Recent progress of continuous intraocular pressure monitoring

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Abstract
Glaucoma, a chronic optic neuropathy, is the leading cause of irreversible blindness in the world. Elevated intraocular pressure (IOP) has been considered to be the major contributor to glaucoma for a long time and is currently proved to be the only modifiable risk factor for the progression of optic neuropathy. IOP fluctuates throughout the day with a circadian rhythm change and is affected by body gesture changes. Moreover, the IOP spike usually occurs at night or in the early morning. Therefore, the current clinical practice of single and static measurements of IOP during office hours is not conducive to the early diagnosis and treatment of glaucoma. This review focuses on current advances in implantable and noninvasive IOP sensors for obtaining 24-hour continuous IOP profiles. The content summarizes and classifies IOP sensors based on their working principles and provides representative examples of the sensors for IOP monitoring. Finally, the review further analyzes the challenges of current IOP sensors for clinical practice and puts forward the prospect of IOP sensors in the future.

KEYWORDS
contact lens, continuous monitoring, glaucoma, implantable sensor, IOP

1 | INTRODUCTION

Glaucoma, a group of progressive neurodegenerative diseases, is characterized by cupping of the optical nerve head and visual field loss. Glaucoma has become the leading cause of irreversible blindness in the world.[1–4] The number of glaucoma patients was more than 76 million by the end of 2020 in the world, which is predicted to increase up to 112 million in 2040.[11] IOP is regulated by aqueous humor which is maintained by the anterior chamber...
angle and ciliary body of the posterior chamber and flows out via trabecular meshwork or canal of Schlemm. The aqueous humor flow is imbalanced when the resistance exists in its outflow pathway, which leads to an increase of IOP. The elevated IOP causes damage to the optic nerve head, resulting in irreversible blindness eventually. Although numerous factors determine glaucoma such as age, family history, high myopia, IOP, and so on, the IOP is proved to be the only modifiable risk factor for glaucoma. Currently, the only available therapeutic approach for glaucoma is lowering the elevated IOP via medication, laser, or surgery. The progression of glaucoma will occur less frequently or stop when the elevated IOP is lowered by 30–50% with medicine. Therefore, accurate and reliable IOP measurements will provide strong support for effective intervention in the progression of glaucoma. In clinical practice, IOP can only be obtained by sporadic measurements during office hours, which can easily lead to misdiagnosis for glaucoma. Although single IOP measurement from office visit lies within the acceptable range, progressive optic neurodegeneration was observed in some glaucoma patients. One possible reason for this could be that the IOP fluctuations and the peaks occur outside of the office measurements. Therefore, glaucoma patients may have developed irreversible visual field loss before being diagnosed. IOP is not a static indicator but fluctuates dynamically in 24 hours with a circadian rhythm. Numerous studies implied that the IOP peak is more likely to occur in the early morning, and IOP during nocturnal or sleeping time is higher than that of daytime. Moreover, sitting or supine posture has a great influence on IOP fluctuations. Recent research indicated that IOP even showed weekly and seasonal changes in the long-term IOP measurements.

There are various commercially available techniques and devices for IOP monitoring, including applanation (Goldmann Tonometer, Haag Streit; Perkins Tonometer, Haag Streit; Pneumatometer, Reichert Technologies), self tonometry-applanation (Ocuton S, EPsia Elektronik & Praezisionsbau), self tonometry-rebound (ICare Tonometry, Tiolat Oy), dynamic contour tonometry (DCT) (Pascal, Ziemer Ophthalmic), intraocular telemetry (Wireless Implantable Transducer, Implandata GmbH), and contact lens sensor (SENSIMED Triggerfish, Sensimed S.A). The Goldmann applanation tonometry (GAT) is considered the “gold standard” for fast and reproducible IOP measurements, which measures the IOP based on the principle of Imbert-Fick law. However, GAT needs local anesthesia to the cornea with hard surface pressing. Therefore, several factors such as corneal thickness, curvature, scleral rigidity, and biomechanic properties will influence the accuracy and reliability of IOP measurements. More importantly, this device can only achieve a static and single measurement but cannot obtain a 24-hour continuous IOP profile. Until now, repeated single IOP measurements are adopted to assess a patient’s 24-hour IOP profile, requiring the patient to be awakened every hour for nocturnal IOP measurements, which greatly increases the workload of ophthalmologists and the discomfort of the patient. Furthermore, it is not in accordance with the physiological law to wake up patients frequently, thereby influencing the stable state of the IOP. These limited discrete values are insufficient to establish IOP peaks. Therefore, clinical measurements are not conducive to the early detection, prevention, and management of glaucoma. The Wireless Implantable Transducer (WIT, Implandata GmbH, Hannover, Germany) can realize 24-hour IOP monitoring. However, The WIT needs to be wrapped in an intraocular lens and implanted into the ciliary sulcus during cataract surgery. This approach can achieve long-term monitoring of IOP to better understand the physiological changes of IOP but accompanied by risks of infections associated with implantation.

There is a strong correlation between the IOP and the curvature radius of the cornea. Researches demonstrated that the central curvature radius of the cornea changes about 3 µm for 1 mmHg fluctuation of IOP. Therefore, the contact lens sensor (CLS) SENSIMED Triggerfish has been developed to achieve wireless continuous IOP monitoring based on the principle of cornea curvature changes. The micro-fabricated strain gauge and antenna embedded in the disposable silicone contact lens were used to measure the corneal deformation and transmit information, respectively. The sensor collects IOP every 5 minutes for 30 seconds, hence up to 288 IOP data can be obtained throughout 24 hours. However, the Triggerfish only reports ocular volume changes related to IOP and the output signal unit is mV rather than mmHg. There is still a debate if IOP changes are translated into the radius of curvature of cornea changes in a way that measurements of the radius of curvature can reliably predict IOP. Later, SENSIMED further developed the CLS-based device to a novel Pressure-Measuring Contact Lens (PMCL). The PMCL composed of a MEMS pressure sensor, an antenna, and a telemetry microprocessor can continuously measure the actual IOP in mmHg over 24 hours. In the 24-hour continuous IOP measurements, differences between the PMCL and Pneumatometer for IOP variations were within ±5 mmHg in fellow eyes for 88% of time points, which was 97.2% between the PMCL and DCT. Even though the Triggerfish and PMCL can provide enough portability and comfort for patients in 24-hour continuous IOP monitoring, the problem that the opaque metal antenna, rigid chip, and pressure sensor will block the visual field cannot be ignored. Without affecting the daily activities of patients, 24-hour continuous IOP
monitoring is of great significance for the diagnosis and treatment of glaucoma. Through 24-hour IOP monitoring, clinicians can observe the effect of eye drops or other drugs on IOP fluctuations, which can facilitate the modification of the appropriate treatment plan to achieve individualized therapy. In the future, IOP monitoring is predicted to be as accessible as the at-home monitoring of hypertension and diabetes.

Recent advances in structure designs, materials, fabrication techniques, sensing approaches, electronics, and measurements have facilitated the development and application of 24-hour IOP monitoring. Most researchers developed implantable or noninvasive biosensors with different approaches for continuous IOP monitoring. Implantable sensors can monitor actual IOP values directly. Non-invasive IOP sensors are mainly combined with soft contact lenses, in which sensing layers with different principles are embedded. In this review, we present an overview of the recent progress in continuous IOP monitoring. First, we introduce an overview of IOP sensors, including implantable and non-invasive devices. Subsequently, several representative principles of IOP sensors are described, mainly including microfluidic devices, piezoresistive devices, RLC devices, optical devices, and other devices. We analyze the latest progress of commercial sensors applied to human IOP monitoring. Finally, we put forward the challenges of IOP sensors and conclude this review with a discussion of future research.

2 | IMPLANTABLE AND NONINVASIVE IOP MONITORING

As shown in Figure 1, current IOP monitoring sensors mainly include ocular implants and noninvasive contact lens sensors. Ocular implants such as microfluidic devices can monitor IOP fluctuations directly according to volumetric changes in the aqueous humor. The sensors need to be implanted in the anterior or posterior chamber, suprachoroidal, episcleral, or ciliary sulcus of the eyeball, and the specific location depends on the structure of the designed implantable sensor. Implantable sensors can directly measure the absolute pressure of the eyeball, but they must be implanted into the eyeball which is not accepted by most patients. In recent years, with the development of some commercial implanted intraocular sensors such as WIT, sensors can be implanted into the intraocular lens during cataract surgery, which increases the acceptability of patients with both cataract and glaucoma. Moreover, implantable sensors in the long-term monitoring process may also be accompanied by some potential risks such as inflammation, pupillary distortion, pigment dispersion, sensor malfunction, and so on.

The contact lens as a universal technology to correct vision and cosmetic purposes has been widely used by 140 million people worldwide. Contact lenses are in continuous contact with human eyes and tears, which provides a unique platform for continuous monitoring of glucose level, lactate level, drug delivery, argument reality (VR), and so on. The development of smart contact lenses has attracted significant interest from companies, including Google, Novartis, and Mojo Vision. Google and Novartis jointly developed a wearable smart contact lens with a wireless chip and miniaturized sensor for glucose monitoring in tears and vision correction at the same time. Mojo vision developed VR contact lenses with multiple image overlay functions to enable the visual freedom of the weak vision population. Soft contact lens sensors have also been developed by most researchers to realize 24-hour continuous IOP monitoring, which is generally utilized to measure the curvature deviation of the cornea caused by IOP.
fluctuations. The sensing layer embedded in the contact lens can detect variations in the curvature of the contact lens, which is caused by the corneal curvature changes. Contact lens IOP sensor is non-invasive and convenient, which makes it easy for patients to accept. However, because of the indirect measurement of IOP by the radius of curvature of cornea, sensors need to be calibrated, which is affected by factors such as corneal thickness, curvature, scleral rigidity, and biomechanic properties.

According to the principles of the sensing elements, the developed implantable and noninvasive IOP sensors are mainly classified as the following types: microfluidic devices, piezoresistive devices, RLC devices, optical devices, and other devices.

2.1 Microfluidic devices

Microfluidic sensors, due to their high scalability, transparency, and biocompatibility, have attracted widespread attention for biomedical applications such as sweat monitoring,[68–70] tear analysis,[71] pulse sensing,[74] drug release,[75,76] and IOP monitoring.[46,77,78] In the application of fluid pressure and flow-sensing, microfluidic sensors can complete fluid monitoring through microchannels without requiring electronic components, which lowers the complexity and cost for microfluidic systems. For example, Yetisen et al. utilized laser patterning and fiber templating to develop a microfluidic contact lens rapidly and accurately, which achieved real-time monitoring of biomarkers in tear fluid.[75] Recently, flexible and transparent microfluidic sensors have been widely investigated for IOP monitoring. Araci et al.[46] reported an implantable microfluidic sensor for IOP monitoring, which obtained the IOP by detecting the position of the aqueous-air interface through a smartphone camera (Figure 2C and D). The interface shifts to the channel’s dead end and opening as the IOP increases and decreases, respectively (Figure 2A). Performance evaluations in a pressurized chamber indicate that the position of the aqueous-air interface shows a good linear relationship with the IOP, and the sensor has a limit detection of 1 mmHg with a sensitivity of 50–137 μm/mmHg. However, this microfluidic device needs to be incorporated with the intraocular lens through a cataract implant surgery or implanted directly in the anterior or posterior chamber of the eyeball (Figure 2B).

Moreover, microfluidic sensors are successfully combined with contact lenses to realize noninvasive IOP monitoring. Wu’s group designed an annular chamber filled with dyed liquid and a microchannel which were embedded in a contact lens for real-time IOP monitoring (Figure 2E). When IOP fluctuates, the position of the dyed liquid interface in the microchannel will change, which can be observed by a smartphone camera (Figure 2F). In the IOP fluctuation range of 8–32 mmHg, the sensitivity of the microfluidic contact lens sensor was 283.2 μm/mmHg on an isolated porcine eye.[40] Araci’s group also developed a microfluidic strain sensor embedded in a contact lens with the principle of detecting volume changes in microchannels through a smartphone camera (Figure 2G, H). They optimized the geometry and the material of the sensor to realize high sensitivity, linear, and stable response (Figure 2I).[77] Furthermore, they made full use of the inherent properties of the microfluidic sensor to suppress the noise signal of rapid fluctuations (such as blinking, ocular pulsation, etc.) in IOP by 9 dB without any electronic components. Software developed by the computer vision toolbox of Matlab was used to monitor and track the position of the gas/air interface in the microfluidic channel (Figure 2I).[79] Lai’s group utilized avocado oil instead of dyed water as the indicator fluid in the microchannel to suppress the diffusion of the dyed water.[78,80] A microfluidic channel with wideness and thickness of both 100 μm was embedded in a PDMS contact lens with a thickness of 250 μm. Reference markers with different lengths in the contact lens were used for displacement calibration of the indicator fluid. Repeatable IOP measurements on different porcine eyes indicated that the fluid displacement has a linear relationship with the IOP, and the sensitivity of the sensor was 28.5 μm/mmHg with a standard deviation (SD) of 2.4 μm.[80] They further designed a double spiral structure for the microchannel that was embedded in the contact lens. The IOP monitoring conducted on enucleated porcine eyes indicated that the average sensitivity of the sensor was 40.8 μm/mmHg with an SD of 29.4 μm in fluid position between all the experiments (Figure 2K), and the returnability of the indicator fluid was over 80%.[78]

Therefore, microfluidic sensors used for IOP monitoring do not require power and data transmission, making the sensor simple, inexpensive, and highly transparent. However, to track the interface position changes of the indicator fluid in the microchannel for continuous IOP monitoring, it is necessary to take images of the contact lens worn on the human eye at intervals (such as once every 5 minutes), which makes the measurement less convenient and interferes with people’s daily routine. The dyed indicator fluid in the microfluidic channel also has the problem of spilling, diffusing, and blocking the view, which is not conducive to long-term IOP measurement.

2.2 Piezoresistive devices

To monitoring the IOP from corneal curvature, strain gauges should be embedded in the contact lens. As the
curvature of the contact lens changes, the resistance of the gauge changes which causes changes in the output electrical signal. The Wheatstone bridge is extremely sensitive to resistance changes, which can significantly improve the accuracy and sensitivity of the measurement compared with the direct measurement with a varistor. When the Wheatstone bridge composed of a pair of piezo-resistors and a pair of compensation resistors is driven by a constant voltage ($V_{EX}$) or a constant current source ($I_{EX}$), the output voltage ($V_{out}$) is as follows:

\[
V_{out} = \left( \frac{\Delta R}{2R_0 + \Delta R} \right) V_{EX} \approx \frac{1}{2} \left( \frac{\Delta R}{R_0} \right) V_{EX}
\]

\[
V_{out} = \left( \frac{\Delta R}{2} \right) I_{EX}
\]

where $R_0$ is the initial resistance of the piezo-resistors. $\Delta R$ is the resistance variation of piezo-resistors. Therefore, the
sensitivity of the voltage-driven Wheatstone bridge is proportional to the $V_{EX}$ and inversely to the initial resistance. For the current-driven bridge, its sensitivity is proportional to the excitation current $I_{EX}$. Since the four initial resistances of the Wheatstone bridge are identical and in the same environment, the increase or decrease of temperature will not make the variation of $\Delta R$, thus the bridge can eliminate the influence of the temperature drift on the measurements.

Ren’s group fabricated strain gauges inserted in a Wheatstone bridge configuration to detect the weak deformation of corneal curvature caused by the IOP fluctuation. The Wheatstone bridge made of Ti/Pt consists of two active strain gauges and two passive strain gauges (Figure 3a), which is sandwiched between polyethylene terephthalate (PET) and polydimethylsiloxane (PDMS) (Figure 3b). The current-driven Wheatstone bridge is adopted and the output voltage caused by the active gauge is as
The current challenges for piezoresistive sensors are achieving wireless transmission of data and energy without affecting the transparency of contact lenses. Currently, integrating a battery or coil with the strain sensor is the main solution for the power supply.\cite{86-88} Donida et al. integrated a commercial piezoresistive pressure sensor with an ASIC manufactured by the standard 0.35 CMOS process to realize circadian and cardiac IOP monitoring. The coupled RF coil is studied and optimized to ensure energy transfer efficiency with a frequency of 13.56 MHz and power consumption of 1.2 mW. The system can read out small signals with a maximum accuracy of 0.027 mmHg and compensate for atmospheric pressure and circadian pressure offset.\cite{86} Maeng et al. designed an octagonal spiral inductor coil (Ti/Cu) embedded on the parylene to achieve a power transfer efficiency of 17.5% on a pig eye at the distance of 20 mm.\cite{87} Agarwal et al. developed a system for wireless, implantable, and low-drift IOP monitoring, which consists of a commercial pressure sensor, an I2C serial communication interface, and a chip fabricated in TSMC 65 nm COMS process. The chip integrated an RF coil for wireless power supply via 915 MHz near-field coupling and data transmission via RF-backscattering.\cite{88} However, silicon chips or metal coils are all opaque, interfering with the visual field of human eyes, thereby affecting people’s daily routine. Meanwhile, in the process of energy transmission through resonance coupling, there are also some challenges in obtaining stable and high transmission efficiency and quality factor. Consequently, utilizing highly flexible and transparent materials instead of metals as energy transmission coils has promising prospects.
Besides, biofuel cell and solar energy are developed as power sources for smart contact lenses and silicon integrated circuits,[89,90] but their lack of power stability, availability, and efficiency will hinder the performance of the system. Therefore, to overcome such restrictions for strain sensors, further studies need to be carried out.

### 2.3 RLC devices

An RLC resonator circuit is composed of an inductor (L), a capacitor (C), and a resistor (R). The resonant frequency of the resonator will shift when the change occurs in either one or two of the above three elements. The resonant frequency can be calculated by the following equation:[48]

\[
f_{res} = \frac{1}{2\pi} \sqrt{\frac{1}{L_sC_S} - \frac{R_s^2}{L_s^2}} \Rightarrow f_{res}
\]

\[
\approx \frac{1}{2\pi} \sqrt{\frac{1}{L_sC_S}} \left( if \ R^2 << \frac{L_s}{C_S} \right)
\]

Therefore, a variable inductor or capacitor is designed by most researchers as the sensing element for intraocular pressure. The RLC circuit can realize the wireless intraocular pressure monitoring through inductive coupling with the external antenna. Using an external antenna to build an inductive coupling link with the RLC circuit, the equivalent impedance from the measurement instrument is as follows:

\[
Z_{eq} = \frac{V}{I} = j2\pi f L_r \left[ 1 + \kappa^2 \left( \frac{f}{f_r} \right)^2 \left( 1 - \frac{f^2}{f_r^2} \right)^2 + \frac{1}{Q_s} \frac{j}{f_r} \right]
\]

where \(V\) and \(I\) are the exciting voltage and current in the external antenna, respectively, \(f\) is the excitation frequency, \(Q_s\) is the quality factor of the RLC circuit at resonance, which is \(R_s^{-1}(L_sC_s^{-1})^{1/2}\), and the \(\kappa\) is the coupling coefficient of the inductive link between the RLC circuit and external antenna.

#### 2.3.1 Inductive element

Variable inductance is utilized as the sensing element to track changes of corneal curvature for continuous IOP monitoring, which mainly includes implantable devices and RLC contact lens sensors. The variable inductance is combined with a capacitor to form an RLC circuit in which resonance frequency changes when the curvature of the cornea changes along with IOP fluctuations. The IOP value can be obtained by calibrating the resonance frequency obtained by the external reading coil and the pressure value measured by the standard tonometer. Kang et al. reported several implantable inductive pressure sensors based on a movable ferrite magnet[91,92] and studied the influence of inner materials (copper and ferrite) on the performance of the sensor.[43] The sensor consists of two parts, in which the top part for data transmission is comprised of a copper coil and a single layer capacitor, and the bottom part for sensing variations in inductance is comprised of a flexible membrane and the inner material (Figure 4A). When an elevated IOP is applied to the sensor, the distance between the copper coil on the top and the inner material on the bottom changes due to the deformation of the flexible membrane, resulting in a change in the resonance frequency with the external circuit. Inductance variations are caused by the eddy current effect for copper used as inner material and the modulation of effective permittivity for ferrite used as inner material, respectively. The resonance frequency shift results demonstrated that when IOP fluctuates, the sensors using copper as the inner material had larger variations in resonance frequency, while the sensors with ferrite were more stable for the phase depth. The evaluation for the inductive sensor on a rabbit eye indicated that the measured responsivity of the sensor was 16.7 kHz/mmHg at a reading distance of 5 mm.[43] However, the sensor needs an anchor to assemble the components and the system is complex and implantable, which lowers the operability of the practical application and the acceptability of patients.

As shown in Figure 4B, when IOP increases from \(P1\) to \(P1+\Delta P1\), the radius curvature of the cornea will increase and tangential stretch deformation will occur. Therefore, most researchers designed simple coils as the basic elements to detect deformations of the cornea. A variable inductive coil made of copper was integrated with a capacitor made of Ti/Au to form an LC circuit that was sandwiched in the medical-grade silicone rubber by molding transfer (Figure 4C).[93] The sensor was tested on a silicone rubber model eye for performance evaluation. The model eye and the sensor were processed in oxygen plasma to achieve hydrophilicity before taking IOP measurements. The dynamic and cyclical IOP measurement results implied that the relationship between the resonance frequency and the IOP was linear and reproducible with a frequency response of 8 kHz/mmHg (Figure 4D). Besides, the inductance coil with different geometry and turn numbers has a great influence on the sensitivity and the reading distance. Kouhani et al. designed a stretchable planar serpentine inductor with a commercial mounted capacitor for both pressure sensing and wireless transmission, which was implanted in the eye to measure the strain of the sclera for IOP monitoring.[94]
Furthermore, they fabricated a constant planar capacitor replacing the commercial capacitor to connect with the variable serpentine inductor, which was embedded in a customized circular doughnut-shaped contact lens to achieve non-invasive IOP monitoring (Figure 4E). Ex vivo tests of the sensor on a canine eye demonstrated that the responsivity of the sensor is 35.1 kHz/mmHg, and the maximum reading distance of the sensor is 9 mm. Therefore, great efforts have been made in the geometry of the variable inductance coil, miniaturization of capacitance, and the contact lens to achieve higher sensitivity and reliability of IOP measurements. However, similar to the SENSIMED Triggerfish®, most researchers utilized the rigid and opaque material copper to fabricate the inductance, which accompanied the issues of small deformations of coils and visual field occlusions. Chen et al. proposed liquid metal instead of the conventional rigid metal to fabricate ultra-soft and comfortable contact lens IOP sensor. An LC resonator is formed by a stretchable inductance coil made of liquid metal (Galinstan) and a chip capacitor, which is coupled with external reading coils for wireless communication (Figure 4F and G). The
liquid metal as sensing elements enables it to be integrated with the soft silicone rubber, ensuring the ultra-flexibility of the contact lens and reducing the rigidity of the system. IOP measurement of the sensor was carried out on fresh porcine eyes in vitro (Figure 4H). Different from the results of conventional metal materials, the resonant frequency static responses of the liquid-metal IOP sensor are nonlinear with average responses of 78.9–86.7 kHz/mmHg and sensitivity of 416–458 ppm/mmHg (Figure 4I).\[95\]

2.3.2 Capacitive element

Variable capacitors have been developed to measure the curvature of the cornea, which are combined with inductances to form RLC circuits for wireless IOP monitoring. The capacitive sensor consists of two electrodes sandwiched with a dielectric layer. The distance between two electrodes changes along with cornea deformations caused by IOP fluctuations, leading to capacitance changes. A variable capacitor consisted of a bottom electrode embedded in a soft silicone lens as the sensing layer and a top electrode embedded in a hard silicone lens as the reference layer (Figure 5A), which was coupled with an inductive coil as an RLC resonant circuit for IOP monitoring.\[96\]

The sensor fabricated by embedding the RLC circuit in the medical-grade silicone was tested on an enucleated porcine eye. The result indicated that the frequency response of the sensor is 23 kHz/mmHg, corresponding to the sensitivity of 200 ppm/mmHg. However, the capacitance and inductance of the sensor were etched by 10 μm opaque and rigid copper foil, which greatly blocks the visual fields of the wearers (Figure 5B). Chiou et al. designed a contact lens IOP sensor system that is comprised of a capacitor, an RFIC, a power receiving, and a signal transmitting antenna (Figure 5C).\[97–99\] The capacitor as the IOP sensing element consists of two parallel diaphragms made of Au/Ti serving as the top and bottom electrodes, between which the poly-2-hydroxyethyl methacrylate (poly-HEMA) is filled as the dielectric layer (Figure 5C). Static and dynamic IOP measurements were carried out on an artificial anterior chamber with the sensor. The setup was placed in a chamber with an environment temperature of 30 °C and relative humidity of 60% to avoid the influence of the contact lens hydration on poly-HEMA. The sensitivity of the sensor measured by the impedance analyzer and RFID module was different, which was 1.2239 pF/mmHg (13171 ppm/mmHg) and 3.0275 pF/mmHg (36026 ppm/mmHg), respectively.\[97\] However, this IOP monitoring system did not integrate the required electronic components into the contact lens. The capacitor-based contact lens sensor needed to wire connection outside of the contact lens for signal transmitting and power supply (Figure 5D). After further study, they integrated the sensor readout circuit, a digital processor, and analog front-end into a chip using 0.18 μm CMOS technology and finally embedded it into the contact lens with the capacitive sensor and the antenna (Figure 5E and F).\[38\] The contact lens sensor powered by a 26.5 dBm incident RF power at the frequency of 920 MHz was placed on a porcine eye for characteristics evaluation. The sensor exhibited a sensitivity of 120 pF with a power consumption of 110 μW in the IOP fluctuation range of 2.25–30 mmHg. However, the disadvantage of the system is that the opaque and rigid metal antenna and the chip will limit the vision field of patients.

Therefore, researchers explored the use of flexible and transparent materials to fabricate electronic components. Zeng et al. used graphene as the bottom and top electrodes of the capacitor to improve the transparency of the sensor. The IOP sensor comprised of a variable capacitor and a copper coil inductor was sealed on the tubing for IOP measurements. The results demonstrated that the sensor had a sensitivity of 507 ppm/mmHg and responsivity of 160 kHz/mmHg.\[100\] Park’s group utilized 1D and 2D flexible materials as the antenna to address the issue of visual field obstruction. They integrated a variable capacitor and electronic devices on a soft contact lens to realize simultaneous monitoring of IOP and glucose level in tear.\[64\]

The hybrid of graphene and silver nanowires (AgNWs) was used as the key material of the spiral coil, which had a transparency of 91% and stretchability of 25%, thereby providing enough comfort and visual field when wearing (Figure 5H). The ecoflex elastomer as the dielectric layer was sandwiched in between two layers of inductive spiral coils, and the sensor was encapsulated in the parylene C. The soft contact lens deforms when an elevated IOP is applied to the cornea, which leads to the thinning of the dielectric layer and bi-axial lateral expansion of the spiral coils, increasing the capacitance and the inductance, respectively (Figure 5G). In the in vitro experiments on a bovine eyeball, there is a linear relationship between the resonant frequency of the sensor and the IOP, which is dictated by a slope of 2.64 MHz/mmHg in the IOP range of 5–50 mmHg.

2.3.3 Data telemetry

Currently, some commercial sensors have been combined with telemetry technology to implant in the eyes of animals and patients for IOP monitoring and biocompatibility investigations.\[29,30,44,51,101\] The implanted capacitive IOP sensor was integrated with an inductive coil that was coupled with an external handheld reading device for data communication and power supply at the radio frequency of 13.56 MHz within a distance of 5 cm (Figure 5J).
FIGURE 5  Capacitive devices for continuous IOP monitoring. A, The cross-section of the capacitive sensor. B, A photograph of the capacitive contact lens sensor. Reproduced with permission. [96] Copyright 2013, Elsevier. C, The internal structure of the capacitor. D, A photograph of the connection between the contact lens and the wireless transmission module on the artificial anterior chamber. Reproduced with permission. [97] Copyright 2016, Institute Of Physics Publishing. E, Schematic illustration of the proposed contact lens sensor and system. F, The hardware architecture of the proposed smart contact lens and system. Reproduced with permission. [38] Copyright 2017, Molecular Diversity Preservation International. G, Schematic illustration of the sensing mechanism of the capacitive IOP sensor. H, Schematic diagram of the contact lens sensor integrating graphene/AgNW antenna. Reproduced with permission. [64] Copyright 2017, Springer Nature. I, The implantable IOP transducer integrating an ASIC and surrounding metal antenna. Reproduced with permission. [34] Copyright 2018, Elsevier. J, A commercial portable reading device for telemetric IOP transducer. Reproduced with permission. [103] Copyright 2016, Elsevier. K, A pupillary distortion photograph of six patients after 1-year implantation with the IOP sensor. Reproduced with permission. [30] Copyright 2015, The Association for Research in Vision and Ophthalmology.
Szuroman et al. investigated the suprachoroidal pressure transducer for telemetric IOP monitoring, respectively. The pressure transducer from Implantdata Ophthalmic Products GmbH (Germany) composed of six capacitive sensors was integrated with an ASIC that was surrounded by metal coils for wireless data communication and power supply (Figure 5I). The sensor embedded in a silicone rubber encasement was implanted in the eye of a New Zealand White rabbit for IOP monitoring and sensor performance assessments. The IOP measurements indicated that the standard deviation between the IOP obtained by the telemetric sensor and the intracameral IOP was ± 1.0 mmHg in the range of 10–45 mmHg and ± 0.8 mmHg in the range of 10–35 mmHg. However, the sensor exhibited malfunction and failure after implantation of 4 weeks and 30 weeks, respectively. After an investigation in safety and biocompatibility of the sensor that was implanted in a rabbit eye, a wireless IOP transducer was implanted in a patient with open-angle glaucoma for the first time by Melki’s group. The wireless IOP sensor baggage in the intraocular lens was implanted into the ciliary sulcus of a 60s woman in the surgery of cataract extraction. Corneal edema and mild iritis were observed in the first month; however, persistent intraocular inflammation, angle narrowing, or pigment dispersion were not observed after the implantation surgery. The IOP measurement results indicated that data from the implantable wireless IOP sensor had a good concordance with the IOP obtained by GAT, which provides a reference for the safety, biocompatibility, and measurement accuracy of the implantable IOP sensor in the human eyes. Based on these positive safety outcomes of the sensor implanted in a human eye, Koutsonas et al. implanted the circular telemetry IOP sensors in the ciliary sulcus of six patients with open-angle glaucoma and cataract. IOP was obtained by subtracting the absolute pressure measured by an external card reader from the pressure value measured by the implantable sensor. After the sensor implantation surgery, all patients showed different degrees of pupillary distortion and pigment dispersion as well as four cases of sterile anterior chamber inflammation (Figure 5K). Moreover, the GAT measurements indicated that five patients had higher IOP than baseline in six months after surgery, which contradicts the expectation of IOP management and reduction through sensor implantation. However, IOP values obtained by GAT returned to baseline levels one year after the implantation surgery, in which two patients had significant IOP fluctuations during a one-year follow-up. Mansouri et al. investigated the safety and biocompatibility of the second generation telemetric IOP sensor implanted in patients with open-angle glaucoma and cataract for analyzing weekly and seasonal changes of IOP. All the participants recorded their daily IOP with the external hand-held devices at least four times a day for an average duration of 721 days. Statistical results indicated that IOP exhibited seasonal and weekly variations, that is, the IOP measured in winter was significantly higher than that in summer, while the IOP on Wednesday was higher than that on other days of a week. This phenomenon provides us a better understanding of the mechanism of IOP fluctuations, which is of great significance for the treatment and management of glaucoma.

Overall, implantable IOP sensors combined with conventional cataract surgeries are beneficial to increase the acceptability of patients towards sensor implantation, which is of great significance to better investigate and understand glaucoma in the clinic. However, the implantable IOP sensor is accomplished with additional risks such as inflammation, pupillary distortion, pigment dispersion, sensor malfunction, and so on during long-term IOP monitoring. These risks should be addressed by further developments of the shape, size, and biocompatibility of the sensor. Furthermore, the phenomenon that IOP deviates from the normal baseline after implantation surgery should be further studied and solved, otherwise, it is contradictory to the purpose of glaucoma treatment.

2.4 Optical devices

The optical method is adopted to develop sensors for real-time IOP monitoring. The system is mainly composed of the following parts: light source, tonometer, spectrometer, and a PC terminal. When the physical properties of the sensor change with IOP fluctuations, the light source provides the excitation required by the sensor. Then the wavelength of reflected light reflected by the sensor is shifted, and the deviation degree is measured by the spectrometer. Finally, the relationship between the wavelength of reflected light and IOP is calculated at the PC terminal. For the optical method in IOP monitoring, several solutions have been studied, and different materials have been used to construct IOP sensors. The reflected light sensor (RLS) composed of a photosensitive transistor and infrared diode can obtain the IOP value by measuring the frequency and amplitude of corneal oscillation (Figure 6A). The proposed sensor tested on porcine eyes demonstrated that it had a measurement precision of less than 0.5 mmHg in the IOP range of 10 –25 mmHg, which fulfilled the clinical requirements. By adjusting the incident angle between the infrared diode and the photosensitive transistor, the signal-to-noise ratio of the system can exceed 40 dB, which can be further enhanced by utilizing the light-emitting or laser diodes with smaller incident angle.
Choo’s group utilized the Si$_3$N$_4$ membrane with bio-inspired nanostructure to realize angle-independent read-out for an optical IOP sensor. They designed a microscale implantable optical IOP sensor which was a hermetically sealed and pressure-sensitive resonant cavity.$^{[45,106]}$ The sensor consisting of two components included a micromachined silicon ring with a flexible membrane and a bottom reflective surface (Figure 6B and C). The sensor should be implanted in the anterior chamber and interrogated using NIR light (800-1100 nm) for IOP monitoring (Figure 6D).
With the increase of the IOP, the gap distance in the optical cavity will decrease, which makes the wavelength in the reflected resonance shift to a shorter wavelength (Figure 6E).\(^{45}\)

Furthermore, short-range-ordered nanostructures with an aspect ratio of 0.45 were developed on Si\(_3\)N\(_4\) membranes, which improved the angle independence of the membrane transmission by 50%. With the IOP variations, the resonant wavelength shifts captured remotely in reflection indicate that the sensor with nanostructure membrane exhibits an excellent linear relationship with the reference pressure in the range of 0–32 mmHg (Figure 6F), and the sensor had a wide-angle performance with a low readout error of 0.26 mmHg. The nanostructured and a flat-surfaced sensor were mounted on a flexible silicone haptic to implant in the anterior chamber of a New Zealand white rabbit for in vivo optical performance and biocompatibility evaluations. The results indicate that the standard deviation of Δ\(\lambda\) and IOP obtained from the nanostructured sensor was 0.6 nm and 0.23 mmHg respectively, while that measured by the flat-surfaced sensor was 1.3 nm and 0.64 mmHg. Contrast experiments implied that cell signal and migration patterns on the nanostructured sensor were much less than that of the flat-surfaced sensor (Figure 6G and H), which indicated that this nanostructure improved the biocompatibility of implants significantly.\(^{106}\)

However, to make the optical sensor achieving accurate IOP measurement, it is necessary to build a precise and expensive spectrometer system, which may bring to the challenge of inaccurate measurement caused by shakes from the daily routine of patients in practical application. Maeng et al. proposed the visual color changes caused by morphology changes in photonic crystals to realize continuous IOP monitoring, which used a smartphone camera to complete quantitative measurements without an optical spectrometer system.\(^{42}\) The photonic crystal with opal nanostructure was fabricated to a pressure sensor that was embedded in a contact lens. When the corneal curvature changes due to IOP fluctuations, a shift occurs in the reflected wavelength because of changes in the lattice distance between periodic nanostructures (Figure 6I). The color change is from the deformation of the photonic crystal (Figure 6J), which can be estimated by Bragg’s equation:\(^{107,108}\)

\[
m\lambda = 2d\eta_{eff} \sin \theta
\]

where \(\lambda\) is the wavelength of the color, \(m\) is the order of diffraction, \(\eta_{eff}\) is the mean refractive index of the system, \(d\) is the spacing between the planes in the lattice, and \(\theta\) is the glancing angle between the incident light and diffraction crystal planes. To amplify the corneal deformation for enhancing the sensitivity of the photonic crystal sensor, a ring-shaped fluid channel was designed and placed on the position of the corneoscleral junction. The sensor was tested on a silicone eye model and a porcine eye, corresponding to the sensitivity of 0.4 and 0.23 nm/mmHg, respectively. The detection limit of the sensor with the spectrometer and smartphone camera was 3.2 and 5.12 mmHg, respectively, which is higher than that of clinical practice for 1 mmHg. Therefore, this sensor should be further improved in reliability. However, IOP fluctuations are identified as changes in RGB value by a smartphone camera, which has a certain positive significance in the management of glaucoma, that is, the sensor provides color changes when the IOP exceeds the threshold. Overall, the optical method for real-time IOP monitoring usually has a better resolution than conventional tonometry, which can fulfill the clinical demand (resolution < 1 mmHg). Moreover, optical sensors do not need any external energy supply, however, they must be excited by the external incident light. For most optical sensors, the influence of the incident light and readout angle on the performance of the sensor cannot be ignored. For practice application, IOP sensors need to meet the characteristics of noninvasive, miniaturization, portability, transparency, easy operation, and so on. There is still a shortage of optical sensors that can accomplish accurate IOP measurements with all necessary features, especially due to the obstruction of the visual field as well as calibration between incident light input and reflected light readout, which needs further researches to address.

### 2.5 Other devices

Split-ring resonators (SSRs), the fundamental components of metamaterials, are developed as passive sensors for real-time IOP monitoring. The structure of an SSR is simple which consists of a metallic ring with a narrow split. Similar to an RLC circuit, electric and magnetic resonances will occur when the SSR is applied with an external appropriate electromagnetic excitation. The resonant frequency of the SSR will change due to variations in the geometry. Therefore, Torun et al. designed the SSR to track the curvature of the cornea for IOP monitoring.\(^{109,110}\) The SSR made of aluminum sheets was embedded in a hydrogel matrix which was placed on a latex rubber balloon to monitor the IOP fluctuations. The sensor excitation and the data transmission were implemented by a pair of monopole antennas. IOP measurements indicated that with the increase of curvature radius of latex rubber, the resonant frequency of the sensor decreases monotonically. After six repeated experiments, the mean sensitivity of the sensor was −24.12 MHz/mm.\(^{109}\) Lam et al. proposed
a dual-resonator sensor composed of a low-frequency resonator and a high-frequency resonator to reduce the IOP error from a single resonator in a variable ocular environment.\textsuperscript{[115]} One-turn inductance and two-turn inductors are connected with two parallel plate capacitors to form high-frequency and low-frequency resonators, respectively. The dual-resonator contact lens mounted on a rubber eye was placed in a beaker filled with salt water to simulate the environment of human tears for sensor evaluation. Shamim et al. reported a single-chip implantable IOP sensor for the first time. The system-on-chip (SOC), fabricated by a standard 0.18 $\mu$m CMOS process, integrated a transmitter antenna of 2.4 GHz and a receiver antenna of 5.2 GHz that harvested energy from incident RF signals.\textsuperscript{[112]} Rickard et al. proposed a novel approach to act as a flexible membrane, sclera can produce mechanical strain when IOP fluctuates. A nanofabricated discrete resistor array sensor of 1.6 mm $\times$ 2.7 mm was implanted in the eye to track scleral tissue displacement.\textsuperscript{[113]}

3 | CHALLENGES AND PERSPECTIVE

In the development of continuous IOP monitoring sensors towards clinical applications, there are still some problems and challenges that need to be resolved. An ideal IOP sensor should meet the following requirements: safety, biocompatibility, transparency, accuracy, reproducibility, independence of corneal curvature and thickness, ease of self-measurement by patients. Furthermore, the IOP measurement results of the developed sensor should be the same as those of the instruments that have been used in the clinic, such as the Goldmann tonometer.\textsuperscript{[114]} According to comparisons in Table 1, these novel IOP sensors mainly focus on the early stages of continuous IOP monitoring. Most of the experimental verifications of IOP sensors were carried out on model eyes or in vitro animal eyes rather than on the human eyes for 24-hour continuous IOP monitoring. The reading distance of some IOP sensors is about 5 mm. However, researches indicated that eyelashes of most people can grow to a length of 8–12 mm,\textsuperscript{[115,116]} therefore, the distance of the external medical devices from the eye should be less than 8 mm to avoid contact with eyelashes.\textsuperscript{[117]} An accurate and reliable 24-hour continuous IOP monitoring can provide a significant understanding of the individual circadian rhythm changes of IOP. To achieve continuous IOP monitoring, IOP sensors are required to measure IOP at regular intervals (such as once every 5 minutes). However, IOP sensors using electromagnetic (EM) radiation for energy supply and data transmission need to evaluate the risks of frequent and long-term EM radiation to the eyes. The human eye is the most sensitive organ of the body to EM exposure. Numerous studies have demonstrated that the temperature in the human eye will rise when it is exposed to EM waves, which will cause ocular diseases such as cataracts and effects on the retina, cornea, etc.\textsuperscript{[118–121]} Moreover, noninvasive contact lenses are developed to indirectly obtain intraocular pressure by measuring changes in the radius of curvature of the cornea. Absolute intraocular pressure cannot be obtained and calibration is required. However, calibration of the contact lens IOP sensor is also a challenge. At present, few sensors are directly calibrated with a GAT tonometer, most of which utilized the pressure in the model eyeball or animal eye measured by a commercial pressure tester for calibration. Because the GAT tonometer needs local anesthesia and pressing the surface of the eyeball when measuring IOP, IOP can only be measured by GAT before and after wearing a contact lens sensor but not at the same time, making it difficult to validate the registered IOP spikes simultaneously.\textsuperscript{[122]} Furthermore, the corneal thickness, curvature, and biomechanics are different for each individual, which should be considered in the calibration of the contact lens IOP sensor. Therefore, further research needs to address the influence on contact lens IOP sensors by variations in corneal thickness, curvature, and biomechanics across the population.

The long-term stability and biocompatibility of the IOP sensor are significant factors to be considered before clinical application. From the key materials used by IOP sensors in Table 1, most devices used metal materials such as Cu and Au that are opaque, rigid, and brittle materials and can easily fail during repetitive mechanical deformations. This will result in performance degradation of the IOP sensor in the long-term IOP monitoring. Therefore, flexible materials as the sensing elements of the IOP sensors are promising for practical application. Moreover, some ultra-thin flexible materials are transparent, which is of great significance for the fabrication of highly transparent IOP sensors, thereby realizing 24-hour continuous IOP monitoring without disturbing the people’s daily routine. Besides, all of the materials utilized for the preparation of IOP sensors must have good biocompatibility. Currently, most of the IOP sensors developed have not been used in human eyes, thereby lacking the evaluation of biocompatibility for the sensor. Efficient and secure energy supply and transmission of IOP sensors still need to be addressed and evaluated. At present, it is common to use metal coils as wireless energy supply and data communication. Developing flexible and transparent conductive materials instead of metal coils to realize energy and data transmission is promising for the preparation of ideal transparent IOP sensors. Ultra-thin, flexible, miniaturized, and highly transparent IOP sensors can bring comfort and convenience to patients. A wafer-scale design of transparent and
### TABLE 1 Comparison of different types of IOP sensors

| Ref | Type           | Key materials                                      | Implantable or noninvasive | Measurement platform | Data transmission | Responsivity/sensitivity |
|-----|----------------|----------------------------------------------------|-----------------------------|----------------------|-------------------|--------------------------|
| [46] | Microfluidic PDMS | Implantable Porcine eye                          | Smartphone camera         | 50-137 µm/mmHg       |
| [40] | Microfluidic PDMS/PET | Noninvasive Porcine eye                          | Smartphone camera         | 0.2832 mm/mmHg      |
| [77] | Microfluidic PDMS | Noninvasive Porcine eye                          | Smartphone camera         | 0.007% per mmHg     |
| [80] | Microfluidic PDMS | Noninvasive Porcine eye                          | Camera                     | 28 µm/mmHg          |
| [78] | Microfluidic PDMS | Noninvasive Porcine eye                          | USB camera                 | 40.8 µm/mmHg        |
| [82] | Piezoresistive Ti/Pt | Noninvasive Silicone model eye                 | Semiconductor tester      | 20 µV/mmHg          |
| [41] | Piezoresistive Graphene | Noninvasive Silicone model eye                | Bluetooth                   | 150 µV/mmHg        |
| [84] | Piezoresistive Graphene woven fabrics | Noninvasive Porcine eye                       | Semiconductor analyzer     | 6.8% /mmHg         |
| [85] | Piezoresistive Graphene Nanowalls | Noninvasive Porcine eye                        | high-precision electric meter | 1.014 kΩ/mmHg |
| [63] | Piezoresistive Cr/Au/Cu | Noninvasive Lewis rat                           | LC circuit                  | 3.5±0.8%/mmHg      |
| [91] | Inductive Ferrite | Implantable Rabbit eye                        | LC circuit ~12 MHz, 5 mm   | 13 kHz/mmHg        |
| [43] | Inductive Copper/Ferrite | Implantable Rabbit eye                       | LC circuit ~12 MHz, 5 mm   | 16.7 kHz/mmHg      |
| [93] | Inductive Cu/Ti/Au | Noninvasive Rubber model eye                   | LC circuit ~205 MHz        | 8 kHz/mmHg         |
| [94] | Inductive Ti/Cu | Implantable Porcine eye                        | LC circuit ~550 MHz        | 57 kHz/mmHg        |
| [39] | Inductive Cu/Ti/Au | Noninvasive Canine eye                        | LC circuit ~500 MHz        | 35.1 kHz/mmHg      |
| [95] | Inductive Liquid metal (Galinstan) | Noninvasive procine eye                     | LC circuit ~185 MHz       | 78.9–86.7 KHz/mmHg |
| [100] | Capacitive Cu/Graphene | Uncertain Tubing                              | LC Circuit 302 MHz, 5 mm   | 160 kHz/mmHg       |
| [96] | Capacitive Copper Foil | Noninvasive Porcine eye                      | LC Circuit ~114 MHz, < 25 mm | 23 kHz/mmHg       |
| [99] | Capacitive Au/Ti/Cu | Noninvasive Porcine eye                        | RFID                       | 0.02 pF/4.5 mmHg   |
| [97] | Capacitive Au/Ti/Cu | Noninvasive Artificial chamber                | RFID 860–960 MHz            | 1.2239 pF/mmHg     |
| [38] | Capacitive Au/Ti/Cu | Noninvasive Porcine eye                        | RFID 920 MHz, 1 cm         | 1.5–120 pF        |
| [64] | Capacitive Graphene/AgNWs | Noninvasive Bovine eye                      | LC circuit ~4 GHz, 10 mm   | 2.64 MHz/mmHg     |
| [105] | Optical Infrared diode | Noninvasive Porcine eye                      | Phototransistor 5 mm       | /                  |
| [45] | Optical SiN | Implantable Rabbit eye                        | Spectrometer 3–5 cm        | Average accuracy of 0.29 mmHg |
| [106] | Optical Si3N4 | Implantable Rabbit eye                        | Spectrometer                | /                  |
| [42] | Optical Polystyrene particles | Noninvasive Porcine eye                  | Smartphone camera         | 0.23 nm/mmHg       |
| [109] | Split-Ring Resonator Aluminum sheets | Noninvasive Latex rubber                  | Monopole antennas ~825 MHz | −24.12 MHz/mm    |
| [110] | Split-Ring Resonator Silver nanoparticles | Noninvasive Latex rubber                | Monopole antennas ~2.5 GHz | 33.2 MHz/mm     |

Lightweight electronics has a potential application in soft contact lenses for IOP monitoring. In the future, like hypertension and diabetes patients, glaucoma patients can participate in their disease management by measuring their IOP in real time. Furthermore, patients can also share real-time IOP data in the cloud, and use artificial intelligence and big data to predict and evaluate IOP. Ophthalmologists can also conduct online assessments and medication guidance based on the shared IOP of patients.

### 4 CONCLUSIONS

In conclusion, reliable and accurate 24-hour continuous IOP monitoring can provide a better understanding of the circadian rhythm changes of IOP. Real-time monitoring of IOP in patients is conducive to early diagnosis and treatment of glaucoma. There are few clinical trials of the developed implantable and non-invasive IOP sensors for 24-hour continuous IOP monitoring. Currently, implantable IOP sensors are combined with intraocular...
lenses and implanted in the eyes during cataract surgeries. In addition to this approach, the acceptability of glaucoma patients with implantation surgery is low. Smart contact lens IOP sensor is promising for diagnosis and treatment of glaucoma in the future. However, challenges such as transparency, security, biocompatibility, reliability, and calibration of contact lens IOP sensors need to be further studied and addressed. In the future, more portable continuous IOP sensors will be put into clinical practice, which brings hope for glaucoma patients to participate in their disease management.

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