ex-PRESS: 3-year follow-up. *Br J Ophthalmol*. 2016;100(9):1269–1273. https://doi.org/10.1136/bjophthalmol-2015-307161.
47. Pinchuk L. The development of a SIBS shunt to treat glaucoma. *J Ocul Pharmacol Therapeut*. 2023. https://doi.org/10.1089/jop.2023.0005.
48. Acosta AC, Fernandez V, Lamar PD, et al. Ocular biocompatibility of QuatromerTM (polystyrene–polyisobutylene triblock polymers) for glaucoma implants. *Investigative Ophthalmology & Visual Science*. 2004;45(13), 2929-2929.
49. Jamke M, Herber R, Haase MA, et al. PRESERFLO ™ MicroShunt versus trabeculectomy: 1-year results on efficacy and safety. *Graefes Arch Clin Exp Ophthalmol*. 2023:1–15. https://doi.org/10.1007/s00417-023-06075-4.
50. Wagner FM, Schuster AK, Munder A, et al. Comparison of subconjunctival microinvasive glaucoma surgery and trabeculectomy. *Acta Ophthalmol*. 2022;100(5):e1120–e1126. https://doi.org/10.1111/aos.15042.
51. Gambini G, Carlà MM, Giannuzzi F, et al. PreserFlo(®) MicroShunt: an overview of this minimally invasive device for open-angle glaucoma. *Vision*. 2022;6(1). https://doi.org/10.3390/vision6010012.
52. Chen XZ, Liang ZQ, Yang KY, et al. The outcomes of XEN gel stent implantation: a systematic review and meta-analysis. *Front Med*. 2022;9:804847. https://doi.org/10.3389/fmed.2022.804847.
53. Echave MC, Saenz del Burgo L, Pedraz JL, et al. Gelatin as biomaterial for tissue engineering. *Curr Pharmaceut Des*. 2017;23(24):3567–3584. https://doi.org/10.2174/0929867324666170511123101.
54. Ra L. Ab interno approach to the subconjunctival space using a collagen glaucoma stent. *J Cataract Refract Surg*. 2014;40(8):1301–1306. https://doi.org/10.1016/j.jcrs.2014.01.032.
55. De Gregorio A, Montali M, Stevan G, et al. Theoretic scientific rationale of double XEN 45 Gel Stent implant in severe glaucomatous ocular hypertension. *Int Ophthalmol*. 2023;43(5):1629–1638. https://doi.org/10.1007/s10792-022-02561-6.
56. Mansouri K, Bravetti GE, Gillmann K, et al. Two-year outcomes of XEN gel stent surgery in patients with open-angle glaucoma. *Ophthalmol Glaucoma*. 2019;2(5):309–318. https://doi.org/10.1016/j.ogla.2019.03.011.
57. Le K, Saheb H. iStent trabecular micro-bypass stent for open-angle glaucoma. *Clin Ophthalmol*. 2014;8:1937–1945. https://doi.org/10.2147/opth.S45920.
58. Losic D. Advancing of titanium medical implants by surface engineering: recent progress and challenges. *Expet Opin Drug Deliv*. 2021;18(10):1355–1378. https://doi.org/10.1080/17425247.2021.1928071.
59. Xia Y, Feng ZC, Li C, et al. Application of additive manufacturing in customized titanium mandibular implants for patients with oral tumors. *Oncol Lett*. 2020;20(4):51. https://doi.org/10.3892/ol.2020.11912.
60. Francis BA, Winarko J. Ab interno Schlemm's canal surgery: trabectome and i-stent. *Dev Ophthalmol*. 2012;50:125–136. https://doi.org/10.1159/000334794.
61. Francis BA, Singh K, Lin SC, et al. Novel glaucoma procedures: a report by the American Academy of Ophthalmology. *Ophthalmology*. 2011;118(7):1466–1480. https://doi.org/10.1016/j.ophtha.2011.03.028.
62. Chen DZ, Sng CCA. Safety and efficacy of microinvasive glaucoma surgery. *J Ophthalmol*. 2017;2017:3182935. https://doi.org/10.1155/2017/3182935.
63. Shalaby WS, Lam SS, Arbabi A, et al. iStent versus iStent inject implantation combined with phacoemulsification in open angle glaucoma. *Indian J Ophthalmol*. 2021;69(9):2488–2495. https://doi.org/10.4103/ijo.IJO_308_21.
64. Haider W, Munroe N, Pulletikurthi C, et al. A comparative biocompatibility analysis of ternary nitinol alloys. *J Mater Eng Perform*. 2009;18(5-6):760–764. https://doi.org/10.1007/s11665-009-9435-5.
65. Shabalovskaya SA. Surface, corrosion and biocompatibility aspects of Nitinol as an implant material. *Bio Med Mater Eng*. 2002;12(1):69–109.
66. Assad M, Chernyshov A, Leroux MA, et al. A new porous titanium-nickel alloy: Part 1. Cytotoxicity and genotoxicity evaluation. *Bio Med Mater Eng*. 2002;12(3):225–237.
67. Wever DJ, Veldhuizen AG, Sanders MM, et al. Cytotoxic, allergic and genotoxic activity of a nickel-titanium alloy. *Biomaterials*. 1997;18(16):1115–1120. https://doi.org/10.1016/s0142-9612(97)00041-0.
68. Beeley NR, Stewart JM, Tano R, et al. Development, implantation, in vivo elution, and retrieval of a biocompatible, sustained release subretinal drug delivery system. *J Biomed Mater Res*. 2006;76(4):690–698. https://doi.org/10.1002/jbm.a.30567.
69. Olson JL, Velez-Montoya R, Erlanger M. Ocular biocompatibility of nitinol intraocular clips. *Invest Ophthalmol Vis Sci*. 2012;53(1):354–360. https://doi.org/10.1167/iovs.11-8496.
70. Samet S, Ong JA, Ahmed IIK. Hydrus microstent implantation for surgical management of glaucoma: a review of design, efficacy and safety. *Eye Vis (Lond)*. 2019;6:32. https://doi.org/10.1186/s40662-019-0157-y.
71. Ahmed IIK, Fea A, Au L, et al. A prospective randomized trial comparing Hydrus and iStent microinvasive glaucoma surgery implants for standalone treatment of open-angle glaucoma: the COMPARE study. *Ophthalmology*. 2020;127(1):52–61. https://doi.org/10.1016/j.ophtha.2019.04.034.
72. Dória RGS, Freitas SH, Hayasaka YB, et al. Evaluation of polyamide surgical mesh as an abdominal ventral implant in rabbits. *Acta Cir Bras*. 2018;33(5):454–461. https://doi.org/10.1590/s0102-865020180050000008.
73. Kim P, Meyer U, Schüpfer G, et al. Tensile strength decreases and perfusion pressure of 3-holed polyamide epidural catheters increases in long-term epidural infusion. *Reg Anesth Pain Med*. 2011;36(2):151–155. https://doi.org/10.1097/AAP.0b013e31820d418e.
74. Vinod K. Suprachoroidal shunts. *Curr Opin Ophthalmol*. 2018;29(2):155–161. https://doi.org/10.1097/icu.0000000000000458.
75. Lass JH, Benetz BA, He J, et al. Corneal endothelial cell loss and morphometric changes 5 Years after phacoemulsification with or without CyPass micro-stent. *Am J Ophthalmol*. 2019;208:211–218. https://doi.org/10.1016/j.ajo.2019.07.016.
76. Sen SC, Ghosh A. Gold as an intraocular foreign body. *Br J Ophthalmol*. 1983;67(6):398–399. https://doi.org/10.1136/bjo.67.6.398.
77. Shaarawy TM, Moschos MM, Sherwood MB. *128 – New Glaucoma Surgical Alternatives*. 2015.
78. Hueber A, Roters S, Jordan JF, et al. Retrospective analysis of the success and safety of gold micro shunt implantation in glaucoma. *BMC Ophthalmol*. 2013;13:35. https://doi.org/10.1186/1471-2415-13-35.
79. Agnifili L, Costagliola C, Figus M, et al. Histological findings of failed gold micro shunts in primary open-angle glaucoma. *Graefes Arch Clin Exp Ophthalmol*. 2012;250(1):143–149. https://doi.org/10.1007/s00417-011-1778-6.
80. Berk TA, Tam DY, Werner L, et al. Electron microscopic evaluation of a gold glaucoma micro shunt after explantation. *J Cataract Refract Surg*. 2015;41(3):674–680. https://doi.org/10.1016/j.jcrs.2014.12.001.
81. Alenazi NA, Hussein MA, Alamry KA, et al. Modified polyether-sulfone membrane: a mini review. *Des Monomers Polym*. 2017;20(1):532–546. https://doi.org/10.1080/15685551.2017.1398208.
82. Zhao W, Mou Q, Zhang X, et al. Preparation and characterization of sulfonated polyethersulfone membranes by a facile approach. *Eur Polym J*. 2013;49(3):738–751. https://doi.org/10.1016/j.eurpolymj.2012.11.018.
83. Myers JS, Masood I, Hornbeak DM, et al. Prospective evaluation of two iStent(®) trabecular stents, one iStent Supra(®) suprachoroidal stent, and postoperative prostaglandin in refractory glaucoma: 4-year outcomes. *Adv Ther*. 2018;35(3):395–407. https://doi.org/10.1007/s12325-018-0666-4.
84. F M, Je D. The role of minimally invasive glaucoma surgery devices in the management of glaucoma. *Optom Vis Sci : official publication of the American Academy of Optometry*. 2018;95(2):155–162. https://doi.org/10.1097/opx.0000000000001173.