



## Review Article

# Advancements in Monitoring of Glucose: Focus on Non-invasive Glucose Monitoring

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## Abstract

Globally, diabetes is expanding quickly day by day and patients need continuous observation of glucose levels. Currently, techniques that are utilized causes pain, as they need blood samples, and need more time to use. To overcome these challenges, new innovations are being explored which include non-invasive and minimally invasive techniques that are easy to use and cause no pain. This review provides an exceptional report on the main advances, which has been at present being worked on, and is accessible in the market. The principle of every technology, its benefits and limitations are referenced exhaustively. Despite the fact that there has been a progression in the advancements, non-invasive techniques could in any case be improved in terms of dependability and usage. The review concludes that there is a requirement for additional investigations to be done under various physiological conditions of the body.

**Keywords:** Diabetes; Glucose monitoring; Minimally-invasive; Non-invasive; Spectroscopy

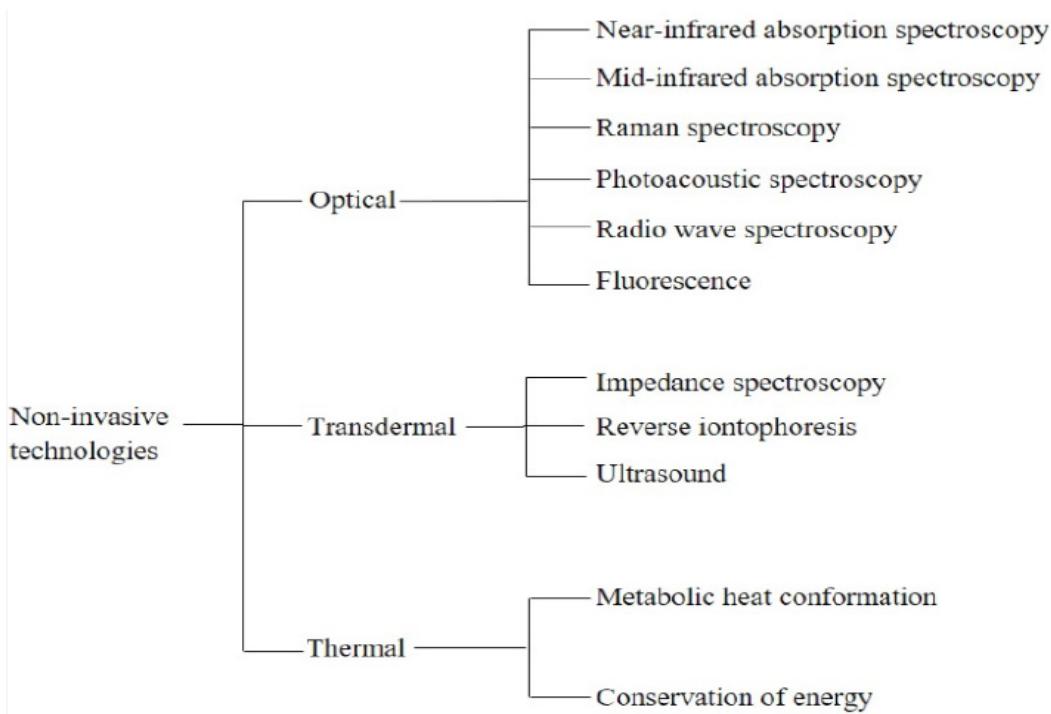
## Introduction

Diabetes Mellitus (DM) is a chronic medical condition that occurs due to irregular insulin levels, which is due to the pancreas that is not functioning properly and does not make enough insulin or not effectively used it by the body. The incidence of diabetes is rapidly rising in low- and middle-income countries. It was the direct cause of 1.5 million deaths in 2019. The levels of glucose were regulated by the insulin that allows body cells to ingest it from the blood circulation system to acquire energy or save it for some time later. But, in case glucose levels remain exceptionally low in the blood for a longer duration, it causes hypoglycemia or if glucose levels are extremely high it causes hyperglycemia. This leads to serious health conditions, like blindness, tissue damage, kidney failure, heart disease, and stroke, and if not treated ultimately lead to death.

Diabetic patients need regular glucose monitoring for the rest of their lives, as there is no cure for diabetes. However, regular blood glucose checking is not very pleasant for most of the patients. Conventional devices utilize the electrochemical method that needs a little quantity of blood, taken from the body either by finger pricking or by a thin lancelet that is embedded subcutaneously. However, these methods cause discomfort, pain, tissue damage, and infection that affect patient compliance. In the past two decades, there was a continuous effort in the development of Non-Invasive (NI) devices that do not necessarily require blood draining and Minimally-invasive (MI) devices that reduce a few of the complications linked to traditional invasive methods.

## Non-invasive Glucose Monitoring: Technologies

The optical, transdermal, and thermal technologies are utilized to monitor glucose (Figure 1).



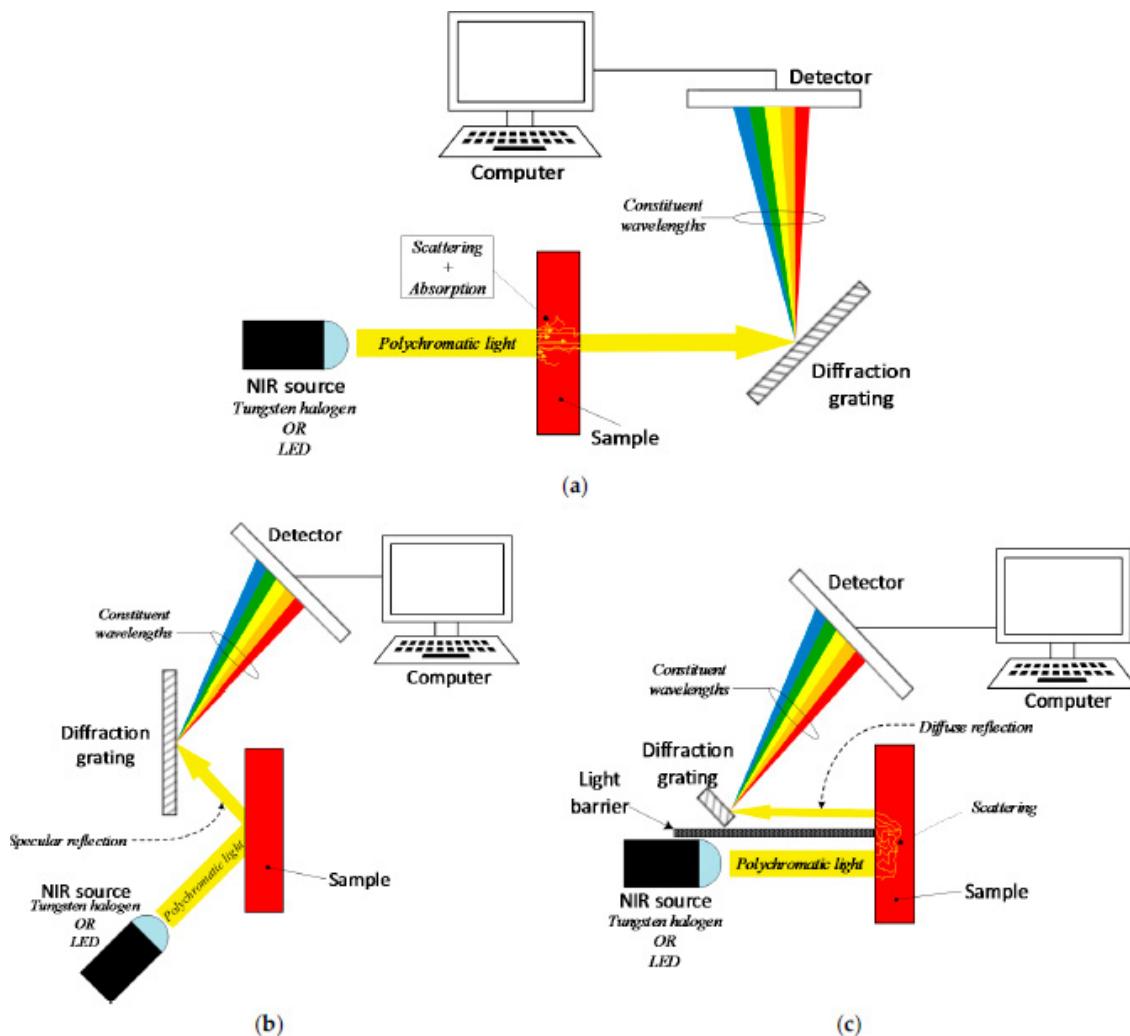
**Figure 1:** Non-invasive glucose measurement techniques.

## Optical Techniques

They utilize various features of light to communicate with glucose in a concentration-based manner.

### Near-Infrared Spectroscopy (NIRS)

It relies upon absorption and dispersing of wavelength frequencies in the 780 nm to 2500 nm range because of atomic vibrations and the revolution of bonds within the molecule. It utilizes three modes for measurement, such as transmittance, reflectance (along with diffuse reflectance), and interactance, and depends on the dispersive spectrometer (Figure 2). It has advantages as well as disadvantages, which are summarized in Table 1.



**Figure 2:** NIR spectroscopy. (a) Transmittance mode. (b) Reflectance mode. (c) Interactance mode.

Advantages	Disadvantages
<ul style="list-style-type: none"> <li>In the NIR band, it is transparent in water.</li> <li>Required minimal expensive materials.</li> <li>The signal power is directly proportional to the analyte concentration.</li> <li>Required least sample production.</li> <li>Works in presence of obstructing materials, similar to glass or plastic containers.</li> </ul>	<ul style="list-style-type: none"> <li>Can give false readings due to heterogeneous distributions of glucose.</li> <li>For accurate detection, glucose concentrations are too low.</li> <li>The scattering level is high.</li> <li>Selectivity issues in determining glucose.</li> </ul>

**Table 1:** Characteristics of NIR spectroscopy.

### Mid-Infrared Spectroscopy (MIRS)

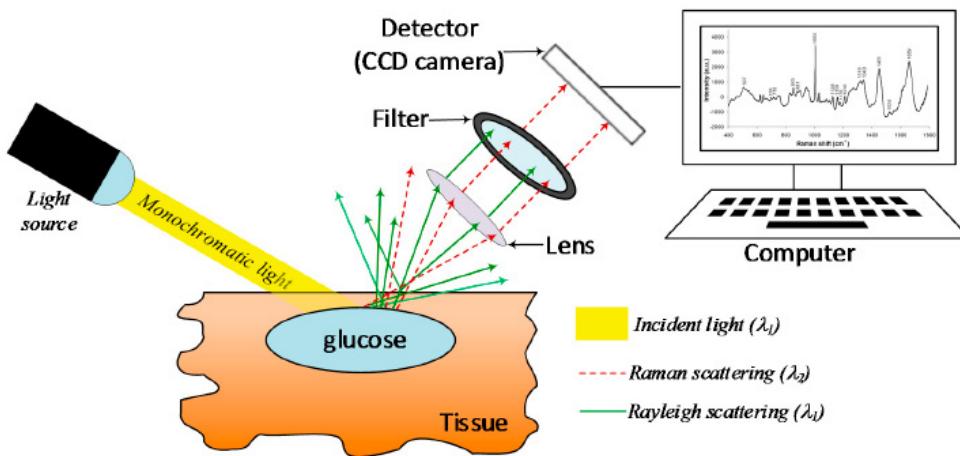
MIRS is known as fingerprint spectroscopy, in which the technique used is vibrational spectroscopy. It depends on a similar technique as NIR spectroscopy, however, utilized in the mid-infrared area between 120 THz (2.5  $\mu$ m) and 30 THz (10  $\mu$ m) (Table 2).

Advantages	Disadvantages
<ul style="list-style-type: none"> <li>The scattered level is low.</li> <li>Absorption bands are profoundly particular and greatly outlined.</li> <li>MIR radiation is strongly absorbed by glucose compared to the NIR band.</li> <li>Specific MIR wavelengths can be absorbed by glucose; hence, the concentration can be estimated with higher precision.</li> </ul>	<ul style="list-style-type: none"> <li>Few micrometres of penetration depth.</li> <li>Due to poor penetration, only reflection is feasible.</li> <li>Strong water absorption.</li> <li>Expensive equipment.</li> </ul>

**Table 2:** Characteristics of MIR spectroscopy.

### Raman Spectroscopy

In view of the Raman Effect, it decides the level of dispersing of monochromatic light. The basic configuration contains a lens that captures a fraction of the radiation that is scattered and directs it to the filter to permit just the Raman dispersed light to be noticed by the detector. The computer processes the signal and gives the corresponding Raman shift (Figure 3, Table 3).



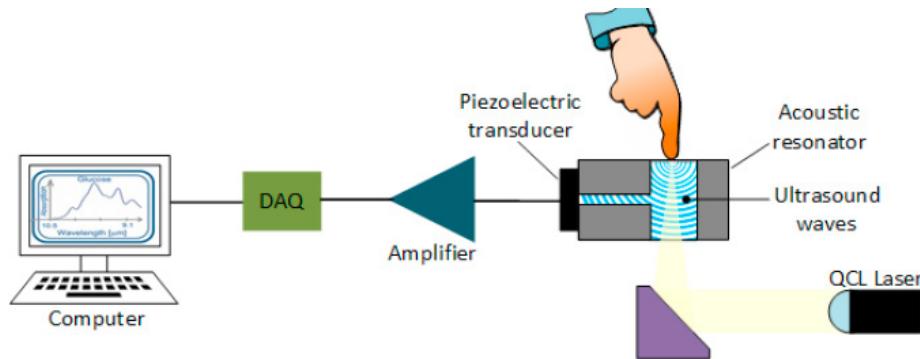
**Figure 3:** Basic Raman Spectroscopy Instrument.

Advantages	Disadvantages
<ul style="list-style-type: none"> <li>Minimal effect to temperature variations</li> <li>Less delicate to water.</li> <li>Appropriate on any surface as it estimates dissipated light alongside obscure substances.</li> <li>Great precision.</li> </ul>	<ul style="list-style-type: none"> <li>Susceptible to impedance from different atoms like haemoglobin.</li> <li>Laser frequency and potency are unstable.</li> <li>Collection duration is long.</li> <li>Prone to noise obstruction, fluorescence, and turbidity</li> </ul>

**Table 3:** Characteristics of Raman spectroscopy.

### Photoacoustic Spectroscopy (PAS)

This uses a similar technology as ultrasound waves; however, it uses a small laser impulse with a frequency that is consumed by a specific particle in the liquid to create microscopic confined heating, because of the particular heat limit of the tissue under assessment. The assimilated heat creates a volumetric extension of the medium that produces an ultrasound wave, which can be identified by the sensors called acoustic or pressure. By following the top-to-top changes of the distinguished signal, it is feasible to match them with the varying levels of blood glucose (Figure 4, Table 4).



**Figure 4:** Non-invasive Photoacoustic spectroscopy.

Advantages	Disadvantages
<ul style="list-style-type: none"> <li>Moderately basic technique.</li> <li>Does not affect water deformity.</li> <li>Not vulnerable to NaCl, albumin, and cholesterol.</li> <li>No influence on PA signals by dissipating particles.</li> </ul>	<ul style="list-style-type: none"> <li>Sensitive to temperature variations, pulsation, movement, and surrounding acoustic sound.</li> <li>Minimal signal-to-sound proportion.</li> <li>Longer duration for integration.</li> </ul>

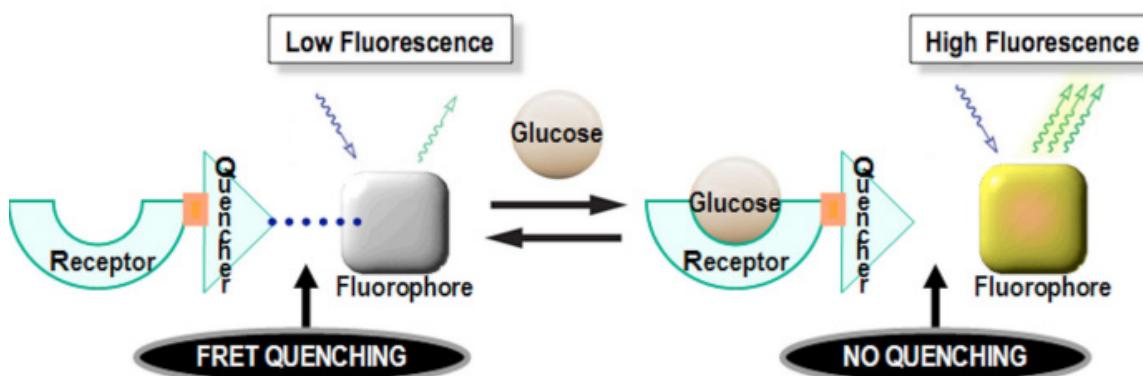
**Table 4:** Characteristics of photoacoustic spectroscopy.

### Radio Wave Spectroscopy

It measures levels of glucose by communicating with radio frequencies of low power through a segment of the body-like area between the thumb and index finger or the earlobe. The development of the device is still under process.

### Fluorescence

Fluorescence is a favorable technology, which is an alternative to electrochemistry and spectroscopy as it provides precise glucose examination in diabetes patients. It emits light by a substance after absorbing light. It happens when approaching light hits a particle or structure, which has characteristics of fluorescent and elevates an electron to a greater energy level (Figure 5, Table 5).



**Figure 5:** Fluorescence Sensor Mechanism.

Advantages	Disadvantages
<ul style="list-style-type: none"> <li>Highly delicate to glucose concentrations as little as 25 <math>\mu\text{M}</math>, permitting even single-atom recognition.</li> <li>High precision because of distinctive optical characteristics of molecules.</li> <li>It can estimate the concentration of analyte because of fluorescence potency and deteriorate times.</li> <li>Does not affect due to the scattering of light.</li> </ul>	<ul style="list-style-type: none"> <li>Prone to obstruction because of pH variations and levels of oxygen.</li> <li>Potential toxicity issues because of foreign material in biological media.</li> <li>The short life expectancy of the fluorophore.</li> <li>Limitations related to photostability and loss of acknowledgment ability.</li> <li>Biocompatibility problems because of nearby tissue injury.</li> <li>Susceptible to auto fluorescence.</li> </ul>

**Table 5:** Characteristics of fluorescence technology.

### Transdermal Technique

It involves glucose estimation through the skin by utilizing electricity or by ultrasound.

### Bioimpedance Spectroscopy (BS)

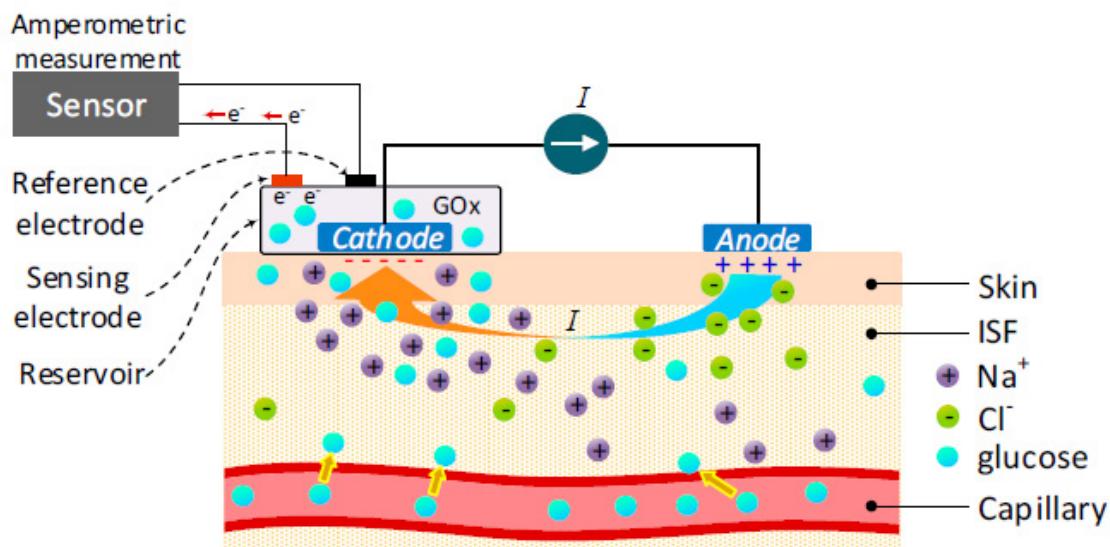
It is likewise called dielectric impedance spectroscopy. It analyses the modifications actuated by blood glucose alterations in the permeability and conductivity of the Red Blood Cells (RBCs) membrane (Table 6).

Advantages	Disadvantages
<ul style="list-style-type: none"> <li>Not expensive.</li> <li>Measurable on the skin without any difficulty.</li> </ul>	<ul style="list-style-type: none"> <li>Delicate to temperature modifications and movement.</li> <li>Delicate to sweat and water.</li> <li>Physiological variations can affect by influencing the cell membrane.</li> </ul>

**Table 6:** Characteristics of bioimpedance spectroscopy.

### Reverse Iontophoresis (RI)

It is a “minimally invasive” mechanism as it depends upon the course of a little electric flow between an anode and cathode present on the outer layer of the skin to gain admittance to a limited quantity of Interstitial Fluid (ISF) (Figure 6, Table 7).



**Figure 6:** Principle of reverse iontophoresis for monitoring glucose.

Advantages	Disadvantages
<ul style="list-style-type: none"> <li>Electrodes making is not hard and can be employed to the skin with the least preparation.</li> <li>In a stable environment, there will be a good connection between glucose levels and the blood.</li> <li>Glucose estimation depends on the notable enzymatic technique.</li> </ul>	<ul style="list-style-type: none"> <li>Skin aggravation because of the current passage.</li> <li>Sensitive to sweating.</li> <li>Rapid alterations in glucose concentration cannot be recognized precisely.</li> </ul>

**Table 7:** Characteristics of Reverse iontophoresis.

## Ultrasound

The propagation duration of ultrasound frequencies is estimated through the media. If the concentration of glucose is higher, then the ultrasonic wave proliferations are faster (Table 8).

Advantages	Disadvantages
<ul style="list-style-type: none"> <li>Can move significant distances beneath the skin or tissue.</li> <li>Do not get affected by changes in the skin complexion.</li> </ul>	Sensitive to ambient conditions.

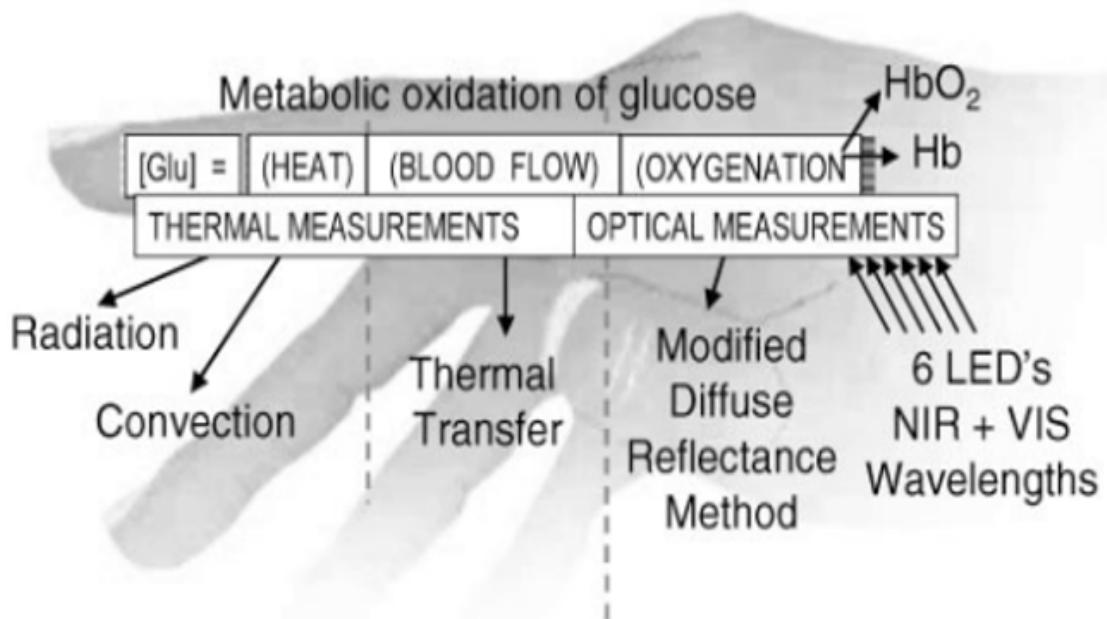
**Table 8:** Characteristics of Ultrasound technology.

## Thermal Techniques

They intend to gauge glucose by distinguishing physiologic indicators, which are linked to metabolic heat production.

### Metabolic Heat Conformation (MHS)

The measurements are taken based on files related to the oxidative metabolism of glucose. Glucose undergoes metabolic oxidation and gives the vast majority of energy for cellular functions. The heat produced by glucose oxidation depends on the unpretentious equilibrium between capillary glucose and oxygen allocation to the cells. So, glucose in the blood can be estimated by the body temperature and the supply of oxygen (Figure 7, Table 9).



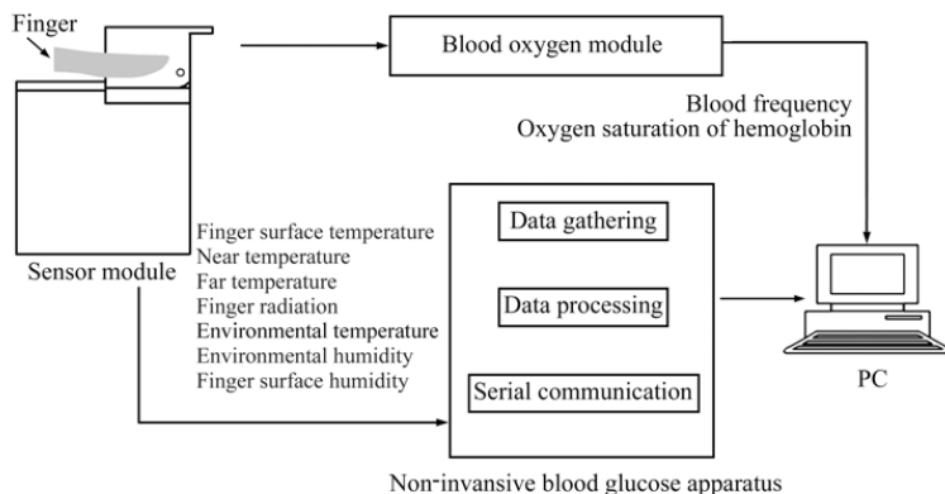
**Figure 7:** Principles of the MHC method.

Advantages	Disadvantages
Physiological parameters are generally simple to estimate utilizing grounded advances.	<ul style="list-style-type: none"> <li>Sensitive to obstructions by environmental conditions.</li> <li>Get affected by sweat.</li> </ul>

**Table 9:** Characteristics of MHC.

### Conservation of Energy

The metabolic process in the whole human body is the energy metabolism procedure. At the point when the supply of oxygen is adequate, the glucose undergoes into reaction. The energy produced by the body transforms into heat and there is an estimation that 80% of temperature disseminates in various structures. The alterations in the blood sugar concentrations lead to modifications in the metabolism of body and influence the various physiological properties, for example, the radiation temperature on the outer layer of the body (Figure 8).



**Figure 8:** Experimental setup utilized in a clinical trial.

### Conclusion

This survey has given a specialized perspective on the current advancements and instruments utilized to monitor the levels of glucose without taking blood samples. Regardless of the fact that there has been a lot of exploration carried out to establish a non-invasive glucose monitoring instrument, the complications and indirect type of the procedure used to measure remain obstructions to the advancement of successful non-invasive technologies that can be executed in easy to use instruments. Some of the instruments have gained extensive headway in the latest years. However, efforts should be made persistently to further assess and develop execution, ease of use, and acknowledgment by the users.