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Review Article

Application of Photoacoustic Spectroscopy for Glucose Level Measurement: A Literature Review

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Abstract

This study addresses the critical need for effective glucose level measurement in managing diabetes mellitus (DM). DM is a serious, economically influential disease that has no cure at present, highlighting the magnitude of prevention, control, and monitoring of blood glucose levels. This study systematically examined 79 articles from Google Scholar and PubMed databases, focusing on non-invasive glucose measurement using the photoacoustic system. After eliminating duplicates, 27 articles were reviewed. Glucose solution was predominantly used as the primary sample. Fixed and tunable lasers, especially near-infrared (NIR) lasers, were highlighted due to their superior penetration and accuracy in glucose measurements. Signal-purification techniques were used to guarantee accurate detection by removing noise. The evaluation involved regression analysis and machine learning integration to determine glucose levels statistically. The choice of sampling sites in volunteers was a critical factor affecting measurement accuracy. The study demonstrated meaningful progress in the development of photoacoustic methods, particularly in monitoring DM.

Keywords: diabetes mellitus, photoacoustic, blood glucose, non-invasive

1. INTRODUCTION

Measurement of glucose levels is a critical step in the management of diabetes mellitus (DM) [1]. DM is serious disease that requires significant attention. DM not only influences the wellbeing of individuals but also has an immense economic effect. However, to date, no cure for DM has been found, and the overcoming this disease still focuses on prevention, control, and monitoring the level of glucose in the blood. Monitoring blood glucose levels in patients with DM is needed by physicians to decide optimal management steps for patients.

Methods for measuring the level of glucose in the blood can be categorized into invasive and non-invasive. Common invasive or conventional methods use techniques that damage parts of the body for blood sampling, such as a fingertip [2]. This approach not only brings discomfort to the patient but also raises the risk of infection in the sampling scar wound [3]. By contrast, non-invasive methods do not need a blood sample to be directly taken from the patient. Some known non-invasive methods such as near-infrared (NIR)/mid infrared (MIR) spectroscopy, polarimetry, optical coherent tomography, Raman spectroscopy, and fluorescent detection that do not bring injury, making them more convenient for patients and enabling monitoring glucose levels without risk of infection in scar sampling [2][4][5]. Each non-invasive method has its own disadvantages. NIR spectroscopy is restricted by light-scattering interference caused by biological networks and spectral overlap phenomena while MIR spectroscopy is constrained by low detection and penetration depths, as well as weak signal output. Raman spectroscopy is restricted by fluorescence signal interference, and polarimetry is limited by small angles of deflection and other tissue interference [5].

An alternative non-invasive method that has recently been popularly investigated for examining glucose in the blood is spectroscopy based on the photoacoustic method. This spectroscopy utilizes photoacoustic phenomena that appear when materials absorb intermittent light radiation and undergo temperature changes that initiate periodic thermoelastic effects so that sound (acoustic) waves can be produced [2]. The main benefit of the

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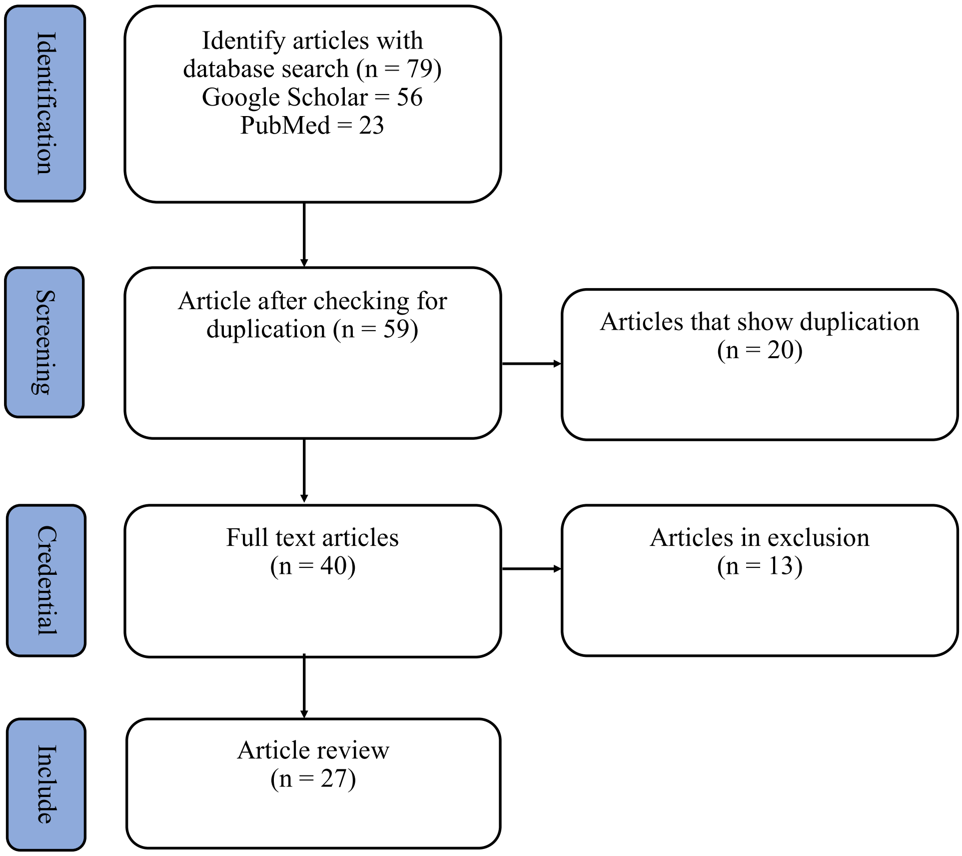

Figure 1. Literature search and selection.

photoacoustic method is its ability to utilize optical scattering, which enables measurements possessing high resolution [6] and high sensitivity [1][7]; it neither needs sample preparation before measurement nor harms the area examined [8].

Photoacoustic spectroscopy (PAS) optimization is governed by numerous factors, including laser sources, resonators, and sensors used to detect acoustic waves. The use of laser sources, for example, MIR lasers in some implementations requires substantial costs and complicated handling. Hence, the focus of this study is restricted to using lasers with visible-light and NIR wavelengths for glucose level measurement. Using laser with visible -light and NIR wavelengths not only minimizes the costs incurred for further studies but also streamlines the glucose measurement, making it more feasible and more widely accessible. Considering the challenges and advantages of each method, this study assesses the use of photoacoustic methods with visible-light and NIR lasers for measuring blood glucose levels, as well as their potential substantial contribution to the development of diagnostic technology, especially in DM in a more effective, more affordable manner, by employing non-invasive procedures for the increased convenience of patients.

2. MATERIALS AND METHODS

This review referred to "Preferred Reporting Item for Systematic Reviews and Meta-Analyses" guidelines employing two databases: Google Scholar and PubMed. The article/literature search used the keywords "photoacoustic" and "glucose measurement" with the Boolean operator "AND" to form a combination of "photoacoustic glucose measurement" or "glucose measurement using photoacoustic".

The early stage of literature searching encompassed identifying the title and abstract. Articles that have keywords were examined at the start. Moreover, whether the article deserves to be reviewed was assessed according to inclusion criteria: articles in the form of original research on the application of photoacoustic for glucose measurement, published between 2015 and February 2024 (Figure 1). Articles that cannot be completely read or not in English are then omitted. The review was arranged in tables according to year, research topic, laser characteristics, samples/ objects, and summary of research results, as shown in Table 1.

3. RESULTS AND DISCUSSIONS

In the preliminary stages of sorting from the Google Scholar and PubMed databases, 79 articles were found. After analysis for identifying duplicates was completed, 20 articles were excluded, resulting in 59 articles. Next, a full-text analysis of the articles was performed; consequently, 40 complete articles which were further analyzed. Some articles were removed because they were not written in English and the discussion only included characterization of tools, not measurements of glucose levels. After the literature search and selection, 27 articles met the criteria and were reviewed in this work (Figure 1).

PAS leverages an incredible phenomenon known as the photoacoustic effect, where materials absorb light and transform it into sound waves. When a material absorbs light, it quickly warms and expands, leading to pressure waves that we hear as sound. This effect is the pillar of PAS, an approach that examines the acoustic waves created to gather information about the sample investigated. Scientists can examine the properties of numerous materials, including solids, liquids, and gases, by merging spectroscopic principles with the photoacoustic phenomenon. This method supplies massive information about the composition, molecular structure, and quantities of specific compounds in the sample. This method's non-destructive attributes make it vital in numerous sectors, including material science, biology, and medicine. Owing to its high sensitivity and versatility, PAS is promising as a powerful analytical tool for investigating the intricate details of unique materials and substances.

PAS offers several advantages over other non-invasive glucose measurement techniques, such as polarimetry and optical coherence tomography (OCT) [2]. While polarimetry is limited by small deflection angles and interference from biological tissues, PAS provides higher sensitivity by directly analyzing the absorption of light and sound waves in glucose-containing tissues. OCT, on the other hand, offers high-resolution imaging but is constrained by shallow penetration depth, making it less effective for detecting glucose levels in deeper tissues. PAS, particularly when using NIR lasers, enables deeper tissue penetration and provides more accurate glucose readings [7]. However, PAS's reliance on precise laser calibration and system complexity may limit its clinical adoption compared to simpler optical methods. A comprehensive evaluation of these methods shows that while PAS holds significant promise, ongoing advancements are needed to overcome practical barriers and ensure its superiority in non-invasive glucose monitoring [4].

While PAS shows significant potential for non-invasive glucose monitoring, several practical challenges need to be addressed before it can be widely implemented in clinical settings or for patient self-monitoring at home. These challenges include the high initial cost of PAS systems, the need for sophisticated infrastructure and expertise to operate the equipment and ensuring the usability of PAS devices for everyday monitoring by patients. First, the cost of developing PAS systems, especially those using tunable lasers, remains high [4]. This could limit accessibility, particularly in low-resource settings. Moreover, the required infrastructure to support PAS systems, including calibration protocols and maintenance of laser sources, could pose significant challenges for widespread use in clinical environments or for patient self-monitoring at home [9]. Addressing these issues through cost-reduction strategies, such as utilizing more affordable NIR lasers and simplifying equipment, is essential. Another key consideration is the usability of PAS for everyday glucose monitoring by patients. For PAS to be feasible for home use, devices must be compact, easy to operate, and provide real-time feedback with minimal user intervention [10]. Integrating PAS systems into existing digital health platforms, such as smartphone applications, could also improve patient compliance and monitoring outcomes.

PAS initially serves as a complementary tool to continuous glucose monitoring (CGM) systems by providing an additional layer of accuracy and sensitivity in glucose detection [11]. PAS can be

Table 1. Review of glucose level measurement using a photoacoustic spectroscopy during 2015–February 2024.

YEAR	RESEARCH TOPICS	LASER SPECIFICATIONS	SAMPLE	SHORT SUMMARY
2015 [13]	Multiple linear regression method to predict glucose levels (*in vitro*)	Laser OPO, 680–2200 nm, pulse duration 7 ns, energy 0.5 –3 mJ	Liquid glucose (0–400 mg/dL)	Optimal absorption of glucose solution at wavelengths of 1430, 1510, 1890, 2020, and 2326 nm. Using multiple regression determines relative error prediction is below 20%.
2015 [6]	Analysis of acoustic waves generated by variations in glucose solution concentration (*in vitro*)	Laser OPO, 600–2500 nm, pulse width 50 µs	Liquid glucose (0–300 mg/dL)	Characterization of photoacoustic signals using signal purification from glucose solutions (rising–falling waves, acoustic peak against concentration variations)
2015 [5]	Prediction of glucose levels using the least square fitting (*in vitro*) algorithm	Laser Nd:YAG, 1300–2300 nm, energy 2 mJ, duration 10 ns	Liquid glucose (0–300 mg/dL)	Prediction of acoustic absorption peaks using standard regression least square algorithm at of 1470 and 1940 nm
2015 [3]	Prediction of glucose levels using least square regression (*in vitro*)	Laser diode, 905–1550 nm, pulse width 100 ns	Liquid glucose (0–500 mg/dL)	Prediction calibration can be improved using kernel polynomials and supporting standard regression methods to achieve mean absolute value of 8.94%
2015 [1]	Investigation of liquid samples using reservoirs/photoacoustic cells (*in vitro*)	Laser diode, 1550 nm, power 34 mW	Liquid glucose (250, 500, and 1000 mg/dL)	Photoacoustic signals are directly proportional to glucose levels. Fluctuations when retrieving data are affected by the temperature
2015 [4]	Prediction of glucose levels using a multivariate linear regression algorithm (*in vitro*)	Laser Nd:YAG, 1300–2300 nm, energy 2 mJ, duration 10 ns	Liquid glucose (0–300 mg/dL)	The best wavelength is observed at 1510 nm. Multivariate regression derives coefficient of correlation of 0.9856
2015 [8]	Peak-to-peak analysis of photoacoustic signals to predict glucose levels (*in vitro* and *in vivo*)	Laser diode, 905 and 1550 nm, pulse width 100 ns	Liquid glucose (0–500 mg/dL) Blood from hands of 30 volunteers	Glucose levels are determined by the advanced analysis of the area under positive and negative signals converted to the frequency phase and examination using Clarke's chart
2016 [14]	Denoising photoacoustic signals in glucose solution using wavelet threshold method (*in vitro*)	Laser Nd:YAG 1450 nm, pulse width 50 µs	Liquid glucose (100 mg/dL)	The results of photoacoustic signal denoising signal purification are evaluated using signal-to-noise ratio and root mean square

Table 1. *Cont.*

YEAR	RESEARCH TOPICS	LASER SPECIFICATIONS	SAMPLE	SHORT SUMMARY
2016 [15]	Dimensional analysis of resonators in photoacoustic systems for glucose solution detection (*in vitro*)	Laser diode, 1600 nm	Liquid glucose (0–30%)	The Helmholtz type is 30 times smaller than the straight type. Sensitivity increases by two times.
2016 [16]	Increase sensitivity using acoustic resonance (*in vitro*)	Laser diode, 1382 and 1610 nm	deionized water	Temperature influences sensitivity. Increased sensitivity is compared with changing the distance dimensions of the laser with the sensor.
2017 [2]	Combination of optical and acoustic spectra to improve measurement sensitivity and accuracy (*in vitro*)	Laser Nd:YAG, 532, 905 dan 1064 nm, pulse width 9 ns	Liquid glucose (0–10000 mg/dL)	The amplitude of the acoustic signal is directly proportional to the concentration of the glucose solution.
2017 [17]	NIR light analysis in photoacoustic systems for glucose measurement (*in vitro*)	Nd:YAG, 800–1030 and 1090–1800 nm, energy 0.09–8 mJ	Liquid glucose (0–400 mg/dL)	According to advanced analysis signal, the intensity of the acoustic signal is proportional to the glucose level and the light absorption coefficient for each change in wavelength.
2017 [18]	Resonant analysis of glucose solution (*in vitro*)	Nd:YAG, 1064 nm, pulse width 9 ns	Liquid glucose (200–10000 mg/dL)	The amplitude of the acoustic signal is proportional to the glucose level using standard regression with correlation of 0.9648.
2017 [19]	Effect of temperature and glucose concentration on acoustic signals (*in vitro*)	Nd:YAG, 1064 nm, pulse width 9 ns	Liquid glucose (40–4000 mg/dL)	The temperature variation is proportional to the change in velocity and change in the concentration of the solution on standard regression analysis
2017 [20]	Acoustic signal analysis on glucose level measurement (*in vitro*)	NIR laser, 1600 nm, pulse width 7 ns, energy 30 mJ	Liquid glucose (0–7 g/dL) and (0–350 mg/dL)	Variations in acoustic signal characteristics noted using standard regression achieve accuracy enhancements of 29.5% and 33.63% from different glucose concentrations due to glucose-related absorption and changes in sound speed.
2018 [7]	Dual laser on the photoacoustic system to measure glucose levels (*in vivo*)	Laser diode, 1382 and 1610 nm, power 5–7 mW	3 volunteers	The intensity of the laser is proportional to the acoustic pressure and affected by temperature. Using standard regression, the correlation is 0.84.
2018 [21]	Effect of temperature on acoustic signals in glucose solution (*in vitro*)	Nd:YAG, 1064 nm, pulse width 9.2 ns, power 1 mJ	Liquid glucose (0–25000 mg/dL)	Photoacoustic signals display satisfactory linearity with light intensity, glucose concentration, and temperature coefficient 0.04/°C examined using standard regression.

Table 1. *Cont.*

YEAR	RESEARCH TOPICS	LASER SPECIFICATIONS	SAMPLE	SHORT SUMMARY
2018 [22]	Combination of NIR spectroscopy, Beer–Lambert's law and photoacoustic measurements (*in vitro*)	Laser OPO, 400–2000 nm, duration 7 ns	Liquid glucose (50–350 mg/dL) Human blood serum 10 mL	The sensitivity and accuracy of the system can be adjusted by changing the length of the optical path and achieve correlation coefficients 0.9025 and 0.9811 using multiple regression.
2019 [23]	Photoacoustic multispectral based sensor on glucose measurement (*in vitro*)	Semiconductor laser, 1540–1840 nm, energy 13.3 µJ	Liquid glucose (1–8 g/dL and 0–400 mg/dL)	The peak amplitude of the photoacoustic signal is due to increased absorption in the first overtone and the combination of C─H and O─H bonds. The coefficient of determination from standard regression is 0.938.
2019 [10]	Photoacoustic-based portable glucose measuring device (*in vitro*)	Laser diode, 1550 nm, pulse width 500 ns	Liquid glucose (1–8 g/dL and 50–350 mg/dL)	In vitro experiments and from multiple regression obtain concentration prediction of 71.43%.
2020 [24]	Using two lasers in the photoacoustic system for glucose level measurement (*in vitro* and *in vivo*)	Laser 1382 and 1610 nm	Liquid glucose (0–400 m/dL) Albumins (0, 16.5, and 33 g/dL) Ear volunteer	The relationship between photoacoustic signals and glucose solution concentrations is linear.
2020 [11]	Monitoring glucose levels using photoacoustic spectroscopy (*in vitro*)	Laser diode, 940 nm	Natural rubber slice hams (1.6, 3.05, and 4.6 mm)	The depth of laser penetration depends on its frequency.
2020 [25]	Prototype of photoacoustic blood glucose level tester with the help of a laptop (*in vitro*)	Laser diode, 520 nm, power 90 mW	Glucose assay (oxidase) strip Human serum albumin	PA resonators are vital for reducing noise. Coefficient correlation from standard regression is 0.9933% to decide correlation between human serum and acoustic signal.
2020 [26]	Time domain photoacoustic wave analysis (*in vitro*)	Laser OPO, 1600 nm, pulse width 9 ns, energy 30 mJ	Liquid glucose (50–500 mg/dL) human blood serum	The result of analysis using multiple regression reveals the correlation between absorption spectrum and glucose concentration may be weak, especially when glucose concentration is low among various disorders.

Table 1. *Cont.*

YEAR	RESEARCH TOPICS	LASER SPECIFICATIONS	SAMPLE	SHORT SUMMARY
2022 [27]	Glucose measurement using a photoacoustic system with a 1535 nm laser (*in vitro*)	Laser diode, 1535 nm, pulse width 4 ns, energy 365 µJ	Liquid glucose (0–10000 mg/dl)	Using standard regression, the higher the glucose concentration, the higher the signal amplitude.
2022 [9]	Compact system for photoacoustic machine learning (*in vivo*) based glucose measurement	Laser diode, 980 nm	Fluid D-glucose (0–300 mg/dL)	Data measurement and analysis of multiple regression use many stochastic techniques and machine learning to determine the amplitude of the signal ('Max') as the signal that possesses the greatest correlation with glucose concentration.
2023 [12]	Combination of machine learning and NIR-based photoacoustic to measure glucose levels (*in vitro*)	Laser diode, 1500–1630 nm, power 5 mW	Fluid D-glucose (20–300 mg/dL)	PA NIR spectroscopy is used to measure glucose solutions, and machine learning and standard regression produce the right measurement. The amplitude of the signal is linearly related with the power and temperature of the laser.

Note: Nd:YAG = Laser neodymium-doped yttrium aluminum garnet; OPO = Optical parametric oscillators; NIR = Near-infrared; PA = Photoacoustic

used alongside CGM to verify readings, especially in cases where CGM data may be inconsistent or require calibration. Furthermore, PAS can be combined with CGM technology to enhance overall glucose monitoring. For example, PAS could intermittently cross-check CGM results, while machine learning algorithms process both PAS and CGM data in real time to ensure the highest accuracy and reliability [12]. This combined approach would strengthen the performance of existing diabetes management systems. Ultimately, with further technological advancements, PAS holds the potential to replace CGM altogether. Its non-invasive nature, combined with improved precision in glucose measurement, offers a promising alternative for continuous glucose monitoring. Studies have also explored the integration of PAS into smartphone-based systems, which would make glucose monitoring more accessible and easier to use in everyday settings [10].

Based on the summary of the review results revealed in Table 1, most studies on glucose measurement using photoacoustic techniques employ glucose solution (D-glucose) as the primary sample. The setup of the photoacoustic system used in measuring glucose levels is shown in Figure 2. Glucose was selected because it is a simple sugar often found in biological metabolism, hence offering representative research results related to photoacoustic responses. Glucose selection is also relevant in the context of DM research, where differences in glucose concentration can produce beneficial insights into specific health conditions. Glucose is the main choice, but some studies employ phantoms as substitutes for research samples, such as ham slice [11] and glucose assay [25] according to data in Figure 3. Figure 3 shows samples for glucose measurement employing photoacoustic methods can be substances that simulate the acoustic and optical properties of biological tissues, hence facilitating more contextual and applicable research. The use of phantoms is more representative of the real patient's state which is more biologically complex accompanied by distinctive tissue properties. Thus, the use of glucose as the primary sample and the alternative use of phantoms in photoacoustic research supplies a solid framework to guarantee relevant, precise results. Some studies employ volunteers as research subjects. The body parts studied include the earlobe [24] and human blood serum [26]. Most studies on PAS for glucose measurement have relied on glucose solutions or phantom samples as primary test subjects. While glucose solutions provide consistent and controlled conditions for testing, they may not fully replicate the complexity of human tissue [19]. Phantom samples, which simulate the acoustic and optical properties of biological tissues, offer a closer approximation but still lack the biological variability found in living biological tissue [11]. This limits the ability to directly translate laboratory results to real-world applications. *In vivo* studies, particularly on human tissue, are essential to address this gap, but they introduce challenges such as varying skin thickness, tissue composition, and blood vessel distribution, which can affect PAS accuracy [9]. Future studies should prioritize human tissue testing to enhance the applicability of laboratory findings to clinical settings.

Research in the field of photoacoustic often encompasses using two types of lasers according to wavelength as sources of photoacoustic radiation, namely, fixed lasers and tunable lasers. Figures 4 – 6 present the distribution of wavelengths employed as radiation sources in photoacoustic systems for glucose level measurement. In the field of photoacoustic, lasers play a key function in acquiring a deeper understanding of glucose levels non-invasively. This process entails laser radiation, fixed and regulated, as an energy source that promotes the photoacoustic response of the sample observed. When the laser is irradiated at the sample, the light energy generated is absorbed by chromophores in the sample, including glucose. The absorption of such energy results in increased temperature of the sample, and in response, acoustic waves are produced [20]. These acoustic waves can then be quantified and examined to comprehend their relationship to the glucose concentration in the sample. The wavelength ranges of visible light and NIR lasers are used to encourage photoacoustic response in the sample. This laser option plays a vital role; fixed lasers are commonly used for standard or comparison purposes, whereas tunable lasers afford flexibility in customizing experiments to specific characteristics. The use of lasers with visible-light and NIR wavelengths provides an engaging aspect in photoacoustic research. Visible-light lasers have a cost-effective advantage because their production and maintenance costs are lower. Other benefits are the ease of integration with experimental systems and the presence of technology that is more economical in terms of cost. However, theory shows that visible-light lasers have considerable disadvantages, including a limited penetration depth compared with infrared lasers, specifically in the context of photoacoustic for glucose measurement of human tissue. Thus, laser light using visible light leads to less accurate approximations of glucose levels owing to the lack of laser penetration into the sample to reach the observed blood vessels.

However, infrared lasers excel with benefits that

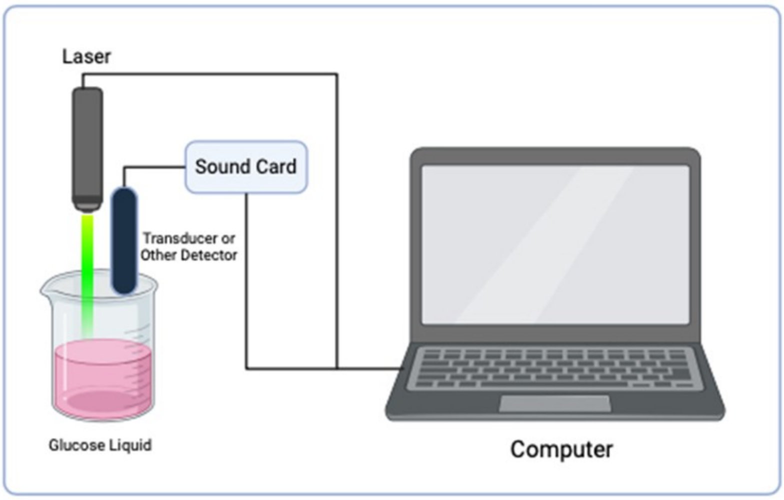

Figure 2. Photoacoustic system for glucose liquid measurement.

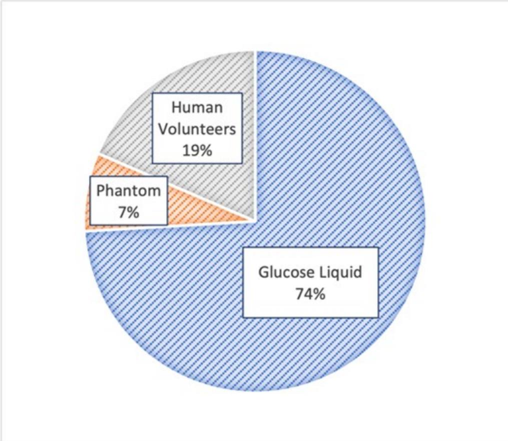

Figure 3. Sample types used in glucose measurement based on photoacoustic systems.

promote their superiority in photoacoustic applications. The success of infrared lasers primarily lies in the increased depth of penetration into the sample compared with visible light [21][22]; infrared lasers can reach deeper into biological tissues, providing an advantage in the measurement of glucose levels because it can access deeper sources of glucose. Moreover, infrared lasers have advantages in terms of molecular determination, enabling a more precise identification of the biological components participating in the photoacoustic response. Thus, lasers with infrared wavelengths seem a more helpful choice to acquire more precise and informative photoacoustic measurements. A tunable lasers is lasers that can be adjusted to emit light at different wavelengths, allowing for more precise targeting of specific molecules such as glucose in PAS systems.

Table 1 shows the methods used to discover the relationship between photoacoustic systems and glucose levels through photoacoustic signal intensity tests. After successfully recording the acoustic signal, the intensity value becomes the crucial point of the analysis, which is then presented in a graph that illustrates the variation in glucose levels compared with the intensity of the acoustic signal. Regression analysis plays a vital role in discovering and assessing the relationship between acoustic signal intensity and glucose levels. Numerous regression analysis techniques have been used to forecast glucose levels, including standard regression for evaluating linear relationships [2][3][5][7][12][18]-[21][23][25][27] and multiple regression that considers more than one predictor variable [4][9][10][13][22][26]. The special regression analysis method is employed based on study requirements, making regression analysis a solid foundation in interpreting research results, and predicting glucose levels.

In addition to regression analysis, signal purification is an important spotlight in the development of photoacoustic techniques for glucose level measurement. Photoacoustic signal analysis is done to remove noise that might influence the accuracy of the results [14][27]. This step enhances the quality of the photoacoustic signal, considering that signal clarity is the key to reliable measurement results. Photoacoustic signal denoising is a process used to improve the clarity of photoacoustic signals by removing unwanted noise that could distort the measurement results. This ensures that the signal corresponds more accurately to the concentration of glucose in the sample. Noise can arise from various sources, such as electronic interference or thermal fluctuations, and must be filtered out to obtain accurate measurements of glucose levels. The Clarke error grid (CEG) graph is also used as a quality assessment tool in the measurement of glucose levels [8][10][12][23][24][26][27]. Recent studies have also investigated the integration of machine learning for glucose measurement. The use of machine learning not only involves detection and prediction but also determines the glucose level of a sample with a higher accuracy [9][12].

In the modern era, the use of machine learning in glucose level measurement holds revolutionary potential. Machine learning (ML) can detect complicated patterns and predict glucose levels with increased accuracy. ML has emerged as a powerful tool for enhancing the accuracy of PAS in glucose measurement. By analyzing complex data patterns from photoacoustic signals, ML algorithms can predict glucose levels with greater precision than traditional methods [12]. Integrating machine learning in photoacoustic data analysis brings new opportunities to obtain deep insights into glucose responses. While regression analysis and noise removal through photoacoustic signal analysis remain the cornerstone, using ML provides an extra layer that brings a predictive, adaptive dimension to non-invasive glucose measurements. By analyzing large datasets generated from photoacoustic signals, ML models can identify complex patterns and correlations that may not be immediately apparent through traditional regression analysis. For example, regression models have been employed to establish the relationship between photoacoustic signal intensity and glucose concentration [23][27]. More advanced algorithms ML techniques, such as neural networks, have the potential to detect subtle variations in signal properties that may be overlooked by simpler algorithms. These models can also compensate for external factors, such as temperature fluctuations and biological variability, making them invaluable for real-time and non-invasive glucose monitoring. Integrating ML into PAS systems represents a significant step toward developing more accurate and accessible glucose measurement tools for both clinical and home use [28]. Algorithms such as support vector machines (SVM) and neural networks have been used to analyze complex patterns in photoacoustic signals, identifying subtle variations that may be difficult to detect using traditional regression models. These algorithms can account for individual variability in skin and tissue properties, allowing for more accurate predictions of glucose levels. Recent advancements in machine learning, including the use of deep learning techniques, are expected to further improve the precision and reliability of PAS -based glucose monitoring [28].

Biological variability plays a significant role in the accuracy of PAS measurements. Factors such as skin thickness, tissue composition, and vascularity can vary widely between individuals and across different body sites, affecting the absorption and propagation of laser light and the subsequent generation of acoustic waves [11]. For example, regions with thinner skin, such as the earlobe, may provide more accurate measurements compared to thicker areas like the fingertip [24]. Additionally, variations in blood vessel density across different body parts can influence the absorption and scattering of laser light, impacting the quality of the photoacoustic signal. As PAS continues to evolve, understanding and accounting for these biological differences is crucial for improving measurement consistency and reliability across diverse patient populations [26].

Glucose measurement through photoacoustic systems also entails testing with the engagement of volunteers, as shown in specific studies examined in this work. Several literature contain records of numerous sampling locations in volunteers, such as hands [8] and ears [24]. The selection of sampling site is a key factor that can substantially influence the measurement results. Studies in this area often aim to investigate various locations to select the best area for acquiring accurate, consistent

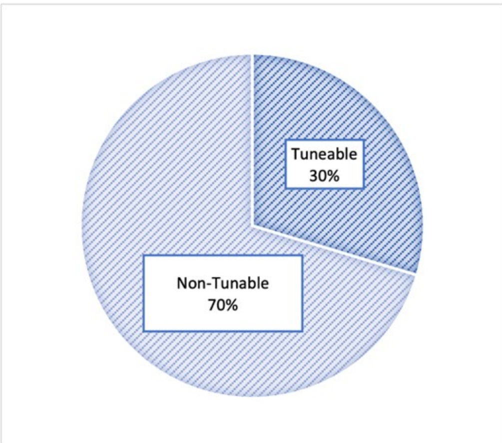

Figure 4. Laser types used for glucose measurement based on photoacoustic systems.

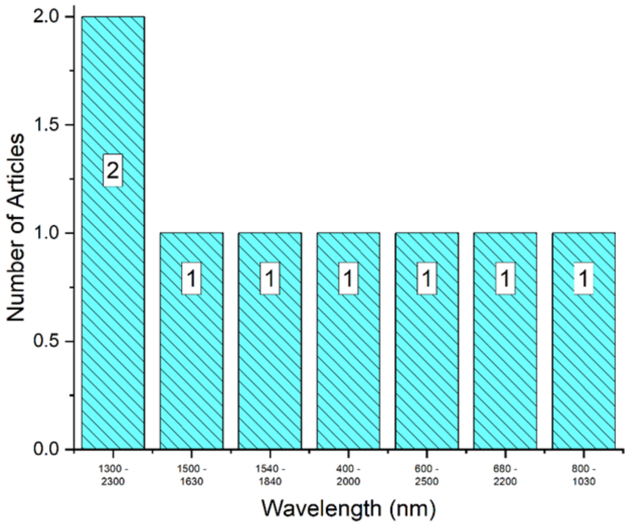

Figure 5. Distribution of tuneable lasers used in photoacoustic system-based glucose level measurement based on their wavelength.

photoacoustic response. For example, in a study in a particular year, certain researchers determine glucose levels in the fingertips using special lasers and specific sampling methods. The outcomes of measuring glucose levels in the hands are then documented. However, comparisons with other studies in the same year, which employ dissimilar lasers and wavelengths in the ear, reveal considerable differences in the glucose response acquired.

Based on the reviewed studies, the earlobe and fingertip are frequently used sampling sites for PAS due to their accessibility and vascularity. However, the choice of site can significantly impact measurement accuracy. For example, the earlobe tends to provide more consistent[results due to its thinner skin and higher blood perfusion compared to the fingertip [24]. Future research should focus on identifying the most reliable sampling sites based on patient-specific factors such as skin type and thickness. Standardized guidelines for sampling site selection would be highly beneficial for ensuring consistent results across different clinical settings.

The value of the choice of sampling sites employed in research for photoacoustic glucose measurement is strengthened by theory saying numerous parts of the human body have distinct optical and acoustic characteristics. Hence, the effect of sampling site selection not only influences the absorption rate of laser energy but also modifies its photoacoustic response attributes. In recent years, studies have observed that hands and ears may have diverse levels of vascularity and skin thickness, affecting the extent to which laser energy can be permeated and absorbed by glucose. Thus, the selection of the appropriate sampling site becomes a key factor in acquiring accurate, dependable data. As technology advances and understanding of the physiological characteristics of various locations in the human body increases, research continues to find the best locations that can maximize the accuracy and consistency of photoacoustic responses to glucose levels.

According to numerous articles reviewed, several important points have not been made so far. The first is to focus on creating non-invasive glucose measurement methods that are more accurate, sensitive, and widely applicable compared with existing methods. The second is that advances in the use of photoacoustic technology for glucose monitoring can be correlated to the possibility of integration with existing DM monitoring systems, so that glucose levels can be checked. Further research potential entails investigating more advanced technologies, using more complex samples, and applying statistical analysis to improve the reliability of results. Compared with medical needs, non-invasive glucose measurement based on photoacoustic systems remains far from ideal. Therefore, more in-depth studies about low-cost, high-accuracy system optimization that can be used widely are needed.

4. CONCLUSIONS

This study discusses sample selection, radiation sources, analysis methods, and sampling locations in photoacoustic studies for glucose level measurement. Most studies employ glucose solution as the major sample, while some use phantoms as alternative objects. This study concludes that most optimizing photoacoustic systems for glucose measurement using NIR lasers hold promising potential for effective, affordable, and non-invasive DM monitoring. Analysis methods for improving the accuracy of glucose measurements include regression analysis, the use of CEG, and ML integration. The selection of sampling sites in volunteers is also a key aspect of this study. The wide-open research potential implies additional investigation of the use of substitute samples other than glucose, the determination of the best laser wavelengths, the establishment of innovative new analytical methods, and more in-depth research into the best location of sampling in volunteer bodies to obtain accurate, consistent measurement results.

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Conceptualization, B. W. P.; Methodology, B. W. P. and R. W.; Validation, B. W. P. and R. W.; Formal Analysis, B. W. P.; Investigation, B. W. P.; Data Curation, B. W. P.; Writing – Original Draft Preparation, B. W. P.; Writing – Review & Editing, R. W., A. S., M. M.; Visualization, B. W. P.; Supervision, M. M.; Funding Acquisition, B. W. P.

Conflicts of Interest

The authors declare no conflict of interest.

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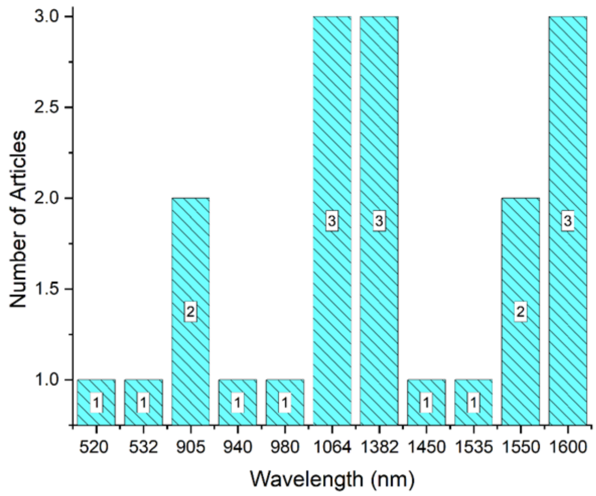

Figure 6. Distribution of nontunable lasers used in photoacoustic system-based glucose level measurement based on their wavelength.

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