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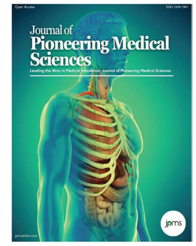

Advancements in Non-Invasive Blood Glucose Monitoring Using Near-Infrared Spectroscopy: A Systematic Review

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Abstract Non-invasive blood glucose monitoring offers pain-free and patient-friendly alternatives to invasive finger-prick testing and minimally invasive Continuous Glucose Monitoring (CGM). Among optical modalities, Near-InfraRed (NIR) Spectroscopy (NIRS) has attracted particular interest because it can probe glucose-related absorbance and scattering features in tissue while remaining compatible with compact, low-cost hardware. This systematic review synthesises developments in NIRS-based non-invasive blood glucose monitoring between 2019 and 2025. Major scientific databases (Scopus, PubMed, Web of Science, IEEE Xplore and ScienceDirect) were searched according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and 16 studies met the inclusion criteria. The included works span laboratory-grade spectrometers, fiber- and free-space optical systems and light-Emitting Diode (LED)-photodiode sensor modules in transmittance, reflectance and interactance configurations, together with chemometric and machine-learning models for calibration. Across these studies, correlation coefficients between NIRS-based estimates and reference glucometers generally ranged from about 0.85 to 0.95, with Root Mean Square Error (RMSE) and Root Mean Square Error of Prediction (RMSEP) values typically between 12 and 25 mg/dL. Clarke Error Grid (CEG) analyses most often placed 85-95% of predictions in Zone A and the remainder mainly in Zone B, indicating clinically acceptable performance under controlled conditions. Recent trends include multi-wavelength NIR sources, LED-based hardware, multimodal sensing and advanced modelling approaches. However, accuracy frequently degrades across subjects, anatomical sites and free-living conditions and no NIRS-based system has yet obtained regulatory approval for insulin-dosing decisions. Overall, NIRS appears most suitable at present as an adjunct for trend tracking and alerts rather than a full replacement for invasive methods and future progress will require larger, more diverse clinical studies and the translation of spectroscopic and machine-learning advances into practical, low-cost reflective NIR sensor platforms.

Key Words Non-Invasive Glucose Monitoring, Near-Infrared Spectroscopy, Chemometrics, Machine Learning, Wearable devices, Diabetes Management

INTRODUCTION

Diabetes mellitus is one of the most serious global health challenges and regular self-monitoring of blood glucose is essential to prevent both acute and chronic complications [1]. Recent global estimates from the International Diabetes Federation (IDF) Diabetes Atlas highlight the growing prevalence of diabetes worldwide [2] and long-term projections indicate a substantial increase in future disease burden, reinforcing the need for scalable and patient-friendly monitoring solutions [3]. Although conventional capillary finger-prick testing is clinically established, it is invasive, inconvenient and costly in terms of consumables. As a result, adherence is frequently suboptimal and there is a long-standing need for reliable non-invasive products, including optical sensing solutions such as infrared (IR) spectroscopy.

Infrared (IR) spectroscopy measures molecular vibrational signatures and spans the Near-Infrared (NIR), Mid-Infrared (MIR) and Far-Infrared (FIR) regions of the electromagnetic spectrum [4]. Each spectral region presents specific trade-offs. NIR benefits from deeper penetration and compatibility with compact light sources but suffers from strong scattering and overlapping absorbance bands; MIR offers more distinct molecular fingerprints but is limited by higher water absorption and reduced penetration depth in tissue [4,5].

These trade-offs help explain why NIR has become the most widely explored optical choice for non-invasive glucose devices despite its analytical limitations. Recent engineering advances have improved feasibility through sensor miniaturisation, early wearable integrations and more sophisticated signal-processing and machine-learning pipelines, with several prototypes targeting continuous monitoring. At the same time, clinical studies stress the impact of personal physiology and environmental conditions, highlighting the need for rigorous calibration, drift control and validation in diverse populations [6].

Recent literature on NIR-based glucose monitoring spans: (i) Supervised learning to enhance NIR spectral predictions as Huber regression and shallow neural networks, (ii) Data-fusion frameworks integrating NIR with other modalities such as millimetre-wave signals to boost sensitivity and (iii) Portable or handheld prototypes that validate non-invasive estimates against reference glucometers [7,8].

Beyond NIR, Raman spectroscopy has also been investigated for non-invasive glucose monitoring because it provides highly specific molecular information; however, Raman signals are weak and can be susceptible to fluorescence background and motion artefacts, which complicate robust *in vivo* deployment [9]. In addition to optical techniques, electromagnetic modalities as microwave/millimeter-wave, have been explored and hybrid approaches can improve robustness by leveraging complementary signal mechanisms [10,11]. Given the balance of feasibility, penetration depth, cost and existing evidence, this review focuses on NIRS as a leading optical pathway toward practical non-invasive monitoring [5,12].

Although many studies report strong correlations and clinically acceptable error metrics, persistent issues remain, including calibration stability over time, inter-site and inter-subject variability and the cost and complexity of instrumentation. Experiences from commercial and regulatory pathways reinforce this picture. For instance, devices based on Advanced Glycation End-product (AGE) fluorescence have received approval for diabetes screening but not for real-time monitoring of glycaemic variability, underscoring the gap between screening tools and devices suitable for insulin dosing [13].

In vivo NIR accuracy is further constrained by several factors: water and other chromophores absorb significant fractions of the incident light, reducing signal-to-noise ratio; layered skin structure as (stratum corneum, epidermis, dermis) affects optical path and sampling depth; physiological variability (hydration, temperature, perfusion, skin pigmentation and thickness) introduces noise that is not specific to glucose and instrument drift reduces model stability over days to months [13,14]. Mitigation strategies include optimisation of the measurement site and effective optical pathlengths, robust pre-processing and advanced calibration methods such as Piecewise Direct Standardisation (PDS) and Partial Least Squares Regression (PLSR).

Despite these advances, there is still limited evidence on practical, low-cost NIRS systems that use compact reflective sensor modules and can be implemented in user-friendly devices for routine self-monitoring. Most published prototypes rely on laboratory-grade spectrometers, broadband sources or complex optical benches, which are not suitable for widespread deployment. This systematic review, therefore, focuses on recent NIRS-based non-invasive glucose monitoring approaches and highlights design choices, performance trends and remaining challenges that directly inform the development of low-cost reflective NIR sensor systems such as those targeted in our ongoing work.

Existing reviews on non-invasive or optical glucose monitoring have provided valuable overviews of invasive, minimally invasive and non-invasive modalities and have occasionally included NIRS-based approaches alongside MIR, Raman and other techniques [5,15,16]. However, most of these reviews either: (i) Aggregate multiple optical modalities without focusing specifically on NIRS, (ii) Emphasise chemometric algorithms while providing limited detail on optical and hardware design or (iii) Predate the recent wave of compact, low-cost reflective NIR sensor modules and wearable-oriented prototypes that has emerged from around 2018 onwards [5,16]. Consequently, there is still no systematic review that concentrates exclusively on *in vivo* NIRS-based non-invasive glucose monitoring between 2019 and 2025, with a combined analysis of optical configurations, wavelength selection, sensor technologies, modelling strategies, validation protocols and real-world translational barriers. This gap motivates the present review.

Therefore, the objective of This systematic review focuses specifically on *in vivo* NIRS-based non-invasive blood glucose monitoring in the period 2019-2025, synthesising evidence on optical configurations, sensor technologies, modelling strategies and clinical validation and identifying gaps that motivate the development of low-cost, reflective NIR sensor systems.

LITERATURE REVIEW

Non-Invasive Glucose Monitoring Landscape

Although invasive capillary finger-prick testing and minimally invasive Continuous Glucose Monitoring remain the dominant clinical approaches for glycaemia monitoring, they are associated with cost, inconvenience and user burden [6,17,18]. Consequently, Non-Invasive Glucose Monitoring (NIGM) has long been described as a “holy grail” in diabetes care [5]. Over the past two decades, numerous optical and physiological modalities have been explored; however, translation to reliable real-world use has been repeatedly constrained by limited accuracy, calibration drift and confounding effects arising from tissue variability and environmental conditions [5,6,19].

Within vibrational spectroscopy, Near-Infrared (NIR) and Mid-Infrared (MIR) techniques are among the most extensively investigated [4,5,12]. Moderate associations between NIR-derived features and blood glucose concentration have been reported using multivariate and machine-learning models, yet performance often varies across individuals and measurement conditions [5,12]. Typical Mean Absolute Relative Difference (MARD) values of approximately 15-25% frequently fall short of standards- or regulatory-grade accuracy expectations [5,12]. In particular, ISO 15197:2013 and U.S. Food and Drug Administration (FDA) guidance for self-monitoring blood glucose systems commonly require that the large majority of paired results fall within tight, clinically defined error limits across the relevant glucose range [20,21]. Moreover, accuracy often degrades when models are transferred to unseen subjects or different environments, highlighting the persistent challenge of calibration transfer [5,12].

Indirect approaches that combine surrogate physiological signals-such as Photoplethysmography (PPG), skin temperature and electrodermal activity-with machine-learning models have also been proposed [19,22]. While some studies report encouraging short-term performance under controlled settings, these models may primarily capture glucose-related trends rather than absolute concentrations and their robustness can deteriorate during physiological perturbations such as exercise, stress and post-prandial dynamics [19,22].

Microwave and antenna-based sensing, which infers glucose changes via dielectric property variations, has likewise been investigated, including hybrid millimeter-wave/NIR schemes [10,11]. However, human evidence remains comparatively limited and performance is often not yet consistent at clinically acceptable levels [10,11]. Overall, despite advances in hardware design, signal processing, feature extraction and modelling, no NIGM modality has consistently met requirements for insulin-dosing decisions [5,19]. Notably, even minimally invasive CGM technologies required extensive iterative refinement over many years to reach clinically trusted performance, underscoring how demanding these standards are [17,18]. At present, NIGM approaches therefore appear most suitable as adjunctive tools for trend tracking, alerts and patient engagement rather than as replacements for invasive or minimally invasive reference methods [5,19].

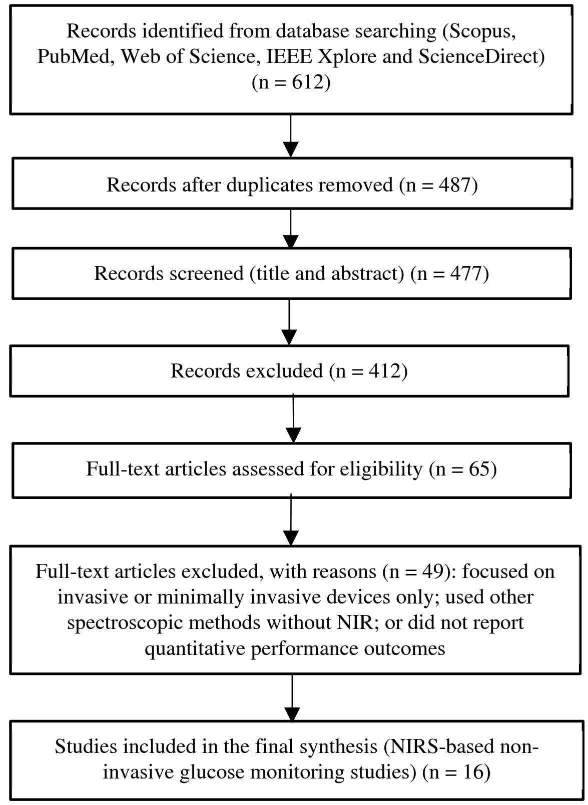

Figure 1: PRISMA 2020 Flow Diagram of the Study Selection Process for NIRS-Based Non-Invasive Glucose Monitoring

Infrared Radiation and NIR-Based Sensing

Infrared (IR) radiation occupies the portion of the electromagnetic spectrum between visible light and microwaves, with wavelengths between approximately 750 nm and 1000 μm (corresponding to frequencies from about 400 THz down to 300 GHz). In the electromagnetic spectrum, wavelength increases and frequency and photon energy decrease when moving from gamma rays to radio waves [23,24]. The position of IR within the spectrum is commonly illustrated in diagrams showing optical and thermal bands (Figure 1) and its thermal sensitivity underpins numerous engineering and medical applications. Infrared thermography, for example, has been used as a non-contact method for mapping surface temperature changes related to vascular activity, inflammation, tumours and musculoskeletal disorders.

IR is typically subdivided into NIR (700-2500 nm), MIR (2.5-25 μm) and FIR (25 μm^{-1} mm), each with distinct physical and chemical properties that determine its diagnostic and industrial applications. NIR is widely used in pharmaceutical and food analysis because water is relatively transparent in this region, whereas MIR offers sharp, characteristic absorption bands that are valuable for molecular fingerprinting. FIR has potential in fields such as astrophysics and medical imaging but strong water absorption and technological limitations have so far restricted its use [25].

IR spectroscopy for glucose sensing usually operates in three modes: transmittance, reflectance and interactance. Each mode is better suited to specific sample geometries, such as thin versus thick tissue. In this review, the main advantages and disadvantages of NIR spectroscopy for

Table 1: Advantages and Disadvantages of Near-Infrared (NIR) Spectroscopy for Glucose Sensing

NIR Spectroscopy	
Advantages	Disadvantages
Water is transparent in the NIR band	Heterogeneous distributions of glucose can give false readings.
Relatively low-cost materials needed.	Glucose concentrations are too low for accurate detection.
The signal intensity is directly proportional to the concentration of the analyte.	High scattering level
Minimum sample preparation required.	Problems of selectivity for the determination of glucose.
The method also works in the presence of interfering substances, such as glass or plastic containers.	

glucose sensing are summarised in Table 1, including water transparency in the NIR band, relatively low-cost implementation, minimal sample preparation and direct proportionality between signal intensity and analyte concentration, contrasted with challenges such as heterogeneous glucose distribution, low analyte concentration, high scattering and limited selectivity in complex biological tissues [6,26].

Previous Research on Glucose Monitoring

Glucose biosensors have evolved into three major categories: invasive, minimally invasive and non-invasive methods. Invasive methods, which remain the clinical standard, rely on enzymatic or hexokinase-based reactions with blood samples obtained by finger-prick. Although accurate and reliable, they are painful, risk infection and provide only intermittent measurements [9].

Minimally invasive approaches, including subcutaneous implants and microstructures sampling methods as microneedles, aim to reduce pain and infection risk while providing more continuous information than finger-prick testing [6,16,27]. Nonetheless, sensor drift, foreign-body response and calibration requirements remain important challenges and long-term robustness can still be difficult to maintain in everyday use [17,18].

The most ambitious frontier is fully non-invasive strategies that use optical and electromagnetic techniques to avoid skin puncture. NIR has shown promise due to its capacity to correlate spectral absorption features with glucose levels, particularly when combined with advanced calibration algorithms and machine learning. However, its accuracy remains limited by tissue scattering, water absorption and inter-individual variability in skin and tissue properties [28]. Outside NIR, microwave sensors leveraging amplitude and resonance frequency changes and terahertz spectroscopy using Attenuated Total Reflection (ATR), have shown correlations with glucose changes in controlled protocols as oral glucose tolerance tests. Nonetheless, penetration depth, water absorption and environmental sensitivity continue to constrain these approaches.

In previous comparative analyses, (IN), (MIN) and (NIN) techniques were systematically compared in a comprehensive table that lists their year, technique, application, method, advantages and disadvantages. This comparison is retained here as Table 2, which provides an overview of IN, MIN and NIN approaches and highlights their clinical roles and constraints [29]. Within this classification, NIR-based non-invasive methods are emphasised as particularly attractive because they can combine optical sensing with machine learning in compact form factors. In the present review, this framework is used to position NIRS as the focus among non-invasive modalities.

As summarised in Table 2, invasive and minimally invasive techniques still dominate current clinical glucose monitoring, offering high analytical accuracy at the expense of pain, infection risk and consumable costs. Minimally invasive approaches such as CGM sensors, microneedles and wearable patches partially reduce discomfort and enable continuous monitoring but remain dependent on skin penetration, calibration and relatively high device cost. In contrast, non-invasive modalities-including NIR-based sensing, saliva and breath analysis, photonic sensors and other optical techniques- are highly attractive from a patient-comfort perspective, yet they continue to face challenges related to accuracy, robustness to environmental and physiological confounders and readiness for routine clinical deployment. This contrast underscores why non-invasive optical methods remain a major research focus despite the current dominance of invasive and minimally invasive technologies in practice.

METHODOLOGY OF LITERATURE SEARCH (PRISMA)

In accordance with the PRISMA 2020 guidelines for systematic reviews [39], the scope, eligibility criteria, search strategies, data extraction procedures and quality assessment methods were defined a priori in a review protocol. The objective of this review was to assess progress in NIRS-based non-invasive blood glucose monitoring in terms of optical techniques, analytical models and clinical validation [8].

A comprehensive literature search was conducted in five major databases: Scopus, PubMed, Web of Science, IEEE Xplore and ScienceDirect. These databases collectively cover biomedical, chemical and engineering research relevant to optical sensing technologies. The search was restricted to peer-reviewed publications from 2019 to 2025 to capture recent developments.

The search strategy combined keywords and Boolean operators such as non-invasive glucose monitoring, blood glucose detection, near-infrared spectroscopy, infrared sensors, machine learning and calibration, supplemented by

Table 2: Overview of Invasive (IN), Minimally Invasive (MIN) and Non-Invasive (NIN) Glucose Monitoring Techniques, Their Applications, Advantages and Limitations

No.	Year	Technique	Author	Application	Method	Advantages	Disadvantages
1	2019	Invasive	Gonzales *et al.* [6]	Fingerstick blood glucose monitoring	A needle is used to prick the finger to obtain a drop of blood, which is then placed on a test strip and inserted into a glucose meter.	Accurate results, simple and easy to use, quick results, portable, suitable for on-the-go monitoring.	Painful, uncomfortable, infection risk, costly test strips and reduces viable testing areas over time.
2	2019	Minimal Invasive	Bao *et al.* [30]	Continuous glucose monitoring (CGM) with a sensor	A sensor is placed under the skin to measure glucose levels in interstitial fluid, transmitting data to a monitoring device or smartphone.	Continuous data, real-time glucose readings, improve glucose control, alerts for hypoglycemia, suitable for daily management.	High cost, sensor discomfort, requires calibration, technical issues may arise and continuous data can be overwhelming.
3	2019	Non-Invasive	Heikenfeld *et al.* [31]	Optical coherence tomography for skin glucose sensing	Uses light waves to take cross-sectional images of the skin to detect glucose-related optical changes.	Non-invasive, no blood samples, continuous monitoring, high-resolution imaging, early detection of glucose fluctuations and lower risk than invasive methods.	Not ready for everyday use, accuracy issues, costly equipment, complex training required, accuracy affected by skin type and external conditions.
4	2020	Invasive	Rodrigues *et al.* [32]	Subcutaneous implantable glucose sensor	Implantation of a sensor under the skin for continuous glucose level monitoring via electrochemical detection.	Reliable, accurate, minimal calibration, low incidence of adverse reactions.	Invasive procedures, infection risk, may require replacements or surgeries over time.
5	2020	Minimal Invasive	Torizal *et al.* [33]	Micro Dialysis-based glucose monitoring	Uses a Micro Dialysis system to sample interstitial fluid and measure glucose with an enzymatic sensor.	Real-time, continuous feedback, high accuracy, minimal discomfort, lower infection risk.	Requires regular calibration, higher cost, complex setup, potential for skin irritation and slight delay in glucose readings.
6	2020	Non-Invasive	Saputra *et al.* [34]	Near-infrared spectroscopy for glucose monitoring	NIR spectroscopy analyses light reflected from the skin to measure glucose levels.	Non-invasive, continuous monitoring, no needles, user-friendly, reduces risk.	Requires refinement for accuracy, needs frequent calibration, variations in skin properties, high development and production costs.
7	2021	Invasive	Boselli *et al.* [35]	Implantable biohybrid Nano sensors for glucose sensing	Combines nanomaterials with biological components for glucose level detection in real-time.	Enhanced sensitivity, less invasive than traditional methods and integrates with digital health systems.	Potential immune responses, biological/environmental factors affecting stability, are costly and advanced manufacturing is needed.
8	2021	Minimal Invasive	Zhang *et al.* [27]	Microneedle-based glucose monitoring	Uses microneedles to collect interstitial fluid, analysed for glucose with a nanoscale biosensor.	Minimal pain, real-time monitoring, reduces infection risk, has high sensitivity and improves patient compliance.	High development costs, needs accurate calibration, potential skin irritation and requires advanced data analysis tools.
9	2021	Non-Invasive	Beduk *et al.* [36]	Breath analysis for non-invasive glucose measurement	Uses a biosensor to detect volatile organic compounds in breath samples related to glucose metabolism.	Non-invasive, no blood samples, simple and quick, potential for early glucose level detection and continuous monitoring potential.	Accuracy issues require advanced technology and calibration, breath composition is influenced by external factors and limited availability.
10	2022	Invasive	Zhang *et al.* [37]	Smart contact lens for continuous glucose monitoring	A smart contact lens detects glucose levels in tear fluid and transmits data to a mobile device.	Accurate glucose detection in tear fluid, real-time data, comfortable like regular lenses, encourages compliance.	Eye irritation, potential sensor/reliability issues, costly and limits accessibility.

Table 2: Continued

No.	Year	Technique	Author	Application	Method	Advantages	Disadvantages
11	2022	Minimal Invasive	Reddy *et al.* [16]	Wearable patch for interstitial fluid glucose sensing	A wearable patch with micro-needles samples interstitial fluid for glucose measurement, transmitting data wirelessly.	Accurate, precise, minimal pain, real-time monitoring, increased comfort, long-lasting accuracy.	High development costs, potential malfunctions, risk of skin irritation, require periodic calibration, limited availability.
12	2022	Non-Invasive	Reddy *et al.* [16]	Saliva-based glucose monitoring	Uses saliva samples with a biosensor for glucose detection, transmitting data to a mobile device.	Non-invasive, no finger pricks, easy sample collection, continuous glucose monitoring and user-friendly.	Requires further studies for accuracy, affected by diet and water, high initial costs and limited availability.
13	2023	Invasive	Shoaib *et al.* [29]	Intravascular glucose monitoring using Nano sensors	Nano sensors embedded in intravascular devices detect glucose levels by binding to glucose molecules.	High accuracy, real-time tracking, minimally invasive and improving patient comfort.	Potential immune reactions, challenges in technology development, infection risk and data storage issues.
14	2023	Minimal Invasive	Saha *et al.* [38]	Continuous glucose monitoring using microfluidics	Microfluidic devices sample interstitial fluid, integrated with glucose-sensitive enzymes for signal generation.	Accurate measurements, continuous monitoring, minimal discomfort, suitable for long-term use.	High development and production costs require calibration, enzyme degradation and potential skin irritation.
15	2023	Non-Invasive	Shajari *et al.* [22]	Photonic sensor for non-invasive glucose monitoring	A photonic sensor detects glucose levels through the skin by analysing light absorption changes.	Non-invasive, user-friendly, reduces pain, continuous monitoring and lower infection risk.	Accuracy issues require frequent calibration, is affected by skin conditions and hydration, expensive and not fully validated.

terms used in previous scoping reviews on optical glucose monitoring [5]. Reference lists of included articles and relevant reviews were also screened to identify additional eligible studies [39].

In accordance with the PRISMA 2020 guidelines for systematic reviews [37], this study applied explicit eligibility criteria. Studies were included if they met all of the following conditions: (i) Original experimental research on non-invasive blood glucose monitoring using near-infrared spectroscopy (NIRS) as the primary optical modality; (ii) *In vivo* measurements on human subjects (e.g., fingertip, earlobe or other peripheral tissue sites), excluding phantoms, tissue-mimicking materials, animal models and in vitro glucose solutions as primary evidence; (iii) Reporting of quantitative performance metrics for glucose estimation, such as correlation coefficients, RMSE/RMSEP, MARD and/or Clarke Error Grid analysis [40,41]; (iv) Publication between 2019 and 2025 to capture the most recent generation of compact NIR sensors, wearable systems and advanced modelling approaches [40] and (v) Full-text articles published in English in peer-reviewed journals or as full conference papers.

Titles and abstracts were screened independently by two reviewers to remove irrelevant records. Full texts of potentially eligible articles were then assessed against the inclusion criteria and disagreements were resolved by discussion with a third reviewer. The study selection process is summarised in a PRISMA flow diagram (Figure 1).

Data extraction captured: optical mode (transmittance, reflectance, interactance), wavelength range, sensor and detector type, modelling approach, sample size, reference method and reported performance metrics. Risk of bias was appraised narratively based on study design, validation strategy and clarity of reporting, following systematic review reporting best practices [39].

The study selection process followed the PRISMA guidelines and is summarised in a flow diagram showing the number of records identified, screened, excluded and finally included in the review (Figure 1).

RESULTS

The initial database search identified 612 records. After removing duplicates, 487 unique records remained. Reduce this to 477 records, which were screened by title and abstract. Of these, 412 were excluded because they did not directly address *in vivo* NIRS-based non-invasive glucose monitoring in humans. 65 full-text articles were assessed for eligibility and 49 were excluded for one or more of the following reasons: focus on invasive or minimally invasive approaches, use of other modalities without NIRS as a primary technique, in vitro or simulation-only studies without human validation or lack of relevant quantitative performance metrics. Ultimately, 16 studies published between 2019 and 2025 were included in the final qualitative synthesis.

Most studies employed diffuse reflectance at easily accessible anatomical sites such as the fingertip or earlobe, which are rich in capillary beds and convenient for repeated measurements [5,12]. Optical design and Monte Carlo-based modelling studies suggest that optimised source-detector geometry and wavelength selection can increase effective sampling depth and partially reduce surface scattering effects [42].

The wavelength ranges used across studies clustered mainly around 900-1100 nm and 1500-1700 nm, balancing penetration depth with glucose-related absorption features. Some systems employed broadband sources covering approximately 780-2500 nm to capture richer spectral information. While broadband spectra increase the number of useful features for modelling, they also raise calibration complexity and hardware cost [40].

Early work primarily relied on classical chemometric techniques, particularly Partial Least Squares Regression (PLSR), to build predictive models from spectral data [5,12]. More recently, deep learning, tree-based models and multimodal fusion of NIR with complementary signals as microwave/millimeter-wave, have been explored to improve robustness [10,11,40].

In line with PRISMA recommendations, all 16 included studies on *in vivo* NIRS-based non-invasive blood glucose monitoring were analysed in detail. These studies, published between 2019 and 2025, report quantitative performance metrics and span different NIR wavelength ranges, optical configurations, sensor implementations, modelling strategies and validation protocols. Collectively, they illustrate current design trade-offs between hardware complexity, signal processing and clinical performance. The main characteristics of these 16 studies are summarised in Table 3.

As summarised in Table 3, the 16 selected NIRS-based studies published between 2019 and 2025 are predominantly experimental *in vivo* investigations, with one in vitro multimodal study and two spectroscopy-focused review articles. Most systems employ reflective NIR configurations within the 800-2500 nm range and increasingly incorporate advanced machine-learning models to improve prediction accuracy. Overall, these studies illustrate a clear trend towards more sophisticated optical designs and data-driven modelling, while still facing trade-offs between system complexity, cost and the level of accuracy required for fully non-invasive clinical glucose monitoring.

Across the NIRS-based studies included in this review, several consistent patterns can be observed. Most *in vivo* systems employed diffuse reflectance at the fingertip or earlobe, with relatively few studies using transmittance or interactance geometries. Wavelength selection was typically concentrated in one or two NIR/SWIR windows rather than full broadband spectra, reflecting a trend toward configurations compatible with LED-photodiode hardware. Classical PLSR models generally achieved correlation coefficients in the range of approximately 0.85-0.90 and RMSE or RMSEP values of about 18-25 mg/dL, whereas machine-learning approaches such as Artificial Neural Networks (ANN) and Support Vector Machines (SVM)

Table 3: Summary of Selected NIRS-Based Non-Invasive Blood Glucose Monitoring Studies (2019-2025)

No.	Year	Author (first)	Study type	NIR wavelength/modality	method	Result
1	2019	Jain *et al.* [43]	Experimental *in vivo*	1560 nm	NIR spectroscopy at 1560 nm combined with Huber regression to reduce outlier effects.	Demonstrates high prediction accuracy and effective non-invasive monitoring in controlled settings.
2	2019	Solihin *et al.* [44]	Experimental *in vivo*	850 nm and 1550 nm	Handheld NIR device used on human subjects and compared with conventional glucometer readings.	Significant correlation with invasive measurements, suggesting potential for support in non-invasive monitoring.
3	2019	Jayarathan, *et al.* [45]	Experimental *in vivo*	940 nm+GSM	Portable NIR device with GSM module for real-time transmission of glucose estimates.	Non-invasive readings comparable to invasive methods and suitable for remote, continuous monitoring.
4	2019	Rachim and Chung [46]	Experimental *in vivo*	Multi-λ visible-NIR reflectance PPG (wrist band).	Wearable wristband with Vis-NIR LEDs and dual photodiodes; ML regression	Rp ≈ 0.86 and ≈6 mg/dL error in 2 h meal test; very promising wearable non-invasive accuracy.
5	2020	Saputra *et al.* [34]	Experimental *in vivo*	~940 nm (reflectance)	Reflective NIR LED-photodiode sensor on the skin; reflected intensity used to estimate glucose.	Feasible non-invasive estimation with good correlation but accuracy still below clinical requirements.
6	2021	Alqudah *et al.* [11]	Experimental in vitro	1550-1850 nm+MMW	Combined MMW and NIR transmission in glucose solutions; ML used to map features to concentration.	Combined MMW+NIR yields lower error and higher accuracy than either modality alone.
7	2021	Althobaiti and Al-Naib [42]	Simulation+experimental	1550-1650 nm (dual-channel)	Monte Carlo simulations to optimise dual-channel NIR sensor geometry, then experimentally tested.	Identified wavelength/configuration combinations that improve sensitivity and SNR for non-invasive measurement.
8	2022	Banihani *et al.* [12]	Review article	700-2500 nm (various NIR systems)	Narrative review of NIR-based non-invasive glucose monitoring devices and performance metrics.	Concludes that NIR is promising but still limited by accuracy, calibration drift and individual variability.
9	2022	Reddy *et al.* [47]	Experimental *in vivo*	800-2500 nm (broadband)	Broadband NIR spectra collected from skin and modelled with calibration/ML algorithms.	High correlation with reference glucose and promising non-invasive accuracy under controlled conditions.
10	2022	Srichanet al. [48]	Experimental *in vivo*	940 nm+vital signs	NIR monitoring integrated with shallow neural networks and features such as heart rate and BP.	Accuracy and robustness improved by combining NIR with additional physiological features.
11	2023	Sun *et al.* [10]	Experimental *in vivo*	1300-1550 nm+MMW	Combined millimetre-wave and NIR sensing; Random Forest model used on multimodal features.	Multimodal approach improves prediction accuracy compared with single-modality sensing.
12	2024	Ge *et al.* [49]	Simulation+experimental *in vivo*	1000-1700 nm diffuse reflectance (six SLD wavelengths)	Monte Carlo simulations plus OGTT measurements on 25 subjects to quantify sensitivity of glucose-induced changes in skin scattering and diffuse reflectance at multiple NIR wavelengths.	Shows measurable glucose-dependent diffuse reflectance sensitivity and provides design guidelines for wavelength and SDS selection in NIRS-based glucose devices.
13	2024	Vanaja *et al.* [50]	Experimental *in vivo*	~940 nm reflectance	Portable non-invasive glucometer using a NIR LED and OPT101 photodiode; finger placed over the sensor and reflected signal calibrated against a standard glucometer.	Demonstrates good agreement between non-invasive estimates and reference glucose in a small human study, confirming feasibility of low-cost NIR hardware.
14	2024	Gómez-Peralta *et al.* [51]	Clinical evaluation	Multi-λ NIR spectroscopy (Glucube device)	Outpatient evaluation with >1900 paired NIR/reference BG measurements.	MARD ≈ 20% and >95% points in acceptable error-grid zones; useful adjunct but not for dosing.
15	2025	Chen *et al.* [4]	Review article	VIS/NIR/FIR (incl. NIR windows)	Review of VIS/NIR/FIR spectroscopy for glucose monitoring, including non-invasive NIR approaches.	Highlights the potential of NIR-based non-invasive methods and emphasises remaining accuracy and calibration gaps.
16	2025	Chen *et al.* [41]	Experimental *in vivo*	Multi-wavelength NIR (LED array)	Multi-wavelength NIR sensor; reflected signals modelled with metric-learning+BP neural network.	Achieves low MARD and Clarke Error Grid Zones A/B, indicating clinically promising non-invasive performance.

often improved correlation toward 0.90-0.95 and reduced errors into the 12-20 mg/dL range. In the subset of studies that reported CEG analysis, typically around 85-95% of predictions fell within Zones A and B, indicating clinically acceptable accuracy in those specific experimental settings.

Across the 16 included studies overall, reported correlation coefficients between NIRS-based estimates and reference glucometer values generally ranged from 0.85 to 0.95**.** RMSE/RMSEP values were typically in the range of approximately 12-25 mg/dL [40,41]. CEG analyses indicated that 85-95% of predictions fell within Zone A, with most of the remainder in Zone B, which is consistent with clinically acceptable performance in controlled settings [5]. However, not all studies consistently met ISO and FDA criteria across all subgroups or test conditions.

A recurring theme in the results was limited generalizability. Models frequently performed well under controlled conditions or within a single cohort but degraded when applied to new populations, different anatomical sites or free-living conditions, particularly in wearable or continuous monitoring scenarios [5,19,40].

Nonetheless, the body of evidence collectively suggests gradual, steady progress in NIRS-based non-invasive glucose monitoring, supported by advances in optics, electronics, pre-processing and modelling. These results provide a technical foundation and realistic performance expectations for the development of next-generation, low-cost reflective NIR systems, including compact LED-photodiode modules like those targeted in our ongoing work.

DISCUSSION

This systematic review shows that non-invasive blood glucose monitoring using NIRS has advanced substantially over the past decade, yet significant technical and physiological barriers still impede clinical translation [5]. NIRS is inherently non-invasive and non-destructive and can potentially support continuous or frequent spot-check measurements [41]. These properties make it attractive for patients requiring frequent monitoring and for healthcare systems seeking cost-effective, user-friendly solutions.

At the same time, precision and repeatability remain decisive criteria for clinical acceptance. Many of the analyses studies report modest error metrics under controlled laboratory conditions, indicating that inter-individual variability and environmental interference remain substantial challenges in real-world use [5,19].

Methodological advances in data analysis are key to addressing these challenges. Traditional chemometric approaches such as PLSR remain widely used, while newer machine-learning and deep-learning models can better capture non-linear relationships and reduce sensitivity to confounders in some settings [5,40]. Multimodal approaches that combine NIR with other optical or physiological signals may further improve robustness when appropriately validated [10,11,22].

Despite these advances, several limitations persist. Models trained on one dataset often fail to maintain accuracy when transferred across devices, subjects or environments and many studies still involve small sample sizes and short trial durations. Importantly, none of the NIRS-based systems reviewed have obtained regulatory clearance for insulin-dosing decisions, underscoring the gap between technological feasibility and regulatory-grade performance [20,21,40].

Ethical and logistical issues also arise, including patient safety in long-term use, data privacy and integration into existing clinical workflows [39]. Nonetheless, ongoing advances in sensor miniaturisation, wearable integration and artificial intelligence maintain strong optimism that NIRS-based non-invasive systems will play an increasingly important role in future diabetes care. Compact, low-cost reflective NIR sensors-such as LED-photodiode modules like those explored in recent prototype developments-have the potential to translate the findings of this review into practical, accessible devices.

This review has several limitations that should be acknowledged. The analysis was restricted to studies published between 2019 and 2025 in English and the included NIRS-based systems were heterogeneous in terms of study design, populations, wavelength ranges and reported outcome metrics [39]. Additionally, many studies employed relatively small and selective cohorts and reported only limited performance indices, which may overestimate accuracy under real-world conditions and limit the generalisability of the findings to routine clinical practice.

CONCLUSIONS AND FUTURE RESEARCH

This systematic review synthesised recent evidence on *in vivo* NIRS-based non-invasive blood glucose monitoring in human subjects between 2019 and 2025. By applying explicit eligibility criteria and PRISMA 2020 methodology, sixteen studies were identified that used NIRS as the primary optical modality, reported quantitative performance metrics and implemented clinically relevant measurement configurations. Together, these studies show that NIRS can capture glucose-related optical changes with moderate to high correlation to reference glucometer readings and can achieve error levels that are clinically encouraging under controlled conditions.

At the same time, the review highlights several persistent limitations that prevent NIRS-based systems from replacing invasive or minimally invasive methods. Reported performance is highly sensitive to calibration procedures, measurement site, skin and tissue properties and environmental conditions and tends to degrade when models are transferred to new subjects or less controlled settings. Heterogeneity in optical hardware, wavelength selection, pre-processing pipelines and evaluation metrics also complicates direct comparison across studies and precludes formal meta-analysis. Importantly, no NIRS-based non-invasive device has yet obtained regulatory clearance for insulin dosing, underscoring the gap between promising prototypes and robust, reliable clinical tools.

Despite these challenges, there is a clear trend toward more compact, cost-effective reflective NIR sensors, early wearable implementations and increasingly sophisticated modelling strategies, including multi-wavelength designs and machine-learning or deep-learning approaches. These developments suggest that NIRS-based non-invasive monitoring is well positioned to support trend-level glucose tracking, alerts and patient engagement, particularly in resource-limited settings. Future research should prioritise larger and more diverse cohorts, standardised reporting of performance metrics, rigorous external validation and long-term studies that explicitly address calibration stability and inter-individual variability. Such work will be essential to translate the advances identified in this review into practical, low-cost NIR devices that can complement existing diabetes management strategies in clinical and home environments.

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