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Review Article

Advancements in nanotechnology for glaucoma detection and treatment: A focus on biosensors, IOP monitoring, and nano-drug delivery systems

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ABSTRACT

Biosensors are essential tools designed to monitor physiologically significant data for diverse applications, including environmental pollution detection, food safety, medication research, and disease diagnosis. The integration of microfluidics, nanotechnology, and advanced electronics has significantly advanced the development of wearable and implantable biosensors for managing chronic diseases such as cancer, diabetes, and glaucoma. Among these, glaucoma remains a leading cause of visual impairment, predominantly driven by elevated intraocular pressure (IOP), with limited treatment effectiveness due to challenges like suboptimal drug bioavailability and therapeutic inefficiency. Despite advances, unmet needs in early diagnosis and sustained management persist, demanding innovative solutions.

Recent advancements in nanotechnology offer transformative potential, addressing these challenges by enhancing both the detection and treatment of ocular diseases. This review explores cutting-edge developments in nano-drug delivery systems and continuous IOP monitoring technologies. Particular emphasis is placed on nanoparticle and nanofiber-based biosensors and contact lenses, which represent a promising leap forward in improving therapeutic precision and patient outcomes in glaucoma care. The manuscript uniquely contributes by synthesizing these advancements and highlighting their potential to bridge existing gaps in glaucoma management.

1. Introduction

Visual perception is essential for human life, with the eyes serving as a critical link between individuals and their surroundings. About 2.2 billion people worldwide suffer from blindness or visual impairment; ageing and changes in lifestyle cause someone to lose their vision every five seconds.[1] Recent advancements in research have aimed at developing innovative therapeutic approaches to diagnose and manage ocular conditions such as cataracts, glaucoma, and diabetic retinopathy. The increasing need for point-of-care diagnostics has led to the development of biosensors as useful instruments in the medical industry. Even at extremely low concentrations, these instruments enable the quick identification of substances that are important to biology.[2,3] Biosensors can identify chemicals like lactic acid, glucose, and cortisol in body fluids and are typically composed of a bioreceptor and a transducer. Additionally, they offer vital information on metrics including brain activity, intracranial pressure, and arterial pulse. Wearable biosensors, designed to be attached to or worn on the body, enable continuous health monitoring without interfering with daily activities. Among these, skin-patch sensors have garnered significant attention for their ability to monitor various physiological parameters,

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including sweat composition, heart rate, body temperature, and limb movements. bladder, brain, or eyes. Conditions including glaucoma, traumatic brain traumas, neurogenic bladder dysfunction, and cardiovascular disorders have all benefited greatly from the use of these sensors.[4,5]

Non-invasive devices called biosensors are made to identify and monitor the body's release of medicinal compounds. These devices enable the early diagnosis of diseases and facilitate continuous monitoring.[6,7] In ophthalmology, eye transducers have significantly enhanced clinical applications, including the measurement of intraocular pressure, humidity, and levels of biomarkers such as lactic acid, glucose, and cortisol. Biosensors hold great potential for providing critical insights into conditions like diabetes, liver disorders, and ocular diseases.[8] They are particularly helpful for early and precise glaucoma screening. The function of biosensors based on nanotechnology in glaucoma treatment and medication administration is the main topic of this review.

2. Anatomy of the Human Eye

The human eye is a spherical organ with a diameter of 24 millimeters and a weight of about 7.5 grams. Its two primary anatomical divisions are the anterior and posterior portions. The tissues that comprise the anterior segment, which is responsible for collecting and focusing light, include the conjunctiva, aqueous humor, cornea, ciliary body, lens, and iris. Conversely, the posterior segment, which aids in light perception, is composed of the choroid, retina, sclera, and vitreous body. Disfunctions in these areas, which are essential for both vision and shielding the eye from outside dangers, frequently result in disorders that affect vision.[9–11] The cornea, a transparent and central structure of the anterior segment, is crucial for light refraction. It has a central thickness of about 0.55 millimeters and a diameter of 11 millimeters, playing a pivotal role in maintaining clear vision.[12]

An important component of the anterior segment is the conjunctiva, which covers the ocular surface from the limbus to the inner eyelids. It is made up of stratified non-keratinized epithelium and goblet cells, and it produces mucin, an essential part of the tear film, which helps preserve the integrity of the ocular surface.[13] The eye is kept safe from outside contaminants thanks to its protective function. Furthermore, the aqueous humor, which sits between the cornea and lens, makes it easier for light to reach the iris and pupil, which control how much light enters the eye.[14] Other crucial structures include the iris, lens, and retina. The iris, a pigmented tissue, adjusts the size of the pupil to control the entry of light and prevent visual blurring under varying light conditions.[15] The lens, composed of crystallin proteins, fine-tunes the image focused by the cornea, aided by its high refractive index. The retina serves as the processing hub for visual data in the rear of the eye. It has photoreceptors that take in light and transform it into neural signals that travel to bipolar and ganglion cells. These impulses pass through the thalamus, midbrain, and optic nerve, which is composed of ganglion cell axons, before reaching the visual cortex for interpretation.[16]

The accommodation mechanism allows the eye to adjust optical power by altering the lens's shape. This adaptability guarantees precise light ray focus into the retina, leading to emmetropia, or flawless vision.[17] The total refractive power of the eye, which is around 60 diopters, is influenced by the cornea, lens, and axial length of the eye. The exterior of the eye is covered with a thin coating of fluid called the tear film, which is made up of secretions from the meibomian and lacrimal glands.[18] Three layers make up the tear film: the lipid layer lowers tear evaporation; the mucin layer smoothes the ocular surface; and the aqueous layer offers protection and lubrication. The tear film serves as a dynamic barrier essential for ocular health. Its stability and composition are critical, with imbalances often leading to conditions such as dry eye disease.[19,20] The human eye's exceptional capacity to support vision while preserving stability and protection is highlighted by its complex structure and function.

Advancements in nanotechnology have provided groundbreaking solutions to address glaucoma at the anatomical and molecular levels. Nanocarriers such as liposomes, nanoparticles, and hydrogels are being developed to enhance the delivery of drugs to the trabecular meshwork, optimize aqueous humor outflow, and protect retinal ganglion cells from oxidative stress. Furthermore, nanosensors are emerging as tools for continuous IOP monitoring, enabling early intervention and better disease management.

The complex anatomy of the human eye, particularly the aqueous humor dynamics and optic nerve health, is at the center of innovations in glaucoma-related nanotechnology. These advancements hold promise for improving outcomes in glaucoma treatment and prevention

3. Ocular Disorders

Vision loss profoundly affects an individual's quality of life, independence, and overall well-being. Damage to ocular tissues, particularly the retina and optic nerve, is a primary cause of visual impairment, often exacerbated by aging. This condition presents significant challenges to the healthcare system, contributing to reduced employment opportunities, diminished quality of life, and increased mortality ratesAbout 252.6 million individuals worldwide suffered from moderate to severe visual impairment or blindness in 2015, making vision impairments one of the main causes of disability.[21,22]

3.1. Age-related macular degeneration (AMD)

The progressive degeneration of the retina, choriocapillaris, and retinal pigment epithelium is the hallmark of AMD, a major cause of blindness in those over 50. While late-stage AMD causes blindness and severe vision loss, which negatively impacts quality of life, early-stage AMD presents as anomalies in the retinal pigment epithelium. A key factor in AMD progression is vascular endothelial growth factor (VEGF), which drives pathological neovascularization. Intravitreal administration of VEGF inhibitors has proven effective in managing exudative AMD by halting abnormal blood vessel growth.[8,23,24]

3.2. Cataracts

Cataracts, the leading cause of blindness worldwide, arise from the crystalline lens's vulnerability to various insults, such as oxidative stress and protein aggregation. Protein misfolding within the lens disrupts its refractive properties, causing cloudiness and vision impairment. Antioxidants present in the lens play a protective role by neutralizing reactive oxygen species, but their depletion results in lenticular damage and cataract formation.[25,26]

3.3. Diabetic retinopathy (DR)

DR is primarily caused by prolonged hyperglycemia, which damages retinal microvessels, leading to microaneurysms, intraretinal hemorrhages, and capillary closure. Over time, excessive angiogenesis exacerbates the condition, causing new, fragile blood vessels to form and leak. These changes, triggered by elevated blood sugar levels, result in vision impairment and, if untreated, blindness.[27–29]

3.4. Dry eye disease

A lack or failure of the tear film causes dry eye disease, also known as keratoconjunctivitis sicca, which results in an uneven and less smooth corneal epithelium. This results in hazy or blurry eyesight. There are two types of dry eye: aqueous tear-deficient and evaporative.[30,31] Vitamin A insufficiency, collagen vascular diseases, and negative medication effects are common reasons.[32]

3.5. Glaucoma

Glaucoma is a group of disorders characterized by progressive optic nerve degeneration, often caused by high intraocular pressure (IOP). One of the leading causes of blindness, glaucoma affects 64.3 million people globally.[33] Increased intraocular pressure (IOP) damages the optic nerve and retinal ganglion cells, causing vision loss. The disease progresses through early, advanced, and extreme stages.[34] By 2040, an estimated 112 million individuals will suffer from glaucoma. Regular IOP monitoring is critical for early diagnosis and management, as oxidative stress and elevated pressure contribute significantly to disease progression.[34,35] Understanding these conditions and advancing diagnostic and therapeutic strategies are crucial in mitigating the global burden of vision loss.

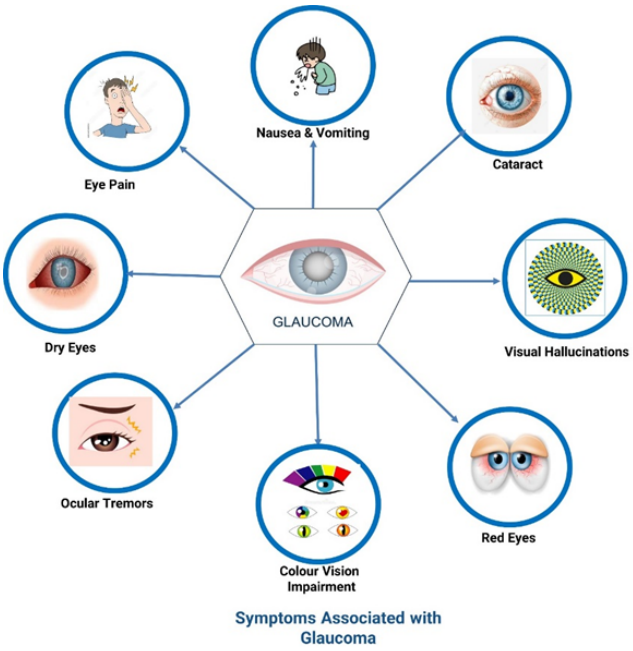

Figure 1:

3.6. Intraocular pressure

IOP is a key parameter in ophthalmic assessments, particularly for patients with ocular hypertension, glaucoma, or those at high risk for these conditions. Elevated IOP is the primary modifiable risk factor for glaucoma and can lead to irreversible blindness.[36] Treatment options include medications and surgery, though IOP typically fluctuates, increasing during the night in accordance with the body's circadian rhythm. Normal IOP values range from 10 to 22 mmHg, with an average of 15.3 mmHg.[37,38]

IOP is measured using a variety of devices, including as contact lens sensors, wireless implanted transducers, applanation tonometers, pneumatonometers, Perkins tonometers, dynamic contour tonometers, and home tonometers. Although Goldmann applanation tonometry (GAT) is considered the "gold standard" for quick and reliable IOP readings, it necessitates multiple nighttime patient awakenings and local anesthetic.[39,40] Wireless implantable transducers (WIT) enable continuous IOP monitoring, though they carry risks of infection related to the implantation process. Home tonometers and contact lens sensors are alternative methods for tracking IOP but may show a 5 mm Hg discrepancy compared to measurements taken by healthcare professionals. Although the Tonopen

is a portable applanation tonometer, it must be calibrated and administered local anesthetic before use.. Although there are still issues with data gathering and implantation, optical sensors for IOP measurement have been proposed. Implanted sensors are able to track changes in intraocular pressure (IOP) independent of external influences, posture, and blinking. However, there is a chance that surgical implantation will result in adverse consequences and ocular injury. Nanoparticle-based IOP sensors offer a promising solution for non-invasive, highly sensitive, and continuous monitoring, with the advantage of being nearly transparent and providing real-time data.[41–43]

3.7. Nanotechnology

The creation and use of materials, devices, or systems with nanometre-scale dimensions is known as nanotechnology. It is expanding quickly across a number of fields and is anticipated to make more strides in biological applications including medication delivery, molecular imaging, and disease diagnostics.[44,45] Nanomaterials have been used in a variety of sectors, including electronics, medicine, food, cosmetics, and energy devices, due to their increased surface area, improved reactivity, and unique mechanical and optoelectronic capabilities.[46]

Chemical, mechanical, and physical changes associated with a particular marker that is essential to the onset of illness can be detected and measured using nanosensors. Because of its unique electrochemical, optical, and mechanical properties, graphene finds utility in biological applications such medication delivery, tissue engineering, biosensing, bioimaging, and phototherapy.[47] Because of its surface area, surface functionality, and biocompatibility, mesoporous silica nanoparticles are utilized as drug delivery vehicles and are very beneficial in a variety of applications, such as sensors and catalysis.[48]

Because of its oxygen permeability, flexibility, transparency, high water content, ability to load medications, and superior biocompatibility, hydrogen-based contact lenses are growing in popularity in the field of ophthalmology. Liposomes are spherical lipid-based vesicles composed of phospholipids and cholesterol that are used to encapsulate hydrophilic and hydrophobic medications in a single system. Because of their unique composition and structural properties, electrospun nanofibers for soft tissue regeneration have attracted attention.[49,50]

Non-covalent bond interactions between many polymer chains result in molecular aggregations known as polymer micelles. A distinct class of macromolecules, dendrimers have a distinct form, size, and a highly branching, three-dimensional structure. Due to their exceptional electrical and optical characteristics, gold and other noble metal nanoparticles (NPs) are employed in a variety of biomedical applications, including medication administration, biosensor creation, and molecular disease diagnostics and imaging.[51–53]

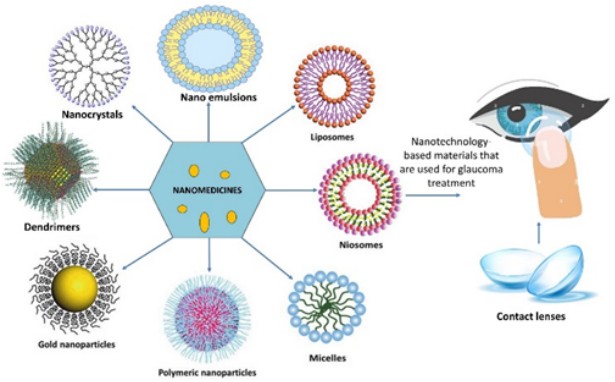

Figure 2: Nanotechnology-drivenmaterials for glaucoma therapy

3.8. IOP-monitoring Nano-based sensors

For individuals with glaucoma, IOP-lowering treatments are essential since elevated IOP is a major risk factor for visual nerve injury. Glaucoma treatment often begins with eye drops aimed at reducing IOP by either enhancing aqueous humor outflow or inhibiting its production. When topical medications fail, laser treatment or surgery may be considered. Furthermore, certain medications have been investigated as nanomedicine formulations for the treatment of glaucoma. Liao et al. produced pilocarpine-loaded gelatin mesoporous silica nanoparticles optimized for continuous release in intracameral glaucoma treatment. These particles were injected into the anterior chamber, effectively lowering IOP. In vivo studies showed that the particles maintained IOP control in ocular hypertension for 21 days.[54,55]

Tang et al. developed an affordable and highly reliable method for fabricating graphene gratings on contact lenses. This was accomplished by employing a Nd: YAG laser to directly laser interference pattern graphene sheet on brand-name contact lenses. The resulting diffraction pattern was essential for monitoring eye health. The graphene film was flexible, conductive, and showed promise as a platform for creating circuits, potentially contributing to smart contact lenses.[56] For the administration of brimonidine, Kim et al. synthesized amino-functionalized mesoporous silica (AMS) particles. The particles were mucoadhesive, remaining in the ocular space for up to 12 hours when applied topically to rabbit eyes. The brimonidine-loaded AMS particles showed significant efficacy in reducing IOP in in vivo models.[57,58]

Timolol maleate and brimonidine tartrate are two medications that are frequently used in conjunction to treat glaucoma. Using a thin-layer hydration technique, these medications were added to liposomes; one formulation was examined in vivo. Timolol maleate and dorzolamide

hydrochloride were loaded into nanofibers by Gagandeep et al., which demonstrated sustained release for up to 24 hours. In vivo experiments showed that applying the nanofiber patch to rabbits with glaucoma significantly reduced their intraocular pressure.[59–61] A technique for loading latanoprost and timolol into contact lenses loaded with micelles was developed by Xu et al. Comparing this formulation to traditional eye drops, the bioavailability and residence duration of both medications were improved. In vivo tests revealed an IOP decrease that persisted for more than 168 hours.[62] Dendrimers, hydrogels, and particles were all combined to create dendrimer gel particles by Wang et al. They evaluated the non-toxicity, corneal permeability, degradability, and release kinetics of brimonidine tartrate and timolol maleate in addition to their drug-delivery capability.[63] The potential of gold nanoparticles as glaucoma medication delivery vehicles was investigated, along with their capacity to target the trabecular meshwork utilizing bare or hyaluronic acid-coated nanoparticles of different sizes.[64]

Vandamme et al. investigated how poly(amidoamine) dendrimers for regulated drug release were affected by size, molecular weight, amount of hydroxyl groups, and surface groups like amine and carboxylate. Longer residence periods were seen in dendrimers with hydroxyl and carboxylic groups, and the size and molecular weight of the dendrimer also affected the retention time.[60] Recently investigated how gold nanoparticles improved the release behavior of timolol, using two methods: loading gold nanoparticles into a timolol soaking solution and incorporating them into contact lenses. Nevertheless, neither technique considerably enhanced timolol's release behavior. Gold-nanoparticle-loaded contact lenses reduced intraocular pressure by an average of 2 mmHg in in vivo experiments, which was comparable to the effects of soaking contact lenses or traditional eye drops.[65] In order to treat glaucoma, Wu et al. suggested combining brinzolamide with liquid crystalline nanoparticles, which would provide longer release and improved ocular bioavailability.[66] Hollow poly(lactic acid) nanoparticles were created by Nguyen et al. to investigate how shell thickness affects the long-term release of glaucoma drugs. Human lens epithelial cells and rabbit eyes were not harmed by pilocarpine-loaded hollow poly (lactic acid) nanoparticles with a thickness of 10–100 nm; however, thicker shells (70–100 nm) demonstrated slower release and decreased drug-loading effectiveness.[67] A microfluidic sensor developed by Agaoglu et al. can identify even the smallest strain changes, which can then be translated into significant fluidic volume expansions. These changes could be easily detected with a smartphone camera. The sensor had high sensitivity, detecting uniaxial strain with a limit of <0.06% and biaxial strain at <0.004.[68] Using smart contact lenses combined with wireless circuits, IOP strain sensors, and transparent silver nanowires, researchers have just created a non-invasive technique for continuous IOP monitoring. The efficacy of this wireless smart contact lens for continuous IOP monitoring was validated in vivo using a rabbit model, underscoring its potential for use in ophthalmic applications.[69]

4. Future Perspectives, Limitations, Ethical and Safety Considerations

Biosensors are essential for point-of-care diagnostics, especially when it comes to tracking conditions where elevated intraocular pressure (IOP) is a major contributing factor. Elevated IOP is closely associated with conditions like obesity, diabetes, retinal vein blockage, and hypertension, though the precise mechanisms and the extent of the association between IOP and these diseases remain uncertain and subject to ongoing debate. As the role of IOP sensors expands, it is crucial that these devices meet a range of requirements, including safety, accuracy, biocompatibility, and reproducibility. Additionally, IOP sensors must be designed to mimic the results typically obtained from traditional hospital-based equipment used to measure IOP, ensuring their reliability for clinical use.[8,42]

The development of effective IOP sensors must prioritize long-term stability and biocompatibility, as continuous mechanical deformation during use could cause material failure or damage. To achieve this, conductive materials that provide effective energy transfer and data transmission may be used to construct transparent IOP sensors, which also show high flexibility. These sensors, being transparent, miniature, and ultra-thin, offer the advantage of convenience for continuous patient use, making them both practical and non-invasive.[70] For wearable IOP sensors, it is also essential to consider features such as water content and wettability during their fabrication. Commercial contact lenses often incorporate materials like pHEMA and silicone hydrogel which are widely used due to their favorable properties.[71,72] However, these materials are susceptible to hydration, which can introduce noise and inaccuracies when monitoring IOP. Other materials such as rubber and polyethylene terephthalate (PET) are also used for fabricating contact lenses, but these have significant drawbacks, including reduced oxygen transmission, excessive hardness, and improper water content, which can affect comfort and sensor performance.[73]

The development of advanced IOP monitoring sensors holds significant potential in helping clinicians and researchers address key challenges in treating various ocular disorders. These sensors can provide crucial data that helps determine the stage of glaucoma, ensuring appropriate treatment plans are implemented. Emerging technologies are revolutionizing IOP monitoring and glaucoma management, with AI-assisted systems

enabling real-time data analysis, predictive insights, and personalized treatments. Wearable biosensors and cloud-based platforms enhance remote patient care. Theranostic devices, combining diagnostics and therapy, offer targeted treatments and continuous IOP monitoring, while smart contact lenses integrate sensors, drug delivery, and AI for user-friendly solutions. Advances in material science are improving device comfort, durability, and scalability. These innovations, combined with telemedicine, promise accessible, precise, and effective care. Future progress depends on interdisciplinary collaboration to transform these cutting-edge concepts into practical, patient-centric solutions for improved ocular health.[74]

However, despite their promise, several limitations hinder their widespread adoption. High development and manufacturing costs make these technologies less accessible, particularly in resource-limited settings. Scalability remains a challenge as the transition from laboratory prototypes to mass production often results in compromised quality or performance. Additionally, clinical adoption faces hurdles such as the need for extensive regulatory approvals, physician training, and patient acceptance of wearable biosensor devices.

A critical aspect of nanotechnology-based IOP sensors is their long-term biocompatibility and safety. Nanomaterials used in these devices must not provoke adverse immune responses or cytotoxicity, as prolonged exposure to ocular tissues could lead to inflammation, fibrosis, or oxidative stress. The accumulation of nanoparticles in delicate ocular environments poses potential risks, including disruption of tear film dynamics and damage to epithelial or retinal cells. Furthermore, material degradation over time could release byproducts that may interfere with ocular functions or require device replacement. To ensure safety, it is essential to conduct extensive preclinical and clinical evaluations of these materials, focusing on their interaction with the ocular surface and internal structures. Optimizing these devices for sustained use without compromising patient health will be a cornerstone of their successful integration into clinical practice.[75–77] To further improve and create integrated systems that can provide thorough insights on the course of glaucoma, more study is necessary. Ultimately leading to more effective treatments and improved patient outcomes.[78]

5. Conclusion

Glaucoma is a serious ocular condition characterized by damage to the optic nerves, which results in gradual and irreversible vision loss over time. The primary contributing factor to glaucoma is the sustained elevation of intraocular pressure (IOP), which, if left untreated, can lead to optic nerve injury. Given the progressive nature of the disease, early detection and effective management are crucial for preserving vision. However, current diagnostic methods face significant challenges, and there is a pressing need for advanced tools to address these issues. To overcome the drawbacks of current methods, a non-invasive, transparent, and extremely sensitive biosensor for IOP monitoring is required.

Recent developments in implanted and wearable biosensors, particularly those that use integrated systems and nanoparticles, hold out a lot of potential for ongoing IOP monitoring. With the possibility for real-time, non-invasive intraocular pressure assessment, these cutting-edge technologies might provide crucial information for the early diagnosis and continued treatment of glaucoma. While these approaches are still in the experimental phase, they offer significant hope for the future of glaucoma diagnostics.

To date, only a limited number of clinical trials have been conducted that focus on the use of implantable sensors for continuous IOP monitoring. This suggests that the field is still in the early stages of development, with further research and refinement required before these devices can be widely adopted in clinical settings. Among the most promising approaches are smart contact lenses equipped with IOP sensors. These wearable devices could provide an efficient and convenient strategy for detecting IOP fluctuations and, by extension, the early signs of glaucoma. However, for these smart lenses to become a reality in clinical practice, more research and development are necessary to ensure their effectiveness in diagnosing glaucoma at an early stage and facilitating timely treatment interventions to prevent vision loss. The clinical implementation of these innovative devices would mark a significant step forward in the fight against glaucoma, offering patients a non-invasive solution for continuous monitoring and better management of their condition.

6. Source of Funding

None.

7. Conflict of Interest

None.

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