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Tear-based glucose monitoring: A non-invasive approach to diabetes control in resource-limited settings

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ABSTRACT

Effective diabetes management may require continuous monitoring of blood glucose (BG) levels; however, conventional methods such as finger-prick testing and continuous glucose monitors (CGMs) remain invasive, costly, and often inaccessible, particularly in rural and remote Aboriginal and Torres Strait Islander (ATSI) communities. Recent advances in nanotechnology have enabled the development of nanosensor-embedded, near-field communication (NFC)-enabled smart contact lenses (SCLs) for non-invasive tear glucose (TG) monitoring. This systematic review, conducted in accordance with PRISMA guidelines, critically evaluated 12 peer-reviewed empirical studies encompassing clinical, cohort, and experimental designs involving both human and animal subjects. Study quality and risk of bias were assessed using NOS, ROBINS-I, and QUADAS-2 frameworks. Across the studies, TG levels demonstrated strong correlations with BG (R^2 = 0.87–0.998), mean absolute relative difference (MARD) values ranged between 12.5 % and 16.7 %, and over 95 % of readings fell within clinically acceptable error grid zones. A physiological lag of 5–10 min between TG and BG changes was consistently observed. Nanosensor-embedded SCLs showed stability, biocompatibility, and effective real-time wireless data transmission, with minimal impact on wearer comfort. Collectively, these findings support the feasibility of tear-based glucose monitoring as a non-invasive alternative to traditional approaches. However, validation in larger, more diverse populations and real-world conditions is required to establish clinical reliability. The potential application of these technologies in underserved ATSI communities underscores their promise for improving compliance, accessibility, and long-term health outcomes.

1. Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose (BG) levels and is typically diagnosed through biochemical assessment of hyperglycaemia (Diabetes Federation, 2019). The condition arises primarily due to either insufficient insulin production by the pancreas or the body's impaired ability to utilize insulin effectively (Diabetes Federation, 2019; Min et al., 2025; Shufen et al., 2025; Lakhani et al., 2025). Insulin plays a critical role in glucose homeostasis, facilitating cellular uptake of glucose for energy metabolism. Globally, diabetes affects over 400 million individuals, with Type 2 diabetes being the most prevalent form (Zhu et al., 2025; Bokieva, 2025). Type 2 diabetes is commonly associated with insulin resistance and relative insulin deficiency, often exacerbated by modifiable lifestyle factors such as obesity, poor dietary habits, and physical inactivity (Burns and Francis, 2024; Ulambayar et al., 2025). In contrast, Type 1 diabetes is an autoimmune condition characterized by destroying pancreatic β-cells, resulting in absolute insulin deficiency (Singh et al., 2024; Sann et al., 2024). Gestational diabetes occurs in pregnancy and has higher associated risks of type 2 diabetes long term. Diabetes is associated with a wide spectrum of multi-organ complications, particularly when glycaemic levels are not adequately controlled. Effective management is essential involving a combination of lifestyle modifications and pharmacological interventions. Lifestyle changes include

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maintaining a healthy body weight, engaging in regular physical activity, and adhering to a balanced diet (Nadhiya et al., 2024; Koenigsberg et al., 2004). Pharmacological therapies encompass insulin replacement and a range of oral or injectable antidiabetic agents (Evans et al., 2000; Krentz and Bailey, 2005).

A cornerstone of diabetes management is the continuous and accurate monitoring of BG levels, which is essential for optimizing treatment and preventing complications (Ong et al., 2023; Sugandh et al., 2023; Chehregosha et al., 2019). The current gold standard for BG level assessment involves finger-prick capillary blood sampling (Olansky and Kennedy, 2010; Al-Worafi, 2024). While this method achieves approximately 95 % accuracy, it may have up to 15 % variability when compared with laboratory-based plasma glucose measurements (Kumar et al., 2025; Fengade et al., 2025; Wang and Feng, 2025). Moreover, the invasiveness, discomfort, and ongoing cost of traditional monitoring techniques pose significant barriers to long-term patient adherence (Religioni et al., 2025; Manzoni et al., 2025). With rapid advancements in medical technology, there is increasing demand for non-invasive alternatives to traditional glucose monitoring. Emerging platforms, such as tear fluid analysis and wearable biosensors, particularly NFC-enabled SCL, offer a promising future for non-invasive, real-time glucose tracking. These innovations have the potential to revolutionize diabetes management by providing patients with more comfortable, accessible, and continuous monitoring solutions (Vadia et al., 2025; Gonçalves et al., 2024).

Non-invasive glucose monitoring through alternative biofluids, including tears, saliva, sweat, urine, interstitial fluids (ISFs), and breast milk (Tricoli et al., 2017), offers a pain-free and accessible substitute for traditional blood-based measurements, particularly valuable for frequent monitoring and use in resource-limited settings (Fig. 1a). Saliva-based glucose sensors utilize colorimetric (Bordbar et al., 2023) and electrochemical (Zhang et al., 2024) detection methods (Fig. 1b); however, their performance can be affected by the complex composition of saliva and fluctuations in pH and flow rate, potentially reducing analytical reliability (Harun-Or-Rashid et al., 2024). Sweat-based monitoring platforms, such as flexible skin patches (Manasa et al., 2022) and wearable devices (e.g., smartwatches) (Binabaji et al., 2024), support continuous, real-time glucose tracking with minimal user intervention (Zivkovic et al., 2025; Nasiri and Tricoli, 2018) (Fig. 1c). Nevertheless, their effectiveness depends on sustained sweat secretion,

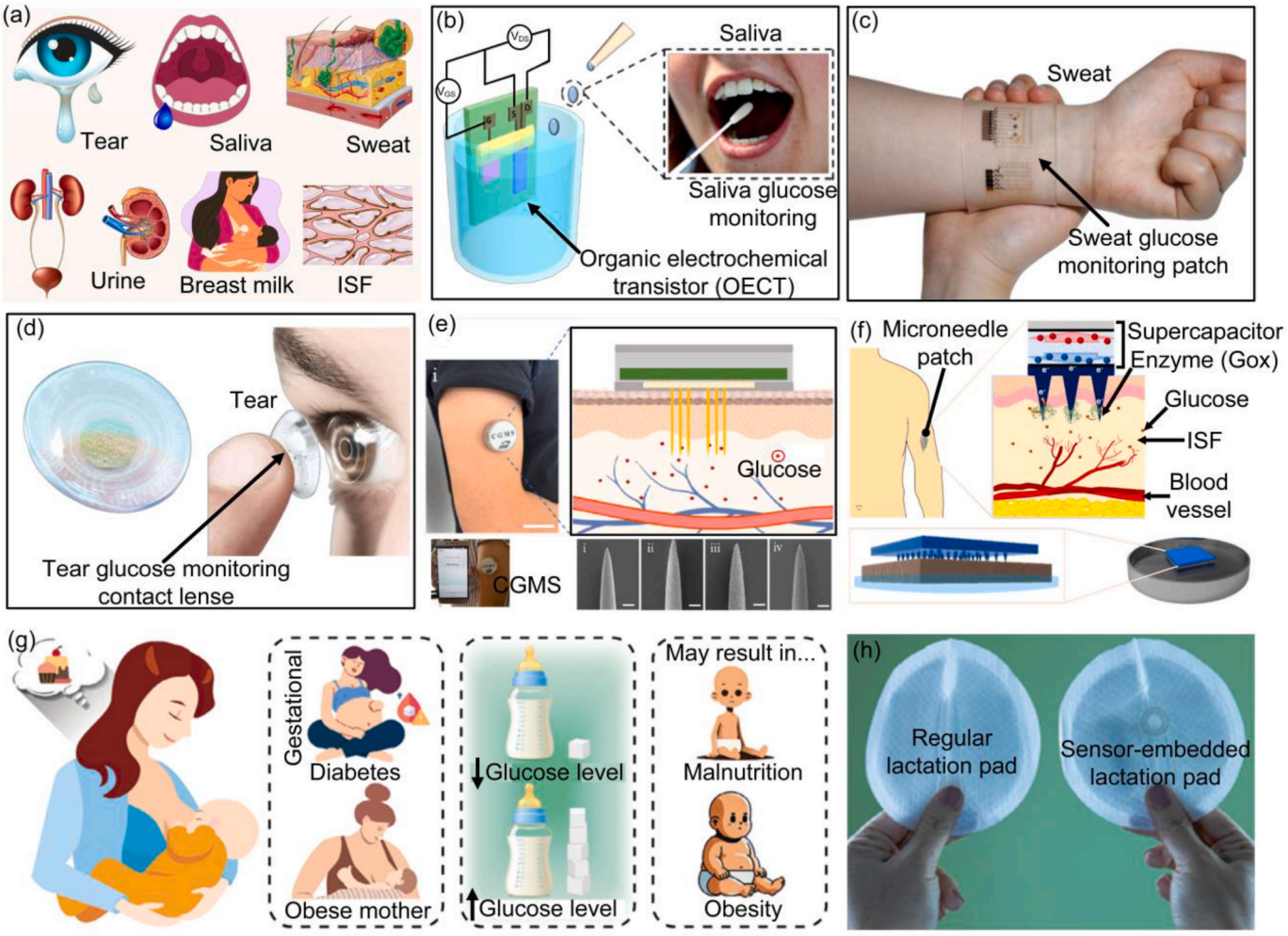

Fig. 1. Non-invasive glucose monitoring using alternative biofluids. (a) Tear, saliva, sweat, and urine offer pain-free alternatives to blood sampling for glucose monitoring. (b) Saliva-based sensors, such as organic electrochemical transistors (OECTs), enable non-invasive detection but are affected by pH variability. (c) Sweat glucose monitoring patches provide continuous tracking but depend on consistent sweat secretion. (d) SCLs detect glucose in tear fluid with high sensitivity, though challenges remain in accuracy and user comfort. Urine glucose testing (a) helps detect hyperglycemia but lacks real-time capability. Advances in nanotechnology, wearables, and wireless communication are enhancing sensor performance, usability, and accessibility for diabetes management. (e, f) Concept of a wearable glucose sensor system based on differential microneedles and its subcomponents, and a self-powered supercapacitor as a glucose sensor. (g) The importance of monitoring glucose in breast milk due to the potential impact of hypoglycemia and hyperglycemia on infant health, Reproduced with permission from Ref. (Al-Shami et al., 2025), 2025, Wiley. (h) Real photo of a commercial regular lactation pad and a sensor-embedded lactation pad, Reproduced with permission from Ref. (Al-Shami et al., 2025), 2025, Wiley.

which can vary with hydration status, temperature, and physical activity (Nasiri and Tricoli, 2018). Tear fluid glucose monitoring, often implemented via SCLs (Xiang et al., 2023) provides a discreet and non-invasive sensing interface capable of detecting low glucose concentrations (Fig. 1d). Despite its promise, challenges persist in achieving high accuracy and specificity due to the low analyte concentration and interference from tear composition (Nasiri and Tricoli, 2018). Urine glucose monitoring is widely used as an indicator of hyperglycemia, yet it remains limited to retrospective analysis and lacks the temporal resolution required for dynamic glucose management (Li and Chen, 2023). Recent advances in nanotechnology, bioelectronics, and artificial intelligence are increasingly addressing these limitations by enhancing sensor sensitivity, miniaturization, wireless data transmission, and integration into user-friendly platforms (Harun-Or-Rashid et al., 2024; Harun-Or-Rashid et al., 2025). These developments are paving the way for more reliable, continuous, and patient-centric glucose monitoring systems.

In addition, minimally invasive analysis of ISFs has emerged as one of the most prominent and clinically advanced strategies for continuous glucose monitoring (CGM). ISF, distributed within the dermal and subdermal layers, is in dynamic equilibrium with blood plasma and reflects blood glucose levels with only a short physiological lag, typically in the range of 5–15 min. This lag is primarily due to glucose diffusion kinetics across the capillary endothelium and interstitial matrix, yet it remains sufficiently short for effective glycemic trend monitoring and therapeutic decision-making. Compared with alternative biofluids such as saliva or sweat, ISF offers lower susceptibility to external contamination and dilution, making it a more reliable surrogate for blood glucose. Microneedle-based sensors (Fig. 1e and f) have revolutionized ISF monitoring by enabling painless and minimally invasive access to this compartment (Kil et al., 2024; Yang et al., 2024). These devices consist of micron-scale projections that penetrate only the stratum corneum, thereby avoiding nociceptors and blood vessels while providing direct access to interstitial compartments. When coupled with electrochemical transduction—most commonly enzymatic amperometry using glucose oxidase—they achieve high sensitivity and specificity in real-time glucose detection. Advances in microneedle materials, such as biodegradable polymers, silicon, and functionalized hydrogels, have further enhanced biocompatibility, mechanical stability, and long-term wearability. In addition, integration with flexible electronics and wireless transmission modules has allowed the development of patch-type devices that support continuous, autonomous glucose monitoring. Such platforms are now being commercialized, underscoring their clinical maturity and translational readiness.

Beyond ISF, unconventional biofluids are also gaining increasing attention for their unique opportunities in targeted health applications. A particularly novel example is human breast milk (Fig. 1g and h), which has recently been investigated as a matrix for noninvasive glucose monitoring with potential implications for both maternal and infant health (Al-Shami et al., 2025). Milk composition is tightly linked to maternal metabolic status, and fluctuations in glucose concentration may serve as biomarkers of maternal glycemic control during lactation. In parallel, monitoring milk glucose content could offer insights into infant nutritional intake and early metabolic health. Unlike ISF, breast milk sensing is still at an exploratory stage, but the concept highlights how biofluid-specific sensing strategies may be tailored to individual life stages and physiological contexts. Taken together, the emergence of ISF-based microneedle sensors and the exploration of unconventional biofluids such as breast milk illustrate the widening landscape of glucose monitoring technologies. These approaches complement tear-, saliva-, and sweat-based sensing by offering context-specific advantages, and collectively they exemplify the broader trend toward personalized, minimally invasive, and patient-centric monitoring strategies that integrate advanced materials engineering (nanotechnology) with real-world clinical needs.

Nanotechnology refers to the manipulation of matter on an atomic, molecular, and supramolecular scale, which ranges from 1 to 100 nm. This niche form of technology involves precision in designing, synthesizing, and utilising materials to create devices at a nanoscale for innovative solutions across various fields (Nasrollahzadeh et al., 2019; International Organization for Standardization, 2003; Sharma et al., 2022; Nasiri, 2019; Jeerapan, 2019). In medicine, it allows for extraordinary potential for diagnosing, treating, and monitoring diseases, a promising application of nanotechnology in medicine has been targeted drug delivery, where engineered nanoparticles are encapsulated in drugs to deliver them to specifically diseased cells and/or tissues, allows a minimising of pharmacological adverse effects and maximisation of therapeutic efficacy (Feynman, 1960; Dessale et al., 2022; Joseph et al., 2023). Additionally, NFC chips are miniscule devices capable of wireless data transmission to an activated reader (Alreshaid et al., 2018; Xu et al., 2024).

Using nanotechnological particles, tear fluid analysis leverages the correlation between glucose levels in tears and blood, proposing a less invasive method of monitoring. Tear fluid samples offer over 20 components, involving minerals, proteins, glucose, and metal ions, present in lower concentrations relative to blood levels (Ventola, 2012; Zou et al., 2018; Amini and Okeme, 2024; Masoudi, 2022; Zabitler et al., 2025). BG concentration levels are 3.9 mmol/L to 5.6 mmol/L, whereas tear glucose levels range from 0.1 to 0.6 mM (Gabriel et al., 2017). Incorporating nanoparticle embedded contact lenses that are composed of glucose oxidase and cerium oxide has found measurable changes in glucose levels when compared to BG levels (Gabriel et al., 2017; Elsherif et al., 2022; Zhang et al., 2011). The application of NFC-enabled contact lenses integrates the glucose analysis to be transmitted to an NFC-enabled device, i.e. smart phone, for access (Omberg et al., 2022). These advancements could see an enhancement in diabetic patients' compliance and overall quality of life, especially for those requiring CGM.

The Aboriginal and Torres Strait Islander (ATSI) population in remote and rural Australia faces significant barriers to diabetes management. Indigenous Australians are nearly four times more likely to have diabetes than non-Indigenous Australians (Australian Institute of Health and Welfare (AIHW), 2020), with prevalence rates reaching up to 17 % in some communities (Australian Institute of Health and Welfare (AIHW), 2020; Taylor et al., 2017). Geographic isolation, limited healthcare facilities, and a shortage of specialized diabetes care impede regular monitoring and timely treatment (Taylor et al., 2017; Ogwu and Izah, 2025). Logistical barriers, such as long travel distances to healthcare providers and limited access to technology for monitoring glucose, exacerbate complications and increase the risk of severe health outcomes in ATSI populations (Ogwu and Izah, 2025; Australian Bureau of Statistics (ABS), 2019).

This review aims to evaluate the accuracy of tear fluid glucose measurements compared to BG measurements, the current gold standard. It will also assess the viability and clinical relevance of tear fluid analysis via contact lens wear, exploring the challenges associated with its use and adherence amongst diabetic populations. This review will investigate the potential of NFC-enabled contact lenses as the medium of non-invasive glucose monitoring with consideration to current capabilities and limitations of the current nanotechnology involved. Furthermore, implementation of innovative technologies in rural populations will be examined, highlighting the potential of non-invasive glucose management in ATSI rural and remote populations. Through systematically reviewing peer-reviewed empirical articles, this study seeks to provide a comprehensive analysis of an advanced glucose monitoring method, guiding future research and clinical practice towards effective, life-improving, and patient-friendly diabetic management solutions. This systematic review will examine peer-reviewed empirical studies to evaluate the accuracy of tear fluid glucose measurement compared to BG, the current gold standard. It will critically assess the clinical performance and reliability of nanosensor-embedded, NFC-enabled smart contact lenses for tear glucose monitoring, with

particular attention to TG–BG correlation metrics such as R^2, MARD, error grid analysis, and the effects of physiological lag. The review will also explore key material and sensor innovations that influence clinical outcomes, stability, and wearer comfort, while identifying research gaps and technical challenges that must be overcome to advance from experimental prototypes to clinically approved devices. In addition, it will consider the broader viability of tear fluid analysis as a non-invasive alternative to traditional finger-prick BG monitoring, including its potential application in Aboriginal and Torres Strait Islander rural and remote communities, where improved compliance and health outcomes are critically needed.

2. Methodology

The preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines (Page et al., 2021) in the design, screening and conduction of this review was followed with a protocol of inclusions and exclusions developed.

2.1. Search strategy

A comprehensive search strategy was developed using relevant keywords, phrases, and MeSH in alignment with Cochrane search guidelines. The core concepts included *diabetes mellitus*, *glucose monitoring*, and *tear fluid analysis*. The complete search strategy is detailed in Table 1. The literature search was conducted across five major databases: PubMed, Cochrane Library, Scopus, Embase, and Google Scholar. Given the niche nature of the research topic, no restrictions were placed on publication date.

2.2. Eligibility criteria

All identified records were imported into Covidence. Eligibility criteria included full-text, peer-reviewed empirical studies published in English, encompassing experimental, observational, clinical trials, cohort studies, randomized controlled trials, and animal studies, all involving populations with Type 1 and/or Type 2 diabetes. Although no restrictions were placed on publication date, preference was given to more recent studies to reflect advancements in glucose monitoring technologies. Studies were excluded if they met any of the following criteria: full text not available in English, non-empirical or non-peer-reviewed publications, insufficient detail regarding methodology, outcomes, or results, or focus on paediatric or gestational diabetes populations.

2.3. Study selection

All retrieved articles were uploaded to Covidence. Screening and data extraction were independently conducted by two reviewers (J.Y. and K.M.), with discrepancies resolved through consultation with a third reviewer (V.P.). The search strategy initially yielded 227 articles. After the removal of 83 duplicates, 144 unique records remained for screening. Title and abstract screening were followed by full-text review, during which all reasons for study exclusion were systematically documented.

Table 1
Search terms for Cochrane, PubMed.

Line	Search terms (exploded, all subheadings)
1	MeSH descriptor: [Diabetes Mellitus] explode all trees
2	glucose monitor* OR glucose measurement* OR glucose analysis
3	tear fluid OR lacrimal fluid OR tear film OR lacrimal film
4	tear analysis OR lacrimal analysis
5	MeSH descriptor: [Contact Lenses] this term only
6	smart contact lens* OR nanosensor contact lens
7	1 AND 2
8	1 AND 2 AND 3
9	1 AND 2 AND 4
10	8 AND 5
11	8 AND 6
12	8 AND 5
13	9 AND 5
14	9 AND 6

2.4. Data extraction

Data extraction was conducted in accordance with the PRISMA guidelines (Page et al., 2021), using a structured Excel spreadsheet to ensure consistency across all studies. This process was carried out by J.Y. and included standardized extraction of key study characteristics such as study design, population, intervention, outcomes, limitations, specific features, and risk of bias. Interventions and outcomes focused on glucose measurement via tear fluid analysis, the integration of nanosensor technologies, NFC-enabled contact lenses, and relevance to diabetic populations. All extracted data were cross-verified by a second reviewer, K.M., to ensure accuracy and consistency.

2.5. Quality assessment & risk of bias

Each included study was assessed in its quality and reliability. Individual study risk of bias was evaluated using an appropriate tool based on the study design: the Newcastle-Ottawa Scale (NOS) for cohort studies (Wells et al., 2013), ROBINS-I (Table 6) for non-randomised intervention studies (Sterne et al., 2016), and QUADAS-2 for experimental studies (Table 5) (Whiting et al., 2011). Each tool allowed for a structured evaluation of potential biases across multiple domains, such as selection or confounding factors, comparability, intervention, outcome/measurement, reference standard and reporting biases. Additionally, the GRADE framework (Guyatt et al., 2008) was applied to assess the overall quality of evidence across the studies for each outcome. Two independent reviewers, JY and KM, conducted these assessments, with a third reviewer, VP, available to resolve disagreements. This combined approach of risk of bias and GRADE allowed for a comprehensive evaluation of the individual study quality and the collective strength of its evidence. Studies were not excluded based on quality or bias; however, it was considered during data analysis and result interpretations.

2.6. Data synthesis

Data synthesis was conducted in accordance with PRISMA guidelines (Page et al., 2021) and is summarized in a flow diagram (Fig. 2), which outlines each stage of the screening and study inclusion process. Relevant data were extracted and synthesized using both tabular and graphical formats, structured across four primary analytical categories. Quantitative analysis focused on: (1) the accuracy of tear glucose measurements compared to BG measurements, and (2) the overall viability of tear fluid as a diagnostic medium. Key statistical parameters included correlation coefficients (R^2), mean absolute relative difference (MARD), and error grid analyses (Pearson, Parkes, and Clarke), as well as reported tear glucose concentration ranges and time lag between tear and BG levels. Qualitative synthesis was employed to evaluate technological dimensions, including: (3) the integration and performance of nanotechnology-embedded contact lenses, and (4) the use of NFC-enabled systems for wireless data transmission. Studies were assessed for sensor sensitivity, operational stability, user comfort, and feasibility for real-time monitoring. Finally, both quantitative and qualitative findings were integrated to (5) evaluate the practical applicability and potential implementation of these technologies in diabetes management within ATSI rural populations.

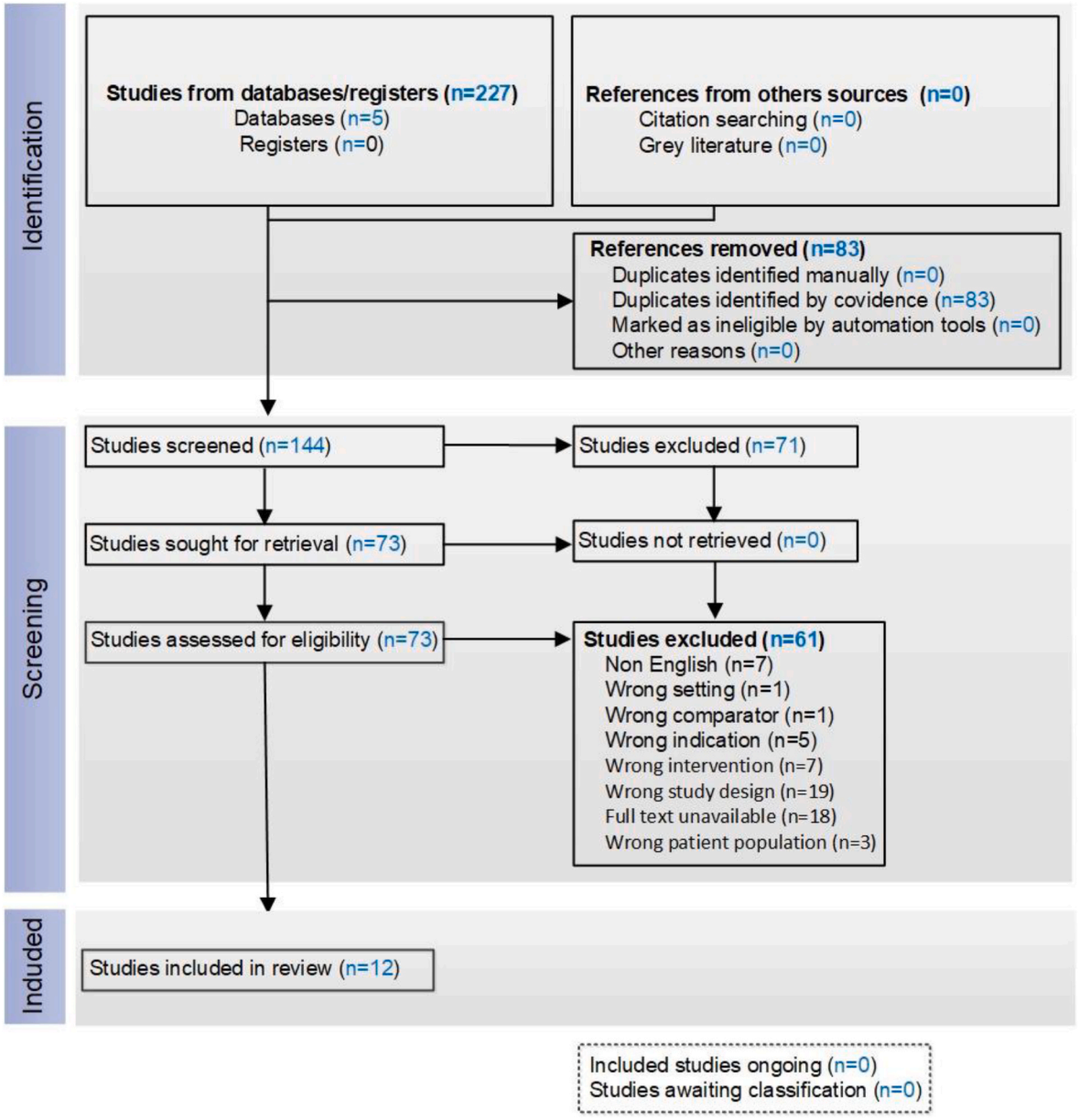

Fig. 2. PRISMA flow diagram summarizing the study selection process. Of 227 records identified from database searches, 83 duplicates were removed, leaving 144 studies for screening. After excluding 71 based on title and abstract, 73 full-text articles were assessed for eligibility. Sixty-one studies were excluded for reasons including language, intervention, study design, and lack of full text. Twelve studies met the inclusion criteria and were included in the final review.

3. Results and discussion

3.1. Study selection

A total of 227 records were identified through searches of primary databases, with no additional studies retrieved from grey literature or reference lists. After removing 83 duplicates, 144 articles underwent title and abstract screening, resulting in the exclusion of 71 studies. The remaining 73 articles proceeded to full-text review, of which 61 were excluded for the following reasons: non-English text (n = 7), incorrect setting (n = 1), wrong comparator (n = 1), unrelated indication (n = 5), inappropriate intervention (n = 7), unsuitable study design (n = 19), full text unavailable (n = 18), and irrelevant patient population (n = 3). Ultimately, 12 studies met the inclusion criteria and were critically appraised (Table 2). These included 2 cohort studies, 2 clinical trials, and 8 experimental studies.

3.2. Quality of studies

Overall, the 12 studies included in this review demonstrated a generally low to moderate risk of bias, supporting moderate to high confidence in the reported interventions and outcomes. The two cohort studies were assessed as low risk of bias using the NOS, reflecting high methodological rigor and reliable outcome reporting. Of the two clinical trials, one was rated as low risk of bias, while the other demonstrated low to moderate risk, primarily due to concerns related to outcome measurement. These limitations were considered in the interpretation of findings. The remaining eight experimental studies were evaluated using the ROBINS-I tool (Table 6) and were all classified as low risk of bias. Detailed risk of bias assessments is provided in Table 3. The quality of evidence was particularly robust among the experimental studies, offering strong support for the viability and accuracy of tear fluid-based glucose monitoring and its integration with advanced sensing technologies.

Table 2
Characteristics & findings of included studies.

Study		Population	International	Outcomes			
Author, Year	Study Type	Sample/ Population	Technological Measurement/Device	Comparative Measure	Detection Range	Conclusions	Limitations
Aihara, 2021 (Aihara et al., 2021)	Cohort Study	20 Human Diabetics 10 Human Non-Diabetics	Tear samples were collected with Microcaps microcapillaries	BG Serum	–	- Association was found between plasma and tear glucose. - Adjustments for prandial states were needed. - It was necessary to eliminate blood-contaminated tear samples.	Blood-contaminated tear samples
Kownaeka, 2018 (Kownacka et al., 2018)	Clinical Trial	6 Type 1 Diabetics	Noviosense glucose sensor in the lower eyelid	Finger-prick BG Continuous Glucose Monitor	0–20 mM	- Stable correlation between tear and BG.	Small population size
Cui, 2022 (Cui et al., 2022)	Experimental Study	8 Human Diabetics 3 Human Non-Diabetics	Mxene nanosheets SERS substrates + gold nanoparticles	BG Serum	1-50 uM	- Significant correlation between tear and BG. - Tear glucose detection as low as 0.39 μM. - No discomfort was reported using nanomaterials and nanoparticles.	Small population size Specific substrate use
Mirzajani, 2022 (Mirzajani et al., 2022)	Experimental Study	Nil	Femtosecond laser ablation fabricating SCL with NFC antennas	BG	0.2–1 mM	- Strong correlation between tear and BG. - Achieved high precision antenna patterns with stable conductivity. - Flexible of soft contact lens was obtained. - NFC-enabled communication was accurate and transmissible to smart device.	Prototype testing only No in-vivo testing conducted
Park, 2024 (Park et al., 2024)	Experimental study	10 Human Diabetics 10 Human Non-Diabetics 4 Rabbit Diabetics 4 Rabbit Non-Diabetics 4 Beagle Diabetics 4 Beagle Non-Diabetics	SCL, containing glucose biosensor, NFC chip and antenna	BG Serum	0.18–1 mM	- Significant correlation between TG and BG. - SCL provided real-time data transmission to smart phone. - SCL provided minimal discomfort to participant and no ocular damage. - Identified lag time adjustments necessary for each user. -Significant range of glucose, with low limit of 0.02 mM.	Small population size Variability in individual lag times
Han, 2023 (Han et al., 2023)	Experimental study	3 Rabbit Diabetics 3 Rabbit Non-Diabetics	HA-Au@Pt Bimetallic electrodes in SCL	BG Serum	1–50 mg dL^{-1}	- Strong correlation between TG and BG. - Wireless data transmission to smart phone. - 10 min delay in accuracy identified and accounted for.	Animal population
Geelhoed-Duijvestijn, 2021 (Duijvestijn et al., 2021)	Clinical Trial	24 Human Type 1 Diabetics	Noviosense glucose biosensor	BG via CGM	0–20 mM	- Strong correlation between TG and BG, with 99.7 % of readings within acceptable ranges. - Demonstrated non-invasive monitoring, with minimal of discomfort.	Small sample size Short testing duration Limit for hyperglycaemia ranges
Chu, 2011 (Chu et al., 2011)	Experimental Study	1 Rabbit Diabetic	Soft contact lens biosensor containing glucose oxidase + PDMS	BG via CGM	0.03–5 mM	- Strong correlation between TG and BG. - Delay of 10 min was noted and accounted for in readings. -Biocompatible flexible material embedded within the contact lens with electrodes. - Evaluated for real-time CGM.	Animal, small-scale study Enzyme leakage decreased sensitivity of biosensor.
Lane, 2006 (Lane et al., 2006)	Cohort Study	48 Human Diabetics (Type 1 + 2) 73 Human Non-Diabetics	Chromatographic analysis of tear	BG	0.14–10 mmol/L	- TG levels were noted to be higher in diabetic subjects and correlated strongly with BG. - Provided highly detailed tear glucose dynamics amongst diabetic and non-diabetic participants.	Sampling technique Technical limitations of glucose
Kim, 2020 (Kim et al., 2020)	Experimental Study	5 Mice Diabetics 5 Mice Non-Diabetics	Nanoparticle embedded contact lens with reflectance spectroscopy	BG	0–5 mM	- Strong linear correlation noted between TG and BG. - Low-cost system using white light for glucose measurement. - Feasibility was demonstrated in animal model.	Animal model Lower limits in human models
Kim, 2017 (Kim et al., 2017)	Experimental Study	1 Rabbit Diabetic 1 Bovine Eyeball	SCL with nanoparticle glucose sensors and embedded antenna	BG	1uM to 10 mM	- Correlation noted between TG and BG. - High sensitivity, transparency of SCL and biocompatibility was seen.	Animal model Small-scale study Early-stages of technology

(*continued on next page*)

Table 2 (*continued*)

Study		Population	International	Outcomes			
Author, Year	Study Type	Sample/ Population	Technological Measurement/Device	Comparative Measure	Detection Range	Conclusions	Limitations
Keum, 2020 (Keum et al., 2020)	Experimental Study	Rabbit Diabetic Rabbit Non-Diabetic (# unknown)	SCL with nanomaterial biosensor, hydrogel polymer, RF communicator	BG	0–50 mg dL^{-1}	- Real-time data was transmitted via RF communication. - Demonstrated correlation between TG and BG. - Monitored tear glucose dynamics with transmission to smart device. - Combined with drug delivery for treatment of diabetic retinopathy.	Animal model Unknown scale of study Early-stages of technology

Tabel 3
Risk of bias assessments – Cohort studies - Newcastle-Ottawa Scale.[16].

Author, Year	Selection/ Confounding	Comparability	Outcome/ Measurement	Overall risk
Aihara, 2021 (Aihara et al., 2021)	Low Risk	Low Risk	Low Risk	Low risk
Lane, 2006 (Lane et al., 2006)	Low Risk	Low Risk	Low Risk	Low risk

3.3. Clinical characteristics & population demographics

The studies featured a range of population selection, demographic, and specific clinical characteristics to assess the aim of tear glucose analysis. Across the 12 studies, there is a total of 212 human participants (Aihara et al., 2021; Kownacka et al., 2018; Cui et al., 2022; Mirzajani et al., 2022; Han et al., 2023; Duijvestijn et al., 2021), 16 minimum rabbit models (Mirzajani et al., 2022; Park et al., 2024; Kim et al., 2017, 2020), 8 beagle models (Mirzajani et al., 2022), 5 mouse models (Lane et al., 2006), and 1 bovine eyeball model (Kim et al., 2020). Of these populations, there was a type 1 diabetes, type 2 diabetes, or a non-diabetic population as a control group, including animal studies. No participants had any history of diabetic retinopathy or ocular trauma. Studies were conducted in Japan, the Netherlands, Korea, China, Turkey, and the USA, providing a cross-sectional view of different healthcare settings and variability in outcomes.

4. Accuracy of TG vs. BG

Previous studies (Aihara et al., 2021; Kownacka et al., 2018; Cui et al., 2022; Mirzajani et al., 2022; Park et al., 2024; Han et al., 2023; Duijvestijn et al., 2021; Chu et al., 2011; Lane et al., 2006; Kim et al., 2017, 2020; Keum et al., 2020) evaluating the accuracy of tear glucose measurements compared to BG consistently show a strong correlation between the two. Although tear glucose levels are generally lower than those in blood, they tend to follow similar trends, particularly in response to changes in BG, making them a promising indicator, especially for diabetic patients. However, the precise range of tear glucose varies widely among individuals and experimental conditions. Although correlation coefficients typically suggest moderate to strong associations (Table 4), inter-individual variability and physiological factors, such as tear film composition, secretion rate, and glucose transport mechanisms, can influence measurement precision. To assess clinical accuracy, statistical tools such as MARD and Error Grid Analysis are frequently employed. These analyses demonstrate that while tear glucose monitoring holds significant potential as a non-invasive diagnostic tool, variations in accuracy across different studies highlight the need for continued optimization. Further calibration and validation are essential under diverse environmental conditions and health states to ensure consistent performance and clinical reliability.

Kownacka et al. (2018) evaluated a non-invasive tear glucose biosensor (Fig. 3a) as an alternative to traditional finger-prick blood sampling for diabetes management. The sensor, coated with a biocompatible polysaccharide hydrogel, was assessed through comprehensive preclinical and clinical studies to determine its accuracy, safety, and feasibility. The NovioSense device was benchmarked against the

Table 4
Data points for tear glucose vs. blood glucose accuracy.

Author, Year	Population	TG Range	r^2, P	MARD	Error Grid Analysis	Time delay	Comments
Aihara, 2021 (Aihara et al., 2021)	Human		p = < 0.001	–	–	–	–
Kownaeka, 2018 (Kownacka et al., 2018)	Humans	0–20 mM	–	12.50 %	95 %	–	–
Cui, 2022 (Cui et al., 2022)	Humans	1-50 uM	$r^2 = 0.998$	–	–	–	Limit detection of 0.32 uM
Mirzaiani, 2022 (Mirzajani et al., 2022)		0.2–1 mM	–	–		–	–
Park, 2024 (Park et al., 2024)	Humans, Rabbits, Beagles	0.18–1 mM	p = 0.944	–	A + B region	5 min lag	Limit detection of 0.02 mM
Han, 2023 (Han et al., 2023)	Rabbits	1–50 mg dL-1	$r^2 = 0.999$		98.60 %	10 min lag	–
Geelhoed, 2021 (Duijvestijn et al., 2021)	Humans	0–20 mM	–	16.70 %	99.7 % in A + B region	–	–
Chu, 2011 (Chu et al., 2011)	Rabbits	0.03–5 mM	$r^2 = 0.974$	–	–	10 min lag	–
Lane, 2006 (Lane et al., 2006)	Humans	0.14–10 mmol/L	$r^2 = 0.9$, P = 0.0003	–	–	–	–
Kim, 2020 (Kim et al., 2020)	Mice	0–5 mM	$r^2 = 0.87$	–	–	10 min lag	–
Kim, 2017 (Kim et al., 2017)	Rabbits	1uM - 10 mM	–	–	–	–	–
Keum, 2020 (Keum et al., 2020)	Rabbits	0–50 mg dL-1	–	–	–	–	–

Table 5
Experimental studies - QUADAS-2.[17].

Author, Year	Patient Selection	Index Test	Reference Standard	Flow + Timing	Overall risk
Cui, 2022 (Cui et al., 2022)	Low Risk	Low Risk	Low Risk	Low Risk	Low risk
Park, 2024 (Park et al., 2024)	Low Risk	Low Risk	Low Risk	Moderate Risk	Low-moderate risk
Han, 2023 (Han et al., 2023)	Moderate Risk	Low Risk	Low Risk	Low Risk	Low-moderate risk
Chu, 2011 (Chu et al., 2011)	Low Risk	Low Risk	Low Risk	Low Risk	Low risk
Kim, 2020 (Kim et al., 2020)	Low Risk	Low Risk	Low Risk	Low Risk	Low risk
Kim, 2017 (Kim et al., 2017)	Low Risk	Low Risk	Low Risk	Low Risk	Low risk
Keum, 2020 (Keum et al., 2020)	Low Risk	Low Risk	Low Risk	Low Risk	Low risk

Dexcom G4 (invasive) CGM and demonstrated high linearity and selectivity toward glucose, even in the presence of six common physiological interferents—ascorbic acid, acetaminophen, lactic acid, urea, citric acid, and pyruvic acid, at relevant concentrations (Fig. 3b). Although the NovioSense platform operates on the same principle of tear-fluid glucose sensing as contact lens-based devices, it is not a corneal contact lens. Instead, it constitutes a flexible, coil-shaped biosensor designed for insertion into the inferior conjunctival fornix beneath the eyelid. In vivo testing in rabbits and sheep confirmed excellent biocompatibility, with no signs of irritation or immune response when positioned in the inferior conjunctival fornix. Cytotoxicity assays using mouse fibroblasts showed a high cell viability rate of 94 %. In sheep, tear glucose measurements correlated strongly with BG values (Fig. 3c), supported by Clarke Error Grid analysis indicating 92 % of readings within clinically acceptable zones. In a Phase II clinical trial involving six patients with Type 1 diabetes, the sensor was worn continuously for 4.5 h, with glucose readings recorded every 15 min. These were compared to capillary BG values and the Abbott FreeStyle Libre CGM. The NovioSense sensor yielded a median absolute relative difference (MedARD) of 12.5 %, closely matching the FreeStyle Libre's 12.0 %, with 95 % of data falling within Zones A and B of the Clarke Error Grid and 70 % within Zone A, indicating high clinical accuracy (Fig. 3d). No adverse effects or discomfort were reported, underscoring the sensor's wearability and tolerability.

Cui et al. (2022) further advanced tear glucose sensing by developing a highly sensitive non-invasive detection method using surface-enhanced Raman scattering (SERS). Their hybrid substrate, composed of gold nanoparticles (AuNPs) and MXene $Ti_3C_2T_x$ nanosheets, facilitated enzymatic glucose detection via glucose oxidase (GOx)-mediated oxidation and leucomalachite green (LMG) signal amplification (Fig. 3e). The GMXeP SERS platform achieved a detection limit of 0.39 μM with a linear response range of 1–50 μM. Tear glucose levels measured using this platform showed a strong correlation with BG values (Fig. 3f), reinforcing its clinical potential. Mirzajani et al. (2022) developed a SCL platform for tear glucose monitoring, integrating a femtosecond laser-patterned NFC antenna, an NFC chip, and an electrochemical glucose sensor (Fig. 3g). The device exhibited excellent selectivity toward glucose over interfering analytes such as urea, sucrose, ascorbic acid, and glycine, and demonstrated a linear detection range from 0.2 to 1 mM with a detection limit of 66 μM (Fig. 3h). Stability testing in artificial tear fluid confirmed consistent performance for up to 16 h (Fig. 3i). In spike-and-recovery experiments, the SCL accurately quantified glucose concentrations, supporting its potential for continuous, real-time tear glucose monitoring using smartphone integration.

Park et al. (2024) investigated the correlation between tear glucose (TG) and BG using a wireless SCL platform across multiple species, including humans, rabbits, and beagles (Fig. 4a). The study demonstrated a strong correlation between TG and BG levels, with Pearson correlation coefficients ranging from 0.924 to 0.97 across all subjects. In normal rabbits, fasting TG and BG levels were approximately 0.45–0.48 mM and 6.21 mM, respectively. Following glucose administration, TG rose to ~1.059 mM and BG peaked at ~11.04 mM. In diabetic rabbits, both baseline and peak levels were elevated—fasting TG and BG were 1.434 mM and 16.32 mM, rising to 2.755 mM and 29.89 mM post-glucose intake (Fig. 4b). Similar trends were observed in human participants. In healthy individuals, fasting BG ranged from 5.05 to 5.83 mM and increased to 9.16–9.44 mM after glucose intake, while TG levels rose from 0.329–0.379 mM to 0.573–0.621 mM. Diabetic participants exhibited slightly elevated fasting values (BG: 6.01–6.63 mM; TG: 0.432–0.474 mM), reaching maximum post-intake levels of 9.21–9.55 mM and 0.57–0.576 mM, respectively. Correlation analysis for representative healthy and diabetic individuals showed Pearson's coefficients of 0.97 and 0.95, confirming a strong linear relationship between TG and BG (Fig. 4c). Parkes Error Grid analysis confirmed the clinical reliability of TG-based readings, with all values falling within zones A and B, denoting acceptable accuracy for glucose monitoring (Fig. 4d). These results support the feasibility of wireless SCLs for non-invasive, real-time glucose monitoring.

In a related study, Han et al. (2023) developed a long-term stable wireless SCL system incorporating hyaluronate-modified Au@Pt bimetallic electrodes (Fig. 4e). In rabbit models, the device showed a strong correlation with BG measurements ($\rho = 0.88$) and achieved 98.6 % of values within the clinically acceptable A and B zones of the Clarke Error Grid (Fig. 4f). Comparative performance analysis showed the SCL performed similarly to commercial glucometers and CGMs, with an estimated lag time of ~10 min between TG and BG levels (Fig. 4g). The device remained stable and sensitive for up to three weeks, confirming its potential for long-term non-invasive glucose monitoring. Duijvestijn et al. (2021) conducted a pilot study evaluating the NovioSense tear glucose biosensor in 24 patients with type 1 diabetes. While TG values were consistently lower than BG, application of a neural network regression model allowed conversion of TG to BG equivalents with improved accuracy. After AI-based calibration, 99.7 % of the data fell within the clinically acceptable A + B regions of the Clarke Error Grid

Tabel 6
Clinical trials and NRT – ROBINS-I.[18].

Author, Year	Confounding	Selection Bias	Classification of Interventions	Measurement of Outcomes	Missing Data	Selection of Reported Results	Overall risk
Kownaeka, 2018 (Kownacka et al., 2018)	Low Risk	Moderate Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low risk
Mirzajani, 2022 (Mirzajani et al., 2022)	Moderate Risk	Low Risk	Low Risk	Low Risk	Moderate Risk	Low-Moderate Risk	Moderate risk
Duijvestijn, 2021 (Duijvestijn et al., 2021)	Moderate Risk	Low Risk	Low Risk	Moderate Risk	Low Risk	Moderate Risk	Moderate risk

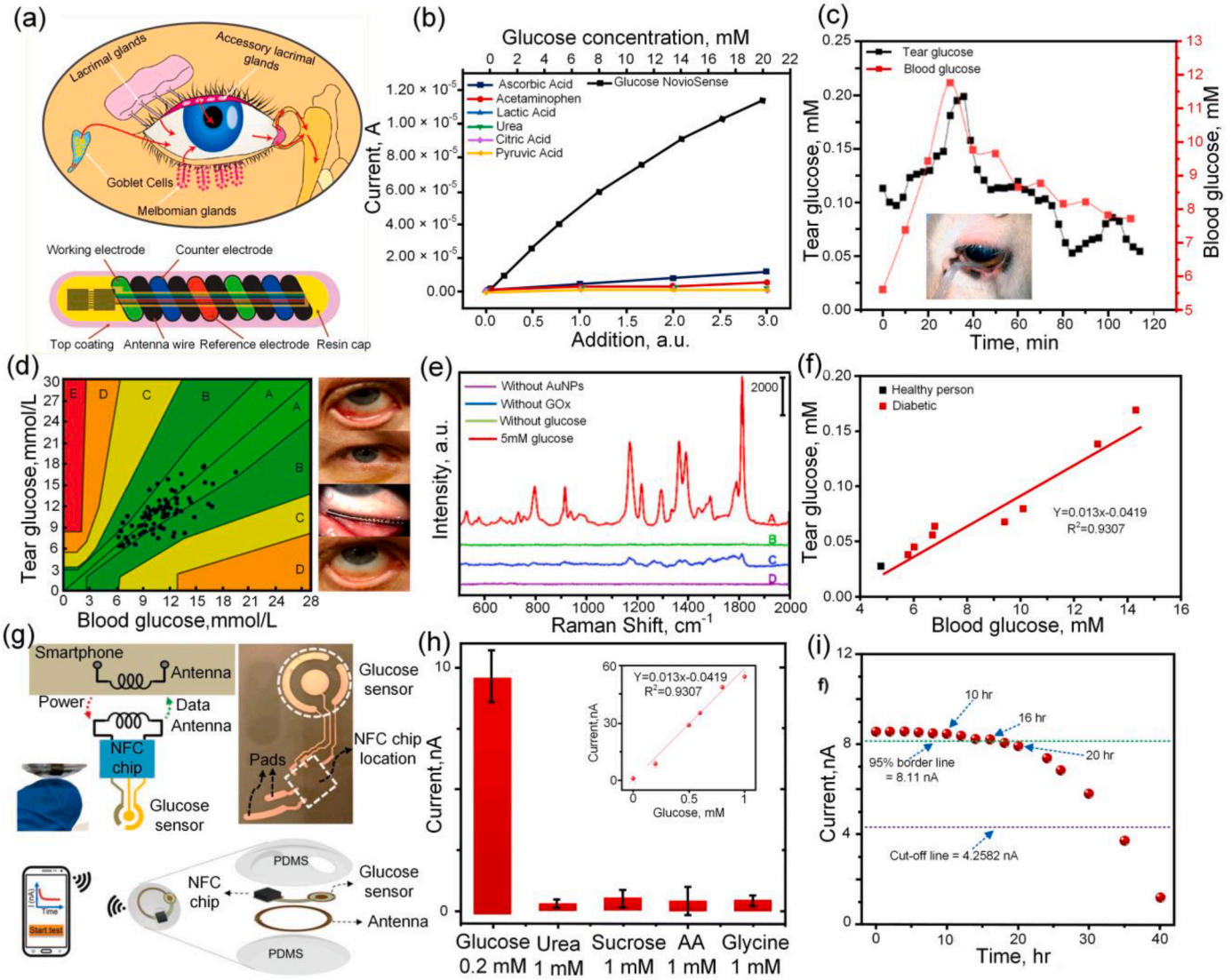

Fig. 3. Smart contact lens systems and analytical performance for tear glucose sensing. (a) Illustration showing the tear fluid production and electronic components of the final glucose monitoring device. (b) The NovioSense device responds to interferences and glucose. (c) A graph of glucose concentration vs time of the trial, where a clear correlation and glucose fluctuation pattern are visible. (d) Clinical comparison of the data acquired from clinical subjects wearing the NovioSense tear glucose sensor vs the FreeStyle Libre, Abbot, Reproduced with permission from Ref. (Kownacka et al., 2018), 2018, American Chemical Society. (e) SERS spectra of LMG. (f) Correlation between tear and BG concentration in normal persons and diabetics, Reproduced with permission from Ref. (Cui et al., 2022), 2022, Elsevier. (g) System-level integration of the proposed antenna and circuit diagram and used for the passive communication mode of the SCL. (h) Selectivity test of the glucose sensor to different interfering molecules and their comparison with the sensor response to 0.2 mM of glucose. (i) Stability test of the glucose sensor after 40h storage in an artificial tear solution, Reproduced with permission from Ref. (Mirzajani et al., 2022), 2022, Wiley.

(Fig. 4j). The sensor met ±15 mg/dL (±15 %) accuracy criteria for 80 % of measurements, with a MARD of 16.7 % and a median absolute relative difference (MedARD) of 13.3 %. Accuracy levels on the first day of use were comparable to those of the Abbott FreeStyle Libre CGM, supporting the feasibility of tear-based glucose monitoring as a viable non-invasive alternative.

Chu et al. (2011) designed and fabricated soft contact lens (CL) biosensors for *in situ* tear glucose monitoring as a non-invasive alternative to conventional BG testing (Fig. 5a). The biosensor was constructed using biocompatible materials, including polydimethylsiloxane (PDMS) and 2-methacryloyloxyethyl phosphorylcholine (MPC) polymer, and incorporated a flexible platinum working electrode and a silver/silver chloride (Ag/AgCl) reference electrode. These were functionalized with glucose oxidase (GOD) to enable selective glucose detection. *In vitro* assessments demonstrated excellent linearity between glucose concentration and output current (R^2 = 0.999) over the physiologically relevant range of 0.03–5.0 mM, encompassing both normoglycemic and diabetic tear glucose levels. *In vivo* testing on a rabbit eye estimated a basal tear glucose concentration of approximately 0.11 mM (Fig. 5b). During an oral glucose tolerance test, tear glucose levels lagged BG by approximately 10 min, peaking at 0.61 mM before gradually returning to baseline. The CL biosensor exhibited favorable stability, wearability, and responsiveness, highlighting its potential for real-time, non-invasive glucose monitoring. Future developments may focus on integrating wireless telemetry to support seamless continuous glucose tracking in daily life.

Kim et al. (2017) advanced this concept by engineering a multifunctional SCL system capable of simultaneously monitoring glucose concentration in tears and diurnal intraocular pressure (IOP) variation (Fig. 5c). Glucose sensing was achieved using a graphene-based field-effect transistor (FET) functionalized with glucose oxidase, providing highly sensitive, real-time detection (Fig. 5d and e). The device was

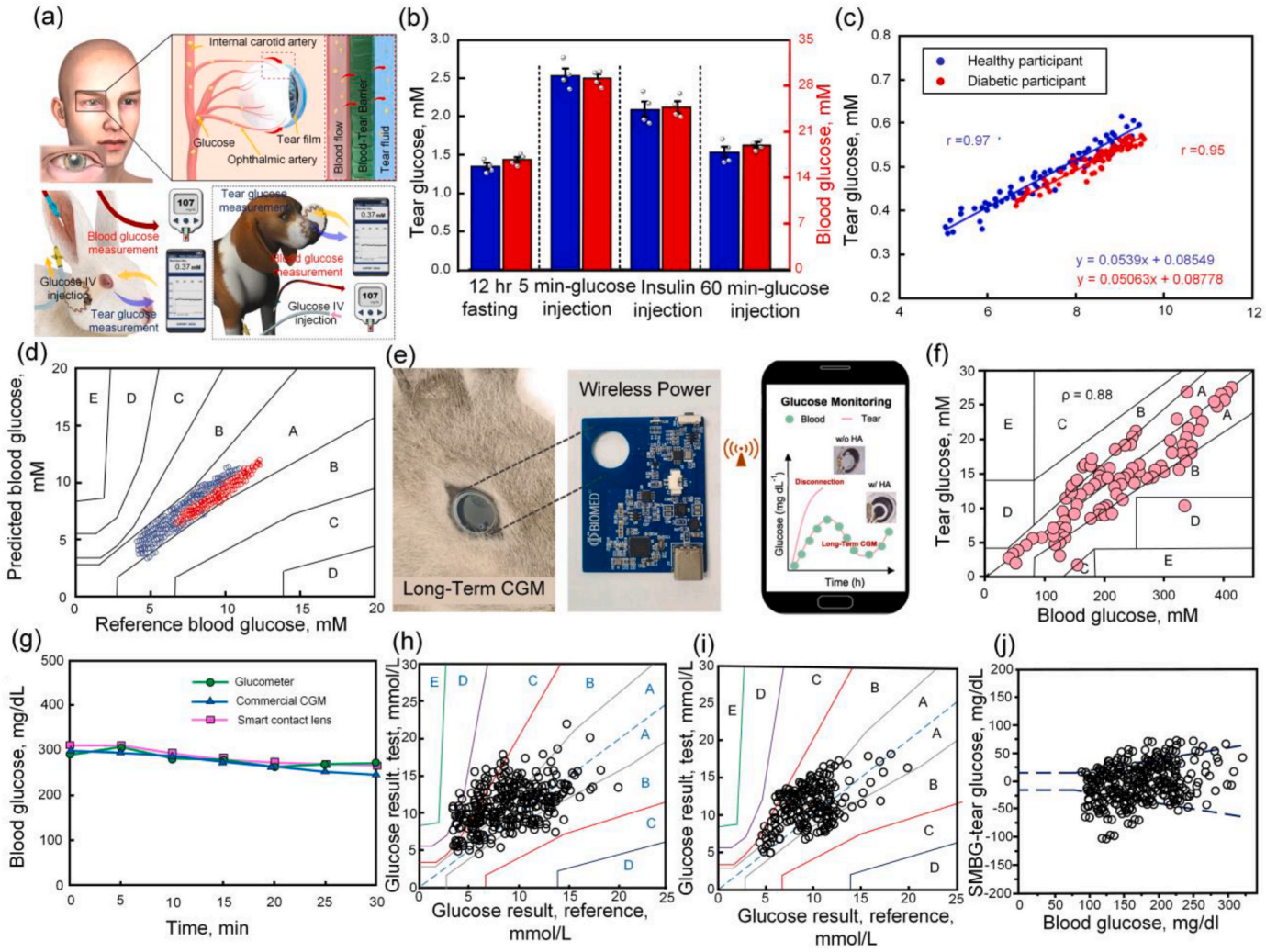

Fig. 4. TG monitoring relative to BG levels using animal models, human subjects, and smart contact lens systems. (a) Schematic illustration of plasma leakage in human eyes. Red arrows indicate the leakage of glucose from the blood into the tear. The rabbit and beagle model for TG and BG measurement. (b) Comparison between the average of TG and BG in four normal beagles before and after injection of glucose, and the error bars indicate mean ± standard error of the mean. (c) Comprehensive Pearson's correlation analysis of four normal beagles and four diabetic beagles. (d) Comprehensive Parkes Error Grid analysis of ten healthy participants and ten diabetic participants, Reproduced with permission from Ref. (Park et al., 2024), 2024, Nature. (d) In vivo CGM of smart contact lens with the hyaluronated Au@Pt bimetallic electrodes for long-term stability via the wireless power and communication system. (f) Clark error grid analysis for the blood and the tear glucose levels for 40 min. (g) CGM with a glucometer, a commercial CGM patch, and our smart contact lens for 30 min, Reproduced with permission from Ref. (Han et al., 2023), 2023, Elsevier. (h) Error grid using previously published algorithm for the tear-to-BG concentration. (i) Error grids produced from the neural network regression model. (j) Analysis of NovioSense data versus BG data following ISO 15197:2013 standard, Reproduced with permission from Ref. (Duijvestijn et al., 2021), 2020, Sage.

validated *in vivo* in rabbit models, demonstrating effective wireless tear glucose measurement. In parallel, IOP monitoring was accomplished via a capacitive-inductive circuit integrated into the lens; pressure-induced shifts in resonance frequency enabled non-invasive and wireless IOP assessment. Validation studies conducted on ex vivo bovine eyes confirmed the reliability of this approach (Fig. 5f). The hybrid sensor platform-comprising graphene and silver nanowires-achieved >91 % optical transparency and high mechanical stretchability, ensuring wearer comfort and unobstructed vision. This dual-function device represents a promising alternative to traditional finger-prick glucose assays and hospital-based tonometry, offering a comprehensive, user-friendly platform for long-term ocular and metabolic health management, as well as for other conditions such as glaucoma management.

In another study, Keum et al. (2020) developed a next-generation smart contact lens capable of both CGM and on-demand drug delivery for the treatment of diabetic retinopathy (Fig. 5g). Fabricated from a biocompatible hydrogel, the lens integrates ultrathin stretchable circuits, a microcontroller, biosensors, a drug delivery module, and wireless power and data communication systems. *In vivo* experiments in diabetic rabbit models demonstrated accurate tear glucose monitoring, with strong correlation to conventional BG measurements (Fig. 5h). Additionally, the lens enabled controlled drug release directly to the ocular surface. The device retained functional stability after storage for up to 63 days, maintaining consistent performance across repeated measurements (Fig. 5i). These findings establish the feasibility of SCLs as a platform for continuous diabetic monitoring and personalized therapy, potentially transforming the clinical management of diabetes and its ocular complications.

Across these studies, varying degrees of correlation have been observed between tear glucose concentrations and the gold-standard BG measurements. The coefficient of determination (R^2), which quantifies the strength of this relationship, was reported to range from 0.8729 to 0.9982, indicating a consistently strong positive correlation (Wang and Feng, 2025; Tricoli et al., 2017; Bordbar et al., 2023; Zhang et al., 2024).

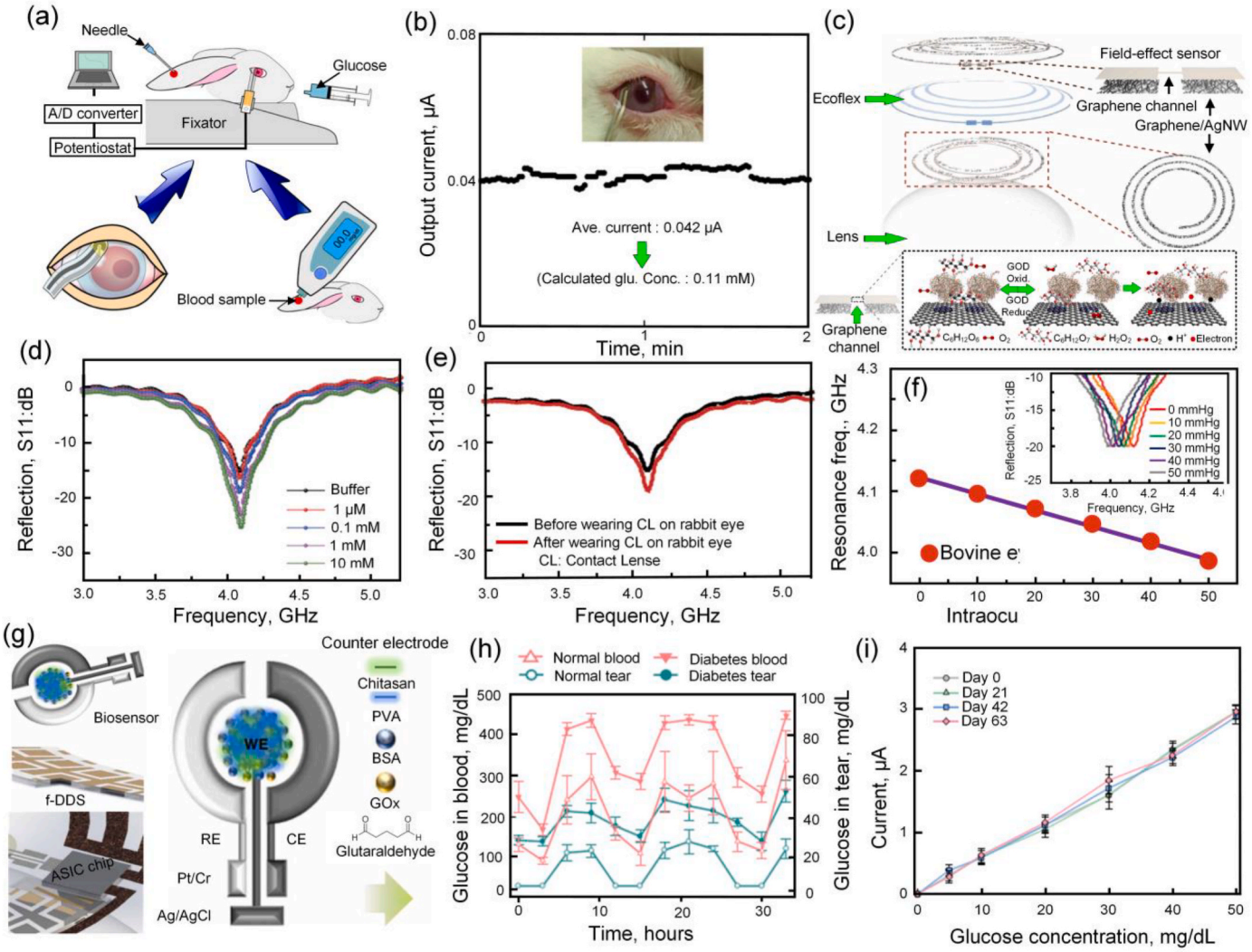

Fig. 5. Representative studies demonstrating the development and application of SCL biosensors for non-invasive glucose monitoring and intraocular pressure sensing. (a) Measurement method of tear glucose concentration with the CL biosensor. (b) Tear glucose monitoring using the CL biosensor on eye site, Reproduced with permission from Ref. (Chu et al., 2011), 2011, Elsevier. (c) Schematic of the wearable contact lens sensor, integrating the glucose sensor and intraocular pressure sensor. (d) Wireless monitoring of glucose concentrations from 1 mM to 10 mM. (e) Wireless sensing curves of glucose concentration before and after wearing contact lens on an eye of live rabbit. (f) Frequency response of the intraocular pressure sensor on the bovine eye from 5 mm Hg to 50 mmHg. (Inset: the corresponding reflection coefficients of the sensor), Reproduced with permission from Ref. (Kim et al., 2017), 2017, Nature. (g) Schematic illustration of an ocular glucose sensor with three electrodes (WE, working electrode; RE, reference electrode; CE, counter electrode). (h) Correlation between blood and tear glucose levels in normal and diabetic rabbit models. (i) The long-term stability of the glucose sensor after storage for 0, 21, 42, and 63 days (n = 3), Reproduced with permission from Ref. (Keum et al., 2020), 2020, Science.

Another key metric for evaluating sensor accuracy is the MARD, where lower values reflect higher accuracy. For instance, a MARD of 12.5 % (Fengade et al., 2025) suggests good concordance with reference values, while a MARD of 16.7 % (Gonçalves et al., 2024) indicates relatively greater variability. Clinical accuracy was further assessed using Clarke or consensus error grid analysis, which classifies results into zones based on the clinical significance of measurement errors. Data falling within zones A and B, indicating either clinically accurate or benignly inaccurate readings, are considered acceptable. Selected studies reported 95 % (Fengade et al., 2025), 98 % (Vadia et al., 2025), and 99.7 % (Gonçalves et al., 2024) of data points within zones A + B, underscoring the clinical reliability of tear-based glucose sensing. Additionally, several investigations (Manzoni et al., 2025; Vadia et al., 2025; Tricoli et al., 2017; Zhang et al., 2024) reported a physiological time lag between changes in blood and tear glucose levels, typically ranging from 5 to 10 min. This lag is attributed to the natural delay in glucose diffusion from the bloodstream into the tear film and must be considered in the context of real-time monitoring applications.

4.1. Overall correlation strength and variability

Across the 12 included studies, TG–BG correlation coefficients ranged from 0.87 to 0.998, indicating consistently strong linear relationships. However, the magnitude of correlation varied depending on study design, population (diabetic vs. non-diabetic), and detection platform. For example, Park et al. (2024) and Han et al. (2023) achieved R^2 values > 0.94 in multi-species testing using integrated NFC SCL platforms, while Lane et al. (2006) reported lower correlations (R^2 = 0.90) in human cohort studies with non-integrated tear sampling. This variability highlights the influence of both device design and sampling methodology on reported accuracy.

4.2. Physiological lag and calibration challenges

A recurrent finding across studies was a 5–10-min lag between changes in BG and TG levels, attributable to glucose diffusion dynamics into the tear film. While some platforms incorporated algorithmic lag correction (Park et al., 2024), others did not, potentially reducing real-time decision-making accuracy. Addressing this lag through predictive algorithms and adaptive calibration remains essential for clinical adoption, as even short delays can influence insulin dosing decisions.

4.3. Implications for clinical translation

Error grid analyses consistently showed >95 % of readings within clinically acceptable zones (A + B), with MARD values as low as 12.5 % (Guyatt et al., 2008). These metrics approach ISO 15197:2013 criteria for BG monitoring devices but still fall short of gold-standard invasive CGM systems in some cases. For clinical translation, further validation is needed in large, diverse human cohorts, under variable environmental and physiological conditions, and over extended wear periods. Additionally, user comfort and biocompatibility data, while encouraging, remain limited to small trials.

5. Microfluidic design and sample handling in smart contact lenses

Microfluidic systems embedded in SCLs are essential for controlled tear fluid sampling and delivery to the sensing interface, enabling accurate, real-time biomarker monitoring. While sensing elements and wireless communication modules are often highlighted, the microfluidic component guides how efficiently a device collects, transports, and refreshes analytes, directly impacting sensor performance and wearer comfort. The microchannel network must maintain a steady flow of representative tear samples while preserving optical clarity and oxygen permeability. Typical channel dimensions range from 50 to 200 μm in width and 10–50 μm in depth, allowing passive, capillary-driven flow without the need for pumps (Yao et al., 2011; Kim et al., 2019). Geometries such as radial channels efficiently move fluid from the periphery to central sensing zones, whereas serpentine patterns can increase analyte–sensor interaction time. Computational fluid dynamics is often used to optimize channel design, minimize dead zones, and ensure unidirectional flow under dynamic blinking conditions (Yazhini and Sreeja, 2025).

Fabrication methods for these delicate structures must combine precision, transparency, and biocompatibility. Soft lithography in polydimethylsiloxane (PDMS) offers flexibility and oxygen permeability, though surface treatments are required to enhance wettability (McDonald and Whitesides, 2002). Laser micromachining enables direct patterning of channels into polymeric lens materials such as poly (methyl methacrylate) or silicone hydrogels (He et al., 2025). Photopolymerization, including stereolithography, allows the fabrication of complex three-dimensional microfluidics in transparent, biocompatible hydrogels like polyethylene glycol diacrylate (PEGDA) (Xu et al., 2025). More recently, printing technologies such as inkjet and aerosol jet printing have been explored for simultaneous deposition of microchannels and conductive sensor traces (Bappy et al., 2025). Material selection is also critical for both the lens body and the microchannels. Silicone hydrogels are common for the base lens due to high oxygen transmissibility, while PDMS, PEGDA, cyclic olefin copolymer, and PMMA are used for microfluidics (Adrus et al., 2025). Surface chemistry strongly influences fluid handling; hydrophilic modifications via oxygen plasma, UV/ozone exposure, or polyethylene glycol grafting improve tear wicking and reduce biofouling. Micro- or nano-textured surfaces can further promote capillary uptake from the tear meniscus.

Tear fluid sampling is typically passive, driven by capillary forces through hydrophilic channels, with the eyelid blink cycle aiding replenishment (Li et al., 2022). Inlet placement at the lens periphery, where tear flow is most active, can enhance capture efficiency. Continuous sample refreshment is crucial for tracking dynamic biomarkers, and natural tear turnover rates of 0.5–2.2 μL/min generally provide adequate exchange (Kuruvinashetti et al., 2025). Channel designs often minimize dead volume and incorporate passive flow-directing features to prevent backflow. Microporous membranes are sometimes used to admit target molecules while blocking proteins and particulates, thereby reducing fouling (Lee et al., 2021).

The integration of microfluidics with the sensing interface requires precise alignment to ensure stable analyte delivery and maintain optical or electrochemical signal quality. Low-power designs that optimize channel geometry for intermittent sensing are increasingly attractive for energy-limited devices. Although challenges remain in consistent sampling under varying environmental conditions and in scalable manufacturing, advances in materials, fabrication, and biomimetic flow control hold promise for improving both the reliability and comfort of microfluidic-enabled SCLs.

6. Current challenges and future directions

Contact lens–based glucose monitoring represents a promising, noninvasive approach to continuously track glucose levels, especially for people with diabetes. By measuring glucose concentrations in tear fluid, these smart lenses offer an alternative to traditional finger-prick blood testing, potentially improving patient comfort and compliance. Despite significant progress in sensor development, material integration, and wireless data transmission, several critical challenges remain before these devices can be reliably used in clinical or daily settings.

A primary hurdle is achieving consistent and accurate correlation between tear glucose and blood glucose levels. Tear glucose concentrations are typically much lower than those in blood, often in the micromolar range, which demands highly sensitive and selective detection methods. Additionally, tear glucose levels can be influenced by factors such as reflex tearing, ocular surface irritation, and tear evaporation, which introduce variability in measurements. These physiological and environmental influences complicate the calibration process and call for improved understanding of the relationship between tear and blood glucose dynamics. Selectivity is another significant challenge, as tear fluid contains a complex mixture of biomolecules—including lactate, urea, and proteins—that can interfere with glucose sensing. Environmental factors such as temperature fluctuations, pH changes, and exposure to cosmetics or eye drops further complicate the detection environment. Developing sensor surfaces and coatings that minimize nonspecific adsorption and fouling is essential to maintain accuracy and long-term stability of the sensing element.

The mechanical and chemical stability of the sensor components within the contact lens environment is also critical. The device must endure repeated blinking, hydration and dehydration cycles, and mechanical stresses without degradation in performance. Integrating reliable, biocompatible power sources—such as wireless energy harvesting, photovoltaic elements, or enzymatic biofuel cells—into the lens structure without compromising comfort, oxygen permeability, or transparency remains a demanding engineering challenge. User safety and comfort are paramount considerations in lens design. All materials and embedded electronics must be non-toxic, breathable, and compatible with ocular tissues to prevent irritation, hypoxia, or adverse immune responses. Ensuring that sensing components do not obstruct vision or affect lens flexibility is vital to wearer acceptance. Moreover, smart contact lenses require seamless wireless data transmission to external devices like smartphones or monitoring systems. This necessitates low-energy communication protocols that maintain signal integrity while safeguarding patient privacy and data security.

Looking ahead, advances in material science are expected to drive improvements in sensor sensitivity and biocompatibility. The incorporation of nanostructured materials, such as graphene or plasmonic nanoparticles, promises enhanced detection capabilities without

sacrificing optical clarity. Parallel innovations in microfluidic engineering, biofouling-resistant coatings, and wireless power harvesting will enable lenses capable of long-term, continuous operation in daily life. Multifunctional systems combining glucose sensing with other biomarkers (such as lactate or intraocular pressure) and drug-delivery modules represent a compelling direction toward holistic ocular and metabolic health management. Artificial intelligence and machine learning will likely play a key role in processing sensor data, enabling personalized calibration, noise filtering, and predictive analytics that account for individual physiological variability and environmental conditions. To achieve reliable clinical translation, extensive validation through large-scale trials and alignment with international regulatory frameworks will be essential.

From a translational and equity perspective, non-invasive, wireless, and portable smart lenses could also improve access to diabetes monitoring in underserved populations, including Aboriginal and Torres Strait Islander communities in remote Australia. Future implementation should prioritise community-informed design to ensure usability, cultural appropriateness, and equitable healthcare outcomes.

7. Summary and conclusion

This review uniquely integrates nanosensor-embedded and NFC-enabled SCLs with analytical performance metrics and clinical applicability, providing a translational perspective. In addition, we highlight equity considerations, apply systematic quality assessment tools, and expand the discussion to multifunctional applications such as intraocular pressure monitoring and ocular drug delivery. Across the reviewed studies, there was strong evidence supporting the correlation between tear and BG levels, with high clinical accuracy and minimal user discomfort. The integration of nanosensor technologies and NFC-enabled systems has enabled real-time, wireless, and user-friendly glucose monitoring. Despite small sample sizes and the early-stage development of some devices, the reviewed technologies consistently showed acceptable accuracy metrics (e.g., R^2 values up to 0.998 and MARD as low as 12.5 %). Additionally, the clinical reliability of these devices was supported by error grid analyses, with most results falling within acceptable zones for medical decision-making. The implications of these technologies are particularly significant for remote and underserved populations, such as ATSI communities, where access to conventional diabetes care is limited. Tear-based monitoring systems offer a non-invasive, portable, and more accessible option that may improve compliance, patient comfort, and long-term health outcomes. Further research is needed to validate these devices in larger, more diverse populations and in real-world settings. Standardization of TG measurement protocols, calibration algorithms to account for inter-individual variability and lag time, and long-term performance assessments will be essential to translate this innovation into clinical practice.

CRediT authorship contribution statement

Jacquelyn Yazdani: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Kamal Mafatia:** Writing – original draft, Conceptualization. **Md. Harun-Or-Rashid:** Writing – review & editing, Writing – original draft, Visualization. **James Jabbour:** Writing – review & editing, Writing – original draft. **Veronica Preda:** Writing – review & editing, Validation, Supervision, Conceptualization. **Noushin Nasiri:** Writing – review & editing, Validation, Supervision, Methodology, Funding acquisition, Conceptualization.

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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Data availability

No data was used for the research described in the article.

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