Review Research

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Non-Invasive Technological Innovation for Blood Glucose Monitoring in COVID-19 Patients with Diabetes Mellitus during Pandemic

Azalia Melati Putri[1], Nuraulia Aghnia Armansyah[2], Septiani Sri Kusuma Astuti[3], Sandra Pebrianti[4]

Faculty of Nursing, Universitas Padjadjaran, Sumedang, West Java[1]

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Correspondence author:
Sandra Pebrianti
Komp. Pataruman Dream Blok B5, Kab. Garut, Jawa Barat.
E-mail:
Sandra.pebrianti@unpad.ac.id

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Abstract

Background: Glycemic control procedures may help reduce the risk of worsening conditions and death in COVID-19 patients with Diabetes Mellitus (DM). Currently, non-invasive blood glucose monitoring technology has been developed to address the challenges of glycemic control in DM patients. **Objective:** This literature review aims to identify non-invasive technology innovations for blood glucose monitoring applied to COVID-19 patients with DM comorbidities. **Method:** The method used is a rapid review by searching for articles on EBSCO-host Academic Science Completed, PubMed, Sage Journals, ScienceDirect, and Taylor & Francis. The study reviewed is scoping the innovation of non-invasive blood glucose monitoring technology with research designs of Randomized Control Trial, Quasi Experiment, Cross-Sectional, and Cohort Study in English with full text, and published from 2019–2021. **Results:** It was found that there were four types of technology and two biomarkers used for non-invasive blood glucose monitoring, namely Skin Autofluorescence, Microperimetry, Raman Spectroscopy, Mid-Infrared Quantum Cascade Laser Technology, and as well as saliva and exhaled Volatile Organic Compound. **Recommendation:** Further research is needed to confirm the effectiveness of this device, mainly to prevent death in COVID-19 patients with DM comorbid.

Keywords: Diabetes mellitus, COVID-19, Non-invasive technology

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) was officially declared a pandemic by the World Health Organization (WHO) in March 2020 (1). The COVID-19 pandemic has caused many casualties in various parts, including Indonesia. According to data from the Ministry of Health, the Republic of Indonesia, in 2021, the confirmed cases of COVID-19 globally have reached 243,561,596 instances, with the death toll reaching 4,947.77 people (2). Death risk is correlated with age, organ failure, and comorbidities of COVID-19 patients (3,4). One study reported that a sizable proportion (30% to 48%) of individuals infected with COVID-19 had at least one chronic condition, including hypertension, cardiovascular disease, diabetes mellitus, respiratory system disease, and other chronic diseases (3). These conditions contribute to significant clinical challenges in diagnosis, progression of prognosis, and disease management (5). The severity of comorbidities causes the individual's health condition to worsen and the risk of death (6).

Diabetes Mellitus (DM) is one of the most common chronic comorbidities found in patients infected with COVID-19 in the intensive care unit (7,8). At the same time, the data on this subject varies between countries. According to studies from China, the prevalence of COVID-19 patients with DM cases was first reported within the 3% to 21% range (9). Meanwhile, according to the Centers for Disease Control and Prevention (CDC), DM cases among confirmed COVID-19 patients have reached 10.9%, with a death rate from diabetes of 10% (10). Based on a study conducted by Wu et al. in 2021, a history of DM is a significant predictor of acute respiratory distress syndrome (ARDS) in COVID-19 patients (11,12). Correspondingly, data from Wuhan City, China, show that COVID-19 patients with DM tend to have a poorer prognosis, especially in older patients (13). In addition, the results of clinical observation studies also show a higher mortality rate in COVID-19 patients with a history of DM, which is two to three times higher than those without DM (7). 14 of the 24 COVID-19 patients suffered DM in the study, and 50% of the group died during the observation period (14). Therefore, it is essential to conduct particular interventions with a history of DM to reduce the risk of worsening conditions and death in COVID-19 patients who have these comorbidities.

The COVID-19 pandemic also presents its challenges for DM patients as a vulnerable population. The policy of limiting social interaction and the concern of DM patients to visit health care facilities cause delays in routine visits, treatment discrepancies, and ineffective health education. The government organized the Chronic Disease Management Program (PROLANIS) for diabetic patients and has been running less than optimally, thus reducing the intensity of checking glucose levels in diabetic patients. Glycemic control is one of the efforts that can be done to reduce the risk of worsening conditions and death in COVID-19 patients with a history of DM. This is based on a study that found that 45.2% of COVID-19 patients with DM had abnormal blood glucose levels (15). In addition, the results of previous studies have also shown that stress hyperglycemia is an independent risk factor in COVID-19 patients in the critical phase (16,17). In contrast, hypoglycemia can trigger cardiovascular events and harm disease prognosis. Therefore, routine blood glucose levels in COVID-19 patients with comorbid DM are crucial to detecting the development of critical cases and the risk of death in COVID-19 patients.

Conventionally, blood glucose monitoring requires an invasive blood sampling process. This procedure usually causes some side effects related to discomfort, pain, and risk of infection (18). Slow natural wound healing in DM patients raises other concerns about invasive blood glucose testing procedures (19). In addition, the reluctance of DM patients with or without needle phobia to perform invasive blood testing procedures makes it difficult to monitor their blood glucose levels (20). On the other hand, the need for more frequent blood glucose checks in COVID-19 patients with comorbid DM demands a practical way to carry out glycemic control without causing trauma to the patient.

To date, non-invasive blood glucose monitoring technology has been developed to address the challenges of glycemic control in DM patients. Several types of technology that have been developed include measuring blood glucose using optical methods and immobilized sensors (21). These two technologies allow DM patients to know their blood glucose levels without any blood sampling procedure. Based on the literature review results, blood glucose measurement with the help of optical methods can provide reliable results (22). Therefore, non-invasive technology can be a solution to monitor blood glucose levels accurately without causing trauma.

With non-invasive technology, blood glucose monitoring can be performed more straightforwardly and less painfully (23). This modification was also carried out to increase the glycemic monitoring capacity while minimizing the potential for coronavirus exposure between patients and health workers. The results showed that COVID-19 patients with comorbid DM whose blood glucose was well-controlled during hospitalization had a lower risk of death than individuals with uncontrolled blood glucose (24). Therefore, non-invasive technology in glycemic control is a promising solution to reducing the potential for worsening conditions and the risk of death in COVID-19 patients with comorbid DM. Thus, a literature review is needed to describe the non-invasive blood glucose monitoring technology developed to date.

OBJECTIVE

This literature review aims to describe the potential use of each type of non-invasive technology in blood glucose levels monitoring of COVID-19 patients with comorbid Diabetes Mellitus to reduce the potential of worsening condition and the risk of death.

METHODS

This literature review employed PRISMA 2020 to describe the potential use of each type of non-invasive technology in blood glucose levels monitoring COVID-19 patients with comorbid Diabetes Mellitus.

Protocol

The design used in this literature is a rapid review. Rapid review is a type of literature synthesis that simplifies or eliminates some of the process components of a systematic review to obtain information in a short time (25).

Eligibility Criteria

The authors employed various types of research methods, including Randomized Control trials, Quasi Experiment, Cross-Sectional, and Cohort studies, to describe the potential use of each kind of non-invasive technology in blood glucose levels monitoring COVID-19 patients with comorbid Diabetes mellitus. The exclusion criteria for this study were articles with non-primary research designs, articles with non-diabetic populations, and research results that did not discuss the implementation of non-invasive tools.

Search Strategy

The authors conducted some searching process to gain relevant articles about the non-invasive technologies for blood glucose level monitoring. During the process, the authors used some keywords such as: “Diabetes Mellitus," "Non-Invasive Blood Glucose Monitoring," and "Blood Glucose Levels."

Table 1. PICO's Search Strategy

Picos Framework	Search Strategy
Populations	Diabetes Mellitus OR Diabetes Type 2 OR Diabetes Mellitus Type 1 OR Hyperglycemia OR High Blood Sugar or High Blood Glucose
Intervention	Non-invasive Blood Glucose Measurement OR Non-invasive Glucometer OR Non-invasive Blood Glucose Control OR Non-invasive Glucose Monitor
Outcomes	Blood Glucose Levels OR Blood Sugar OR Blood Glucose
Studies	RCTs, Quasi-Experimental, Cohort Study, Cross-Sectional

Study Selection

Five databases include EBSCO-host ASC, PubMed, Sage Journals, ScienceDirect, and Taylor & Francis. The authors investigated some relevant articles published in the English version. After eliminating several similar studies, the authors collected relevant articles.

Synthesis of Results

The findings of this review describe and explain the potential use of types of non-invasive technologies in blood glucose levels monitoring of COVID-19 patients with comorbid Diabetes mellitus. This literature review used PRISMA as the article selection process, as shown in figure 1.

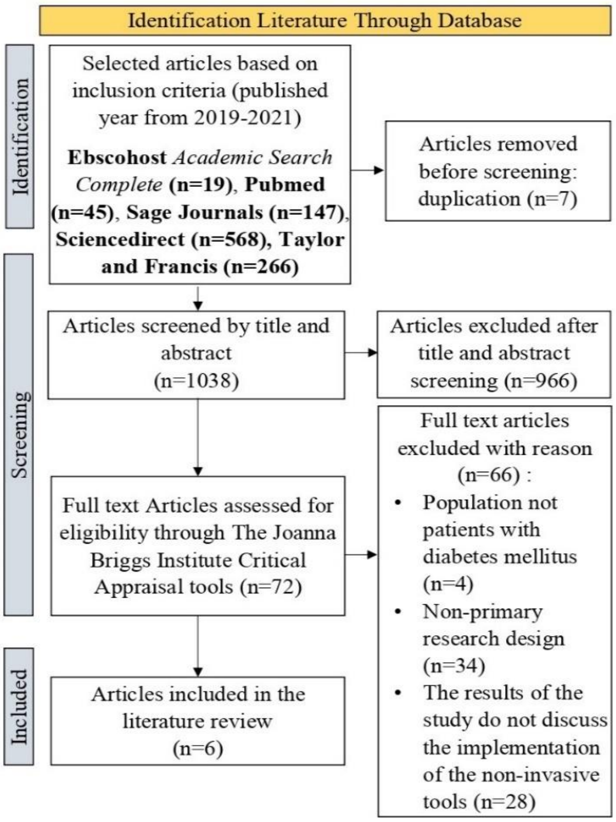

Figure 1. The Study Selection Process Adapted from PRISMA 2020

RESULTS

Study Characteristic

One hundred forty-five articles from databases were obtained. The journals were analyzed by employing a critical appraisal method with good article standards above 60% of the criteria and relevance to the topic. This research covers several aspects: publication year, approach designs, research goals, population, intervention, and conclusion. The initial search result consisted of 19 EBSCOhost Academic Science Complete journals, 45 PubMed journals, 147 Sage journals, 568 ScienceDirect journals, and 266 Taylor and Francis journals. However, we excluded 966 articles because the reasons including not relevant to the objectives.

Finally, 6 most relevant articles were extracted in this study, including two Cohort study articles, one quasi-experiment article, one randomized controlled trial article, and one cross-sectional article.

Table 2. Study Included with JBI Critical Appraisal Tool

Author, Published Year	JBI Critical Appraisal Tool	Study Design
Rigo et al. (2020)	81.8% (9/11)	Cohort Study
Sharanjeet-Kaur, et al. (2019)	63.6% (7/11)	Cohort Study
Kumar A., et al. (2020)	84.6% (7/11)	RCT
Trefz et al. (2019)	100% (8/8)	Cross Sectional
Li H. et al., (2019)	77.8% (7/9)	Quasi Experiment
Lubinski T., et al., (2021)	77.8% (7/9)	Quasi Experiment

Total 6 articles identified as suitable for review discussed various non-invasive blood glucose monitoring technologies from 2019 – to 2020. Studies were from the following countries: Germany (2), Malaysia (1), France (1), the Philippines (1), and China (1). Of the 6 articles, four types of technology and two biomarkers were used for non-invasive blood glucose monitoring. All studies focused on blood glucose non-invasive monitoring intervention with samples ranging from 12 to 915 participants.

We described the findings of this review article by using mean themes. Detailed explanations were narratively described as follows:

Sensor Technology System

The glucose-sensing mechanisms ensure all the requirements for long-term use, which can be used as a future technology for glucose monitoring with more straightforward procedures. Several glucose-sensing mechanisms are found as solutions, such as Skin Autofluorescence, Microperimetry, Raman Spectroscopy, and Technology Central Infrared Quantum Cascade Laser and Photothermal Detector (26).

1. **Mid-Infrared (MIR) Quantum Cascade**

This technology utilizes optical spectroscopic techniques that take advantage of the absorption or reflection properties of the skin by shooting light of specified wavelengths (27,28). IR rays can reach the interstitial fluid (ISF) layer, which can vibrate glucose molecules in the blood painlessly and do not cause skin irritation (28). Measurements via MIR are considered splendid and have accuracy comparable to the CGM system and are close to invasive glucometers when measuring blood glucose levels in the range of 50 mg/dL - 350 mg/dL).

2. **Skin Autofluorescence (sAF)**

Based on Rigo et al.'s (29) study, skin Autofluorescence (sAF) is a detector of glucose memory in type 2 DM patients. The relationship between the concentration of advanced glycation end products (AGEs) in the skin when tested using a skin biopsy (30) showed that the fluorescent properties of some AGEs can evaluate the occurrence of glycosylation in a person with type 2 diabetes.

3. **Raman Spectroscopy**

This technology is an optical method with several advantages: it can produce molecular structure information with high spatial resolution while it may be measured qualitatively, has good chemical stability, does not require sample destruction, and does not require reagents or separation (31,32,33). Blood glucose examination can be done precisely and accurately by paying attention to the location and characteristics of the nail tissue that will be traversed by the light sensor wave (34). The two layers' characteristics are almost transparent with a high density of blood vessels. The measurement results can be obtained precisely and accurately because the light sensor transmission can be carried out optimally (34,35). Thus, the results of measurements with Raman spectroscopy have been proven not to reduce the prediction accuracy, and 100% predicted glucose concentrations were acceptable within the clinically relevant range.

4. **Microperimetry**

Microperimetry measures the retina's sensitivity by providing the minimum light intensity that the patient can perceive through light spots that stimulate specific areas of the retina (36).

Non-Sensor Technology System

Blood testing remains the gold standard in the diagnosis. Still, this invasive method can cause a risk of infection associated with phlebotomist procedures, anxiety related to pain, and fear of needles (37-38). These feelings may lead to a greater risk of patients not complying with health service standards (38). Several recent studies have found non-blood glucose values that can answer the problem due to invasive procedure because it involves no needles at all. These studies include using Breath Volatile Organic Compound (VOC) and saliva as biomarkers.

1. **Breath Volatile Organic Compound (VOC)**

This tool measures blood glucose through the metabolites' content in exhaled breath. This is because the breath has been identified as a suitable biomarker to assess oxidative stress caused by glycemic variability (40). Long-term metabolic control has the potential to be a more suitable measure to prevent complications from diabetes. This examination procedure is carried out by taking breath samples through a sterile funnel and then analyzing them using proton-transfer-reaction time-of-flight mass spectrometry (PTR-ToF-MS) and selected-ion-flow-tube mass spectrometry (SIFT-MS). MS) (41,42).

2. **Salivary Glucose Level**

Saliva as a systemic sample is helpful for the diagnosis and research of DM conditions (43). The presence of glucose in salivary secretion is a persistent fact because diabetes can significantly affect the secretion, composition, flow rate, buffer capacity, viscosity, electrolytic ion composition, and protein content in saliva (44,45). Measurement of glucose levels with saliva is considered adequate and has high accuracy (42,45,46). A significant correlation was found between salivary glucose and serum glucose in diabetic patients indicating that salivary glucose concentration is directly proportional to serum glucose (43). In addition, in the Chinese study et al. (2018), researchers were also able to establish a positive correlation between blood glucose and salivary glucose ($r = 0.715$, $p < 0.001$) and stated that salivary measurements had an accuracy of about 85%.

Table 3. The Implementation of Non-invasive technology glucose monitoring

No	Author	Method	Setting	Objective	Intervention	Finding
1	(Rigo et al., 2020)	Retrospective Study Design	France	To evaluate the value of skin autofluorescence (sAF) as a biomarker for patients with Type 2 Diabetes Mellitus.	HbA1c is measured with autofluorescence measurements on the sample's skin surface. The client's HbA1c was also recorded in the last three years.	The findings suggest that sAF reflects elevated blood levels of HbA1c in these patients. An increase in HbA1c indicates the presence of vascular complications such as retinopathy, DKD, a history of foot ulcers, microangiopathy, and macroangiopathy.
2	(Sharanjeet-Kaur et al., 2019)	A Prospective Interventional Study	Malaysia	To determine the relationship between HbA1c values with retinal sensitivity using Microperimeter.	All participating patients underwent a medical examination of the ocular history, blood glycemic test (HbA1c), and comprehensive optometric examination by using the microperimetry examination.	The findings showed a decrease in retinal sensitivity in samples with high HbA1c measurements. This indicates that retinal sensitivity can be a marker in patients with diabetes mellitus.
3	(Kumar et al., 2020)	A Randomised Control Trial	India	To determine the difference in glucose concentration in saliva in diabetic patients and ordinary people.	With the spitting technique, all respondents were taken as much as 2 ml of saliva samples. These samples were processed by centrifugation at 2000 rpm for 2-3 minutes and analyzed to determine their estimated glucose levels.	This finding showed that salivary glucose levels were significantly higher in type 1 and type two diabetes patients than in healthy respondents. Saliva can be utilized to reflect and monitor blood sugar blood glucose levels in patients with diabetes.
4	(Trefz et al., 2019)	A Cross-Sectional Study Design	Germany	To identify exhaled VOC (Volatile Organic Compound) as an alternative to hyperglycemic samples.	Breath samples were taken every 5 minutes for 9 hours from 8 am to 5 pm. The samples will be analyzed using PTRToFMS, and masked CGM was synchronized throughout the experiment. At least 93 breath samples were taken for each volunteer.	Hyperglycemia and associated oxidative stress are immediately reflected in the concentration of volatile organic compounds in the exhaled air. Continuous monitoring of exhaled VOCs provides non-invasive information on metabolic adaptations associated with T1DM even at the early stages of disease progression, and VOCs have unrestricted availability, immediate response to

						metabolic adaptation, and non-invasive tool
5	(Li et al., 2019)	Quasi Experimental Design	China	To identify the accuracy of the use of the Raman spectrum in detecting blood glucose levels through the epidermis of the skin and interstitial fluid.	The volunteers were asked to drink 250 ml of water with 75 g of glucose for 5 minutes and then place their fingers on a stable clay medium for blood glucose measurement using Raman spectroscopy. Thirty measurement spectra were taken for each volunteer in each series.	Raman spectroscopy containing significant blood characteristic peaks was obtained by focusing the laser on micro-vessels in the superficial layer of the nail fold. The results of the evaluation of the method showed promising results. Thus, this tool's prediction of blood glucose levels is acceptable within a clinically relevant range.
6	(Lubinski et al., 2021)	Quasi Experimental Design	Germany	To evaluate the results of the measurement of levels of blood glucose using a non-invasive glucometer combined with skin excitation with quantum infrared cascade laser and photothermal detection	The test was performed by three primary glucose measurements at 5-minute intervals, along with non-invasive measurements of the fingers of another respondent. The duration of the non-invasive measurement is determined by the sum of the averaged IR spectra and does not exceed 30 s.	High accuracy in blood glucose is shown on zone A and B's grids. The mean and median percentage differences between the invasive reference method and the non-invasive method were 12.1% and 6.5%. These results indicate that a non-invasive blood glucose test that combines mid-infrared spectroscopy and photothermal spectroscopy is comparable to the effects of measurements using a minimally invasive glucose meter and finger puncture device.

DISCUSSION

COVID-19 patients with comorbid DM require long-term monitoring of blood glucose levels, including more than four times daily, to detect disease progression and prevent the risk of death (48). Invasive blood glucose monitoring is carried out by taking blood samples by pricking the fingertips with a needle is used for continuous monitoring and can cause skin irritation, risk of infection, and increased discomfort for repeated measurements (49).

Therefore, many experts have started to develop non-invasive technology as an alternative option that is effective and efficient in optimizing glycemic control in DM patients. Based on the finding of the studies discussed in this review, there is reasonably strong evidence that non-invasive technology glucose monitoring is an effective way to improve glycemic control in covid-19 patients with comorbid DM. Interventions and results of non-invasive glucose measurements such as feasibility, accuracy, and satisfaction of self-management of diabetes.

Of the many non-invasive sensor technologies for monitoring blood glucose that has been developed, Raman spectroscopy and Mid-Infrared Quantum Cascade can be the most promising methods among other sensor technologies. Safety and accuracy for the patient are the most important advantages of this method. Raman spectroscopy and Mid-Infrared Quantum Cascade can obtain molecular structure information with a high spatial resolution to provide clear and accurate information regarding blood glucose in a person and are also effective in their use (27,33). This non-invasive technology allows blood glucose management to be carried out without causing pain and reducing the risk of infection. In addition, non-invasive technology can facilitate DM patients to check their blood glucose levels independently at home. Blood glucose measurement with non-invasive technology is proven to produce reliable data with a minimal error percentage (22).

However, the error may be related to the time delay between interstitial glucose and blood glucose. Measurements made in whole tissues are mainly due to the effect of glucose on the interstitial and intracellular compartments (50). This error affects the level of measurement accuracy and must be corrected. One possible way to consider is to increase the sensitivity of each technique and reduce the interfering factors (noise). Based on the proposed integration algorithm, technological improvement can significantly improve the integration result. Although further work is needed to improve the reading accuracy, the unique concept of combining multiple non-invasive techniques seems to offer a promising

Another device for monitoring glucose is non-sensor technology that utilizes saliva and Breath Volatile Organic compounds (VOC) as biomarkers to monitor blood glucose levels in DM patients. Breath and saliva have been identified as relevant biomarkers for measuring blood glucose levels with an accuracy of up to 85% (38,42). The use of these two biofluids still requires further analysis to reduce the risk of bias, considering that both are very sensitive to food or drinks that have just been consumed.

CONCLUSION

The development of non-invasive technology for monitoring blood glucose can be an alternative to reducing the potential worsening conditions. It also risks death in COVID-19 patients with comorbid DM. It remarkably improves the quality of nursing care through safe, comfortable, and convenient glycemic control without causing pain to the patient. In addition, non-invasive sensors and non-sensory blood glucose monitoring have also gone through a series of trials that have proven their accuracy with a minimal percentage of the error to be relied upon to provide continuous real-time blood glucose monitoring.

Our analysis shows that non-invasive blood glucose monitoring technology has excellent accuracy, mainly on devices equipped with sensors. In addition, using this method is considered safer and more comfortable to monitor blood glucose levels sustainably. Therefore, we recommend further research to confirm the effectiveness of this device, mainly to prevent death in COVID-19 patients with DM comorbid.

LIMITATION

This study is limited to discussing various types of non-invasive blood glucose measurement technology that have great potential for monitoring blood glucose levels in COVID-19 patients with comorbid diabetes mellitus. There are no controlled studies that can determine blood glucose monitoring as an independent factor in reducing the risk of death in COVID-19 patients with diabetes mellitus. However, blood glucose monitoring is a critical aspect of the care of DM patients. Further development is needed to create a ready-to-use tool design. Although some study results have the potential to be unidentified when searching through the database, hand tracking will significantly assist the process of optimal article identification.

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