A Review: Non Invasive Sensing System for Detection Glucose Level

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Abstract. Attributable to the probability of rapidly increasing numbers of diabetic patients in the world, and due to the effect of COVID-19 virus and the hazardous of life-jeopardizing critical cases that require continuous nursing monitoring the glucose level (CNMGL). The contamination possibility and the pain of the traditional measuring systems limiting the number of blood glucose checking, which decreases the diabetic patient controlling their blood glucose level (BGL). Now the indigency for a non-invasive glucose detecting system (NIGDS) is highly praised. The aim of the review of the NIGMS and their challenges to the future transcend these challenges. The last reviews of NIGDS discuss the measuring system concerned with their techniques but this study has been reviewing the detection system by their measuring site and collects the complication of measuring systems in each site. The main contribution of our works is to demonstrate that all the previous studies of glucose detection systems depend on the invasive calibration for each patient before starting the measurements due to the high numbers of parameters that interfere with glucose measurements. Toward NIGDS that is wearable and monitors the patient blood glucose continuously.

1. Introduction

Now diabetes mellitus (DM) is a serious communal illness in most countries of the world essentially the Middle East [1], which is a collection of syndromes that disturbance the patient control of BGL because of the diminished insulin production or the existence of an insulin-resistant element that deny the action of insulin hormone [2, 3]. The statistic about the diabetic patients is estimated an expected to highly increase in 2030 to be approximately between 366 million to 552 million patients. Diabetes is actually a serious common disease that increasing rapidly and cause a lot of mortality in adults. The repeated monitoring of diabetic patient's blood glucose is very important in diabetic management to maintain the blood glucose within the normal physiological range to avoid diabetic complications such as kidney damage, heart failure, or blindness and to enable a diabetic patient to live within a healthy lifestyle [4]. The excessive elevation in patients’ blood glucose could produce patient death in addition to serious chronic complications [5]. The commercial glucometer is a painful invasive device and could be used in limited times a day due to its desolation and depression [6]. In the last decades, a variety of different biomedical sensors have been deliberate to measure and detect the patient BGL [4]. The non-invasive glucose detection methods are studied and classified according to the most usual sites of measurements and discuss the glucose detection sensors with their specification and limitations toward an accurate innovative non-invasive glucose
detection system. The measurement site must contain glucose with a concentration of constant relation to blood glucose, stable temperature site, and the site should be reached easily.

2. Non-invasive glucose detection through patient’s eye
The eye is a specific sense organ which is received the light from the visual images of the scene and transfer it to the brain as an electrical signal. There are several types of glucose detection from the eyes site [7].

2.1. Polarimeter contact lens sensing system
The system applied two linear polarized lights on aqueous humor, which is the fluid of the anterior chamber of the eye that contains glucose in an approximate concentration of blood glucose and has a very low scattering effect comparing to patient skin, and because of glucose specification of organic optically active molecules due to its chiral unsymmetrical shape, then the plane of the light of polarization will be rotated to some degree [8, 9]. The concentration of glucose can be determined by equation 1.

\[
[\alpha]_\lambda = \frac{\alpha}{Lc}
\]

(1)

Where \([\alpha]\) is the specific rotation of glucose at a given wavelength (\(\lambda\)), L is the optical length, and C is the glucose concentration. Due to this equation that shows the specific rotation factor of glucose is inverse proportional to the applied wavelength in the visible, then the system must use short wavelengths. This polarimeter sensing system uses two wavelengths in order to neglect the albumin charity effect according to equation 1[10]. This system has several limitations such as the system sensitivity to fluctuations in laser intensity, glucose concentration in the aqueous humor are approximately equal to that of blood but With one minute delay time, eyes motion artifact that changes the path length, the eye cornea cause linear polarized light to deformed becomes slightly elliptical, the safety of coupling two lasers into the patient eye, and the complexity of the system [11, 12]. The polarimeter contact lens also has several specifications that also produce an additional limitation such as its oxygen permeability, the expansiveness of its disposable character, and the lens must design to operate at physiological tear pH [8, 13].

2.2. Infrared spectroscopic sensing system
The system applied four bands of infrared lights on aqueous humor and measure the reflected light from the eye lens and enable to predict glucose level but with an acceptable range due to the complication of detection reflected light that shows only 0.1 percent of the incident due to the strong absorption of infrared light by water and the danger of heat energy of lasers limit the increase if the light flux [7, 14].

2.3. Enzymatic tear contact lens glucose meter
The glucose sensing disposable colorless contact lens is based on tears glucose concentration measurement by an enzymatic method like the fingerpicking detection method due to measuring the amount of consumed oxygen, which is related to the glucose level [15, 16]. Glucose measurements in tears are limited by their concentration is ten times lower than blood glucose concentration and with a thirty-minute delay time. Glucose measurements also may be affected by other components and analytes that are contained in tears, such as Ca2+, Mg2+, Na+, K+, lactate, cholesterol, histamine, and urea. The used sensing contact lens material must be biocompatible, stable environmentally, such as it must be non-polarized, with limited leaching effect, and must have stable pH (the acidity or basicity) with the eye solution [15, 17].

2.4. The amperometric tear strips glucose meter
Non-invasive glucose sensing system by needle type like strip sensor, that enables to measure glucose level by an amperometric electrode that detects the glucose from the electrochemical change that is related to enzymatic change. Uric acid and ascorbic acid produce interferences with glucose measurements that must be minimized by calibration method but still, a low ratio affects the result. The volume of the tearing sample must be fixed with 1 microletter for every sample [18, 19]. Another study uses the blood glucose strip to
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detect the glucose level in tear, but it has more interference and inaccuracy comparing to the tear strip glucometer [6].

2.5. NovioSense glucometer device
A bio-fluid thin-film sensor is used to detect glucose levels, by placing the sensor in the lower punctum of the eye in the lower palpebral conjunctiva region. The sensor contains a thin flexible coil covered by a polymer material shielded by a polysaccharide biocompatible outer cover. However, of this biocompatible shield, some volunteer suffer from eye irritation [20, 21].

2.6. Two fluorescence contact lenses sensing system
Fluorescence technique based on eye lenses produce photo fluorometer signal in response to tear glucose level, this fluorescence is produced by tissues excitation with the blue light of 488nm and detect the light fluorescence within two wavelengths at 514nm and 574nm, 514nm are very sensitive to glucose concentration in contrast with 574nm are not sensitive to glucose concentration, by subtracting the 574nm signal from 514nm signal, resulting in a fluorescent signal with the best relation to glucose level and eliminated abundant artifact and any signal not related to glucose concentration [22]. However, this detection system is suffering from complexity in biocompatibility, eye irritation, and system delay is equal to 15 min due to the time required for tear glucose to mimic the blood glucose and time required for tear glucose to diffuse into the 500µm thick contact lens [23].

2.7. Holographic visualized glucose meter lens system
Holographic glucose meter technique is based on measuring tears glucose concentration by specific contact lens that contains organized spacings and coated with 7 µm hydrophilic material which has the ability to hydrogel bound, this hydrophobic material swallow the tear that contains glucose and the lens spacing between fringes increased according to glucose concentration. When this 100 µm thickness specific lens is illuminated by white light, the longer wavelength will be diffracted and the color of the hologram light reflected off will change. The wavelength of reflected light is directly related to the lens fringes spacing and glucose concentration in tears, this holographic color is visualized and its wavelength could be detected by a spectrometer to produce valuable glucose measurements [24, 25]. The limitations of this technique are high price disposable contact lens, irritation and discomfort ability of lens, the delay time between BGL and tears glucose level, and the poor system sensitivity without invasive calibration [24, 26].

3. Non-invasive glucose detection through patient’s finger
A finger of a hand is the usual glucose detection site, which contains blood vessels, the elevation of blood glucose will affect the finger by producing a combination of peripheral neuropathy with peripheral vascular disease, which could lead to finger gangrene and in severe infection cases finger amputation. There are several types of glucose detection from the finger site [27].

3.1. NIR glucometer system
This system uses near-infrared NIR with a wavelength from 600nm to1300nm to detect blood glucose from the patient finger. The best-penetrated properties NIR focused to pass through patient finger but the percentage of transmitted, scattered and reflected light is depended on tissue chemical composition. The change in the percentage of transmitted light due to the BGL changes produces a glucose optical signature, but the sensitivity of the system and the temperature of tissue fluctuation, and the difference in the hemoglobin percentage may affect the system accuracy [28]. It is found that the range from 950nm to 1000nm has the best glucose correlations, but with limitation of interference with environmental parameters, patient skin thickness, body temperature, blood pressure, and concentrations of body water, albumin, and triglyceride [29]. Another study shows a good glucose correlation with a 940 nm infrared source with a well-shielded detector that can produce an acceptable result with more common tools [30]. However, at the beginning of research in the NIR glucometer system, they used wavelength from 1050 to
2450 but they suffering from inaccuracy due to the use of unsuitable wavelength to the tissue optical properties and the water absorption in this wavelength range. However they use strict calibration and signal processing, but still, the detected light suffering from the high scattering and absorption of light in addition, which limited it’s related to BGL [31, 32].

3.2. **MIR glucometer system**
This system uses mid-infrared MIR with the wavelength of both 5820nm and 5890nm to detect blood glucose from the patient finger by using a photoacoustic sensor but the system size, price and precise wavelength in the quantum cascade laser system produce complexity that prevents the patient self-usage, the low MIR penetration in patient tissue prevent the photodetection of light and weighted the photoacoustic sensing method [33, 34]. Another study implemented a MIR photoacoustic in-vitro system to detect BGL in deep skin layers, by using lasers of (9132-9900) nanometre wavelength, after immersing the skin by water to measure the generated ultrasound concerning the photoacoustic effect and due to the change in light absorbance, the system enables to measure the BGL [35, 36].

3.3. **Microwave glucometer system**
This system uses a microwave system with 0.8 Giga hertz applied on the patient finger and measure the reflected signal by a band pass filter to detect the dielectric properties of the finger that change linearly related to patient glucose level but with limitation of filter linearity and the initial system working time is near five minutes to reach stability [37, 38]. Another study uses a microwave sensor by tracking the measurements of maximum amplitudes for different frequencies (10 mega-hertz to 2 giga-hertz), the maximum amplitude is related to finger BGL [37, 39]. Limited by the decrease the system precision with drifting away from normal glucose range [40, 41].

3.4. **Metabolic heat confirmation glucometer system**
Metabolic heat confirmation method estimate BGL Noninvasive by optically and thermally measuring multivariable vital parameters that involves blood hemoglobin, blood oxygenation, blood flow rate, and body temperature and convert the information to BGL estimation. By applying six LED lights with different specific wavelengths at visible and near-infrared regions (470nm, 535nm, 660nm, 810nm, 880nm, and950 nm) and measuring the reflected light signals and the thermal conductivity of the finger due to blood flow [42, 43]. This is limited by the interference with ambient light, humidity, and temperature, also a calibration with venous glucose measurements for each patient is very important for a good resultant [42, 44].

3.5. **Electromagnetic glucose monitoring system**
The electromagnetic sensing system is based on the relationship between glucose concentration and blood conductivity [45]. By applying an external moving magnetic field to produce an eddy current through the patient tissue that can be measured and is strongly affected by glucose concentration and blood dielectric parameter. The glucose measurements are limited by the effect of change in body temperature and any physiological disease that changes the patient dielectric tissue parameter [46, 47].

3.6. **Raman spectroscopic glucose detection system**
Raman spectroscopic system measured the BGL by applying light with 785nm laser on the patient finger and measuring the low intensity higher wavelength scattered light, At the NIR region light which has good penetration, low water absorption properties, and low water scattering properties. Using a sensitive CCD detector to detect scattered laser intensity which is related to tissue glucose level. The system suffering from low laser stability for long acquisition time and motion artifacts [48, 49].

3.7. **Acousto-optic glucose detection system**
The acousto-optic detection system is based on the interaction of both electromagnetic light waves and the mechanical sound wave in the band of ultrasound, the ultrasound wave is facilitating the light passaging
and transmitting through the patient tissue, with the light wavelength that mimicking the glucose level of
the patient blood, glucose detection level is possible after an invasive calibration [50].

4. Non-invasive glucose detection through patient wrist
A comfortable noninvasive watch is also a glucose detection favorable site.

4.1. Wrist enzymatic reverse iontophoresis glucowatch system
This system uses an amperometric sensor that detects the chemical base response to its interaction with
the patient's wrist skin. The chemical base is a glucose oxide enzyme dissolved with hydrogel, result in glucose
level detection when measuring the voltage change correlated with the oxygen consumption rate [51, 52]. Reverse
iontophoresis is a method for stimulation blood glucose to march out from the patient skin to
measure it noninvasively. Iontophoresis is an active method of injection drugs inside the body through the
skin accomplice by an assistant electrical current. In contrast with reverse, iontophoresis is a method of
extracting blood glucose outside the body through the skin by an assistant electrical current. The electric
current is produced by applying an electric potential between two surface electrodes (anode and a cathode)
[51, 53]. The electrical potential caused a migration of sodium and chloride ions from the skin's inner layers
towards the surface electrodes, this ion's movement generates an electric current. Glucose molecules are
uncharged but moved with ions and pass through the skin and collected at the surface cathode electrode.
Therefore, the glucose is measured at the skin surface using an enzymatic glucose meter that will measure
the current change that is related to the glucose amount. But the glucose-measuring spends a long time
(more than 7 min) to huddle with a sufficient amount of glucose, this long time will produce skin irritation,
and an increase in sweat amount, which will affect the glucose reading measurements [54, 55].

4.2. Wrist FIR glucowatch system
This system uses a far-infrared FIR that emits from the wrist to detect blood glucose level, this light is
within (5000-12000) nanometres wavelength of 37°C body temperature, part of the FIR energy is absorbed
by blood glucose within 9400nm, that absorption makes possible detection of emits FIR concerned with
BGL this system is limited by poor FIR emission and the expensive detector [56, 57].

4.3. Wrist glucometer based on bioimpedance spectroscopic system
Bioimpedance spectroscopic system is established on the relation measurement of glucose concentration
and the impedance of patient tissue. BGL impacts the sodium and potassium plasma concentration, which
will change the blood resistance to electrical current and the blood impedance [53, 58]. To measure BGL,
it's important to measure tissue impedance to electrical current flow for a broad electrical frequency range
(from 100 Hz to 100 MHz) and calculate the relation between glucose concentration and tissue impedance
[57, 58]. The limitation of this system is the tissue impedance change due to different diseases and the body
hydration state [53, 58].

5. Non-invasive glucose detection through forearm
The forearm could be a good glucose detection site.

5.1. Forearm glucose detection based on localized reflectance of regulated temperature method.
This technique applies four lights with different wavelengths (590, 660, 890, and 935) to the patient's
forearm skin and detects the reflected light for two hours. The skin temperature is changed every 6 min
between 22°C to 38°C to change the reflective index, the skin temperature is fixed four times in each
temperature change cycle, for measuring reflected lights at specific skin temperature [59, 60]. The change
in glucose concentration modulated the scattering light and the reflected light due to its change to the
microvessels scattering factor. Several parameters limited the glucose detection in this method, such as light
detector position, and several diseases that modulated tissue properties of scattering light [59, 61].

5.2. Forearm glucose detection based on optical coherence tomography method.
The optical coherence tomography is a diagnostic system, which detects the interferometric information and its relation to glucose concentration, by applying a low coherent light with 1300 nm on the patient forearm by interferometer system, and compare between both the interferometric signals (light reflected from the reference mirror and the light backscattered from tissue sample), detecting the interferometric signal by photodetector and processed the signal. Calculating the delay time of backscattered light and measure the light intensity is done by the signal processing system. For infrared light source applied on human tissue, the total attenuated light is dominated by scattering light, and due to very low absorption ratio comparing to the scattering, this makes the direct relationship between increasing glucose and decreasing refractive index and due to increasing refractive index of interstitial fluid and decrease scattering coefficient mismatch between the refractive index of scattering center and refractive index of interstitial fluid [62, 63]. This method is limited by tissue in heterogeneity, motion artifacts, patient physiological effects (skin temperature, blood pressure, and heart rate), and the diseases that change the patient tissue scattering coefficient, another important limitation is the need for calibration with first reading with an invasive glucose measurements [62, 64].

5.3. **Photoacoustic spectroscopic glucose detection system**

The photoacoustic spectroscopy method is based on the ultrasound mechanical wave generated due to the applied laser light on tissue. Two pulsed NIR lights within 905nm and 1550 wavelength are applied to produce an elevation in tissue temperature that is dissipated as an ultrasound vibration in a sample, using a specific light wavelength that mimics the blood glucose and not affected by tissue water content, the detected ultrasound is related to blood glucose concentration. A piezoelectric sensor measure the electrical signal that is generated due to the ultrasound wave and pressure changed on the PZT crystal side [65, 66]. This glucose detection method is limited by low sensitivity and the change in environmental temperature and pressure that interface with the glucose estimation measurements [67].

6. **Non-invasive glucose detection through abdomen**

The wide detection area that is found in the abdomen also could be a detection site.

6.1. **Abdominal ultrasound and electrochemical glucometer system**

Ultrasound and electrochemical glucometer systems demonstrate a trans-dermally method to measuring BGL by using a conjunction of an ultrasound array and electrochemical biosensor that contain glucose oxidase hydrogel and ampere-metric electrodes [68, 69]. By using ultrasound which is generated from flex-tensional transducer class V of low frequency (1-100 ) KHz. The BGL mensuration results after 20 min by measuring the diffusion rate of glucose from the hydrogel to the skin using the electrochemical biomedical sensor [70, 71].

7. **Tympanic membrane**

7.1. **Thermal emission spectroscopic glucometer**

The thermal emission spectroscopic glucose measuring system is based on the very sensitive tympanic thermometer to naturally heat emitted from the tympanic membrane. Glucose molecules absorb the infrared radiation in the range of 9.8µm and 10.9µm, the intensity of thermal infrared emitted from the tympanic membrane within range of 9.8µm and 10.9µm wavelength is directly related to glucose concentration [72, 73]. The advantages of this technique are the good reproducibility and superficial blood vessel in the tympanic membrane that covers with a thin layer, but this technique is limited due to the interference with different pathophysiological parameters that cause temperature variation and also limited by motion artifact [72, 74].

8. **Conclusion**
It is very important to measuring BGL several times a day for the diagnosis and therapy of diabetes patients, they need several measurements a day and continuous monitoring, especially now day diabetic COVID-19 patients to achieving the most effective drug strategy for the diabetic patient, and produce the best physiological BGL control. Non-invasive glucose measuring systems through patient eye has the most expensive and complex design due to eye high sensitivity and need the very inert material to avoid eye irritation and to produce acceptable biocompatibility, stability to leaching effect, furthermore the delay time between tear glucose and blood glucose that decrease the preferability to the eye measuring site. Patient finger and wrist are the best detections cite due to their superficial blood vessels, comfortability and lesser irritation cite. All the previous studies are suffering from several challenges which are the limited accuracy, components price, and delay in detection BGL time, or complicated detection procedure that need to new commercial effective system and could be used personally. The main conclusion of our works is to demonstrate that all the previous studies depend on the invasive calibration for each patient before starting the measurements due to the high factor numbers that interfere with glucose measurements.

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