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A Survey on Design and Development Techniques of Non-invasive Glucometer

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ABSTRACT: Diabetes has been one of the leading causes of death around the world for many years. Since it is not curable, one of the measures of controlling this disease is daily monitoring of blood glucose levels. The conventional method of blood glucose measurement is painful which involves pricking the finger every day. Non-invasive techniques of glucose measurement provide the best alternative for a diabetic to monitor the glucose levels comfortably. Efforts were made in this direction by exposing the blood tissue with radiofrequency wave and correlating the glucose concentration with radio frequency transmission coefficient. Later Near Infrared Spectroscopy permitted the utilization of the Near Infrared Radiation straightforwardly on the skin abstaining from pricking and measures the light consumed by glucose particles. This paper thus reviews various types of non-invasive blood glucose measurement techniques.

I. INTRODUCTION

Diabetes Mellitus (DM) is a group of metabolic diseases that affect the body's ability to regulate blood glucose levels. Type I diabetes (an autoimmune sickness) is prominent in children and youngsters in which their bodies show reluctance to produce insulin. These patients ought to take insulin injections every day to preserve lifestyles. In Type II diabetes (a metabolic disease) diabetes, the body cells have the capability to provide insulin but in an inadequate quantity consequently using it improperly.In the long run, the prolonged elevation in blood glucose levels causesevere damage to huge and small blood vessels leading to complications related to mortalit ysuch as cardiovascular ailment, neuropathy, retinopathy and nephropathy. Hence continuous monitoring of glucose levels is required. A conventional glucometer, which is invasive measures glucose levels through the blood samples taken by piercing the fingertip and accumulating adequate quantity of blood. But it causes pain, skin irritations and even infections thus making the patient feel discomfort. The best alternative is non-invasive glucometer. Non-invasive methods are still under research by various research groups working on feasible techniques for measurement of glucose levels.

II. NON-INVASIVE TECHNOLOGIES

Bio impedance spectroscopy

Principle

Bio impedance is a measure of the imperviousness to electric current coursing through the tissues of a living organism.[1] The impedance range, or dielectric spectrum, is measured in the recurrence scope of 0.1 to 100 MHz. Variations in plasma glucose concentration instigate an abatement in sodium particle fixation and an expansion in potassium particle focus in red blood cells.[2] These varieties thusly changes the layer capability of red platelets, which can be assessed by deciding the permittivity and conductivity of the cell film through the dielectric spectrum.[3-5]

Advantages

It has the ability to separate among extracellular water and intracellular water and along these lines it can give a gauge of body cell mass, in this way describing the blood bio impedance properties. The gadget is anything but difficult to apply and periodic in value contrasted with different gadgets.

Limitations

The impediment of this innovation is that it requires an equilibration procedure, wherein the client must rest for an hour prior to beginning the measurements.[3] Problems stay to be settled, for example, the impacts of temperature and body water content (e.g., skin dampness, sweat, general hydration) should be resolved.[6]

Raman Spectroscopy

Principle

Raman spectroscopy depends on the utilization of a laser light to prompt swaying and pivot in human liquids containing glucose. The way that atomic vibration impacts the outflow of scattered light makes it conceivable to gauge glucose focus in human fluids.[7]

Advantages

Raman spectroscopy more often than not gives more keen and less covered spectra when contrasted with NIR spectroscopy. The power of otherworldly elements is relative to the grouping of the specific species, and the spectra are less influenced by temperature variations. Likewise, it is moderately a great deal less touchy to water, and the impedance from glow and fluorescence wonders is just unassuming.

Limitations

The principle constraints are identified with unsteadiness of the laser wavelength and power, and long phantom securing

times. Low power light source used to counteract harm fundamentally lessens the flag to-commotion proportion however obstruction from different mixes stays as an issue.

Electromagnetic sensing

Principle

Like bio impedance spectroscopy, this system evaluates dielectric parameters of blood. The qualification between them is that an electric current is used in bio impedance spectroscopy, while the electromagnetic coupling between inductors is utilized as a part of electromagnetic sensing.[8,9] The sensor makes utilization of electric streams to endless supply of the dielectric parameters of the blood, which can be brought about by changes in glucose levels.[10] The recurrence go utilized as a part of this procedure is 2.4–2.9 MHz But relying upon the temperature of the explored medium, an ideal recurrence is to be resolved, at which affectability to glucose changes achieves its most extreme.

Advantages

A particular recurrence range can separate the impact of blood glucose and minimize the qualities of different substances, for example, cholesterol, which may skew readings. It is moderately sheltered as no atoms of the body experience ionization.

Limitations

Temperature strongly affects this type of estimation, since it impacts the ideal examination recurrence. Moran et al detailed that the blood dielectric parameters are influenced by a few parts other than glucose.[10]

Fluorescent technology

Principle

This system tracks the nearness of glucose particles in blood utilizing fluorescence reagents. Many methodologies exist, for example, measuring changes in fluorescence reverberation vitality exchange between a fluorescent benefactor and an acceptor, or measuring glucose-incited changes in inherent fluorescence of enzymes.[11] Studies had drawn out that glucose levels in tears reflect fixations like those in blood, and hence, fluorescence of tears can be utilized in non-obtrusive glucose observation. This approach can track blood glucose with a rough 30-minute slack time and does not experience the ill effects of impedance from varieties in the light power of the surrounding environment.[21] The photonic detection is accomplished with polymerized crystalline colloidal clusters, which react to various fixations.

Advantages

This innovation is exceptionally delicate; it can distinguish single particles, bringing about next to zero harm to the body. Additionally, it conveys the terms of fluorescence intensity and rot times, both of which are free of dissipating light and fluorophore focus, which can decrease misfortune through dissemination or corruption.

Limitations

Photonic detection can experience the ill effects of solid scrambling phenomena, particularly in fluorescence innovation. There are much more impediments, for example, short lifetimes and biocompatibility, which should be managed, conceivably by the utilization of colorimetric assays.[12]

Near infrared spectroscopy

Principles

Near infrared (NIR) spectroscopy is situated in the wavelength area of 730–2500 nm. The standard is that the assimilation estimation of NIR recurrence should be possible by a specimen situated in the way of an NIR shaft. It permits blood glucose estimation in tissues by variations of light power, in terms of transmittance and reflectance. Huge number of scientists focused on that the outcomes gave positive suggestions on the connection between anticipated qualities and the reference glucose levels. Despite the fact that estimation errors of NIR spectroscopy are too expansive for clinical purposes, these exploratory outcomes show the likelihood of non-intrusive blood glucose measurements.[13]

Advantages

The high affectability of the photoconductive finders is the important favourable position of NIR spectroscopy. Since water is sensibly straightforward to the flag data transfer capacity utilized by NIR, it makes conceivable to use for blood glucose sensing. What's more, the measuring signal has high vitality contrasted to MIR spectroscopy. Even more, it has more favourable circumstances that this technique is less costly than MIR, materials required are relatively low in cost, and there is an extensive variety of business items accessible. These points of interest make NIR famous in this exploration range.

Limitations

Regardless of much encouraging work, specialists are attempting to conquer critical inadequacies, specifically, the scanning weight that must be connected, physiological contrasts not identified with blood glucose, the moderately little part of glucose in blood, feeble relationship, and equipment affectability and dependability.

Photoacoustic spectroscopy

Principle

Ultrasound innovation depends on low-recurrence ultrasound, which infiltrates the skin for blood glucose monitoring. This approach has hypothetical potential however the further research in this heading is kind of steady. A technique, named photoacoustic spectroscopy, is being utilized, which depends on the utilization of a laser light for the excitation of a liquid and for measuring the subsequent acoustic response.[14] The rule of the photoacoustic technique is that a vitality source illuminates the skin surface, bringing about warm extension in the lit up zone. An acoustic wave discharges in light of the vitality of

the warm development. The glucose level identification with this procedure depends on measuring the progressions of the top to-crest estimation of the flag, as per the glucose substance of the blood.

Advantages

This innovation can give higher affectability in the assurance of glucose, in view of the generally better photoacoustic reaction of blood, as contrasted to water. This makes it less demanding to recognize hydrocarbons and glucose.[15] Moreover, the laser light wavelengths utilized have a wide range, from bright to NIR.

Limitations

The innovation is delicate to temperature variances and weight changes. Also, the photoacoustic flag might be influenced by scattering marvels when the laser light transverses a thick medium, bringing about an unfriendly impact like that of NIR spectroscopy. Additionally, the instrumentation required is costly and delicate to environmental parameters.

Reverse iontophoresis

Principle

It depends on the stream of a low electrical current through the skin, between the electrodes situated on the skin surface. An electric potential connected between the terminals causes the movement of sodium and chloride particles from underneath the skin toward the cathode and anode, separately. Sodium particle relocation chiefly adds to the current generation.[36] During this convective stream, glucose atoms, being impartial gets extricated through the epidermis surface. The iontophoretically removed glucose flux mirrored the glucose fixation profiles in the blood.[16]

Advantages

Simple use of the anodes on the skin surface is leverage of this innovation. A physiologically applicable liquid specimen is gathered, in which connection exists between glucose focuses in the physiological liquid and in blood. [16]

Limitations

The gadget produced with this innovation, GlucoWatch had genuine down to earth disadvantages of bringing on skin disturbance because of cathodes, situating of the terminals set up for no less than an hour which make inconvenience to the patient, wrong readings, particularly when the patient was sweating. Likewise, quick changes in glucose levels can't be identified. [16]

III.COMPARATIVE STUDY OF INVASIVE & NON-INVASIVE GLUCOMETERS

In this section the comparison of invasive and non-invasive glucometers manufactured by different companies is done considering the parameters sensor life span and accuracy.[17]

Table: Commercially Available Continuous Glucose Monitoring Systems[17]

S.No	Device/Company	Technology	Sensor Life span	Accuracy
1	Dexcom Seven Plus	Invasive	168 H	MARD: 16% MAD in hypoglycemia: 16mg/dL
2	Dexcom G4 Platinum	Invasive	168 H	MARD: 13% MAD in hypoglycemia: 11mg/dL
3	Guardian Real-Time (Medtronic)	Invasive	72 H	MARD: 17.6% EGA (A+B): 99.6%
4	FreeStyle Navigator (Abbott)	Invasive	120 H	MARD: 12.8% MedARD: 9.3% EGA (A+B): 98.4%
5	HG1-c (C8 Medisensors)	Non-invasive (Raman spectroscopy)	-	MARD: 38 *mg/dL* MedARD: 30 *mg/dL* EGA (A+B): 92% Blood glucose
6	GlucoTrack (Integrity Applications Ltd.)	Non-invasive (thermal ultrasound and electromagnetic)	6 months (ear clip lifespan)	MARD: 29.9% MedARD : 19.9% EGA (A+B): 92%

Criteria of exactness gives a level of the contrast between the deliberate and a reference glucose profile. It incorporates Mean Absolute Deviation (MAD), Mean Absolute Relative Difference (MARD), and middle total relative contrast (MedARD), characterized as,[17]

$$MAD = \frac{1}{N}\sum_{i=0}^{N}\left|\widehat{Gi} - Gi\right|$$

$$MedARD = median_i\left\{\frac{\left|\widehat{Gi} - Gi\right|}{Gi}\right\}$$

$$MARD = \frac{1}{N}\sum_{i=0}^{N}\frac{|\widehat{Gi} - Gi|}{Gi}$$

where N is the quantity of glucose estimations, $\widehat{Gi}$ andGi speak to the deliberate and the reference glucose levels, separately. The reference glucose levels are normally measured by Yellow Springs Instrument (YSI) blood glucose analysers and blood glucose meters. Clinical assessment criteria, for example, the Clarke Error Grid Analysis (EGA),[18] evaluate the clinical precision of the glucose estimations as far as influencing choices for directing blood glucose levels. The EGA gives the disseminate plot of a reference glucose meter and the glucose meter under assessment, separated into five zones (An E) speaking to various levels of danger. The clinically acknowledged zones are the zones A and B.

IV. RECENT TECHNOLOGICAL ADVANCES

The recent technological advances are targeted on less invasive techniques (e.g. microneedles), non-invasive techniques based on optical methods (e.g. kromoscopy, raman spectroscopy, NIRspectroscopy , photo acoustic spectroscopy) and transdermal techniques (e.g. reverse iontophoresis and sonophoresis). Glucotrack by using integrity packages makes use of an ear clip and measures glucose levels using ultrasonic, electromagnetic and thermal technology.[19] Abbott developed freestyle liber which could take glucose readings as oftentimes a day as wished via a patch worn on the back of the upper arm.[20]Mediwise's glucowise sensor squeezes the skin between the thumb and the forefinger and displays reading in real time on the screen.[21] Symphony by using echo therapeutics makes use of a transdermal sensor and a wi-fi transceiver to display real time glucose information.[22]Cnoga clinical has advanced a tool that makes use of pores and skin color to diagnose high blood stress and measure glucose levels without piercing the skin.[23]Quick LLCintroduced the iquicklt saliva analyzer which could measure glucose levels and transfer the findings wirelessly using saliva samples.[24]

Other approaches are directed to the implementation of fully implantable glucose sensors which are completely unobtrusive to the patient's daily life and can be implanted in the human body.[25] In order to manage the diabetes treatment, CGMS (Continuous Glucose Monitoring System) products are streaming into market with function, wear ability, accuracy and security being the challenges during research. To assist the patients whose pancreas shows inability to control insulin, recent research focuses on artificial pancreas which can imitate pumping of insulin by pancreas automatically.[26]

V.CONCLUSION

In this review, the latest technologies and devices for non-invasive glucose monitoring have been described. Rigorous research towards the development of economically feasible, accurate and reliable devices is still in progress dealing with various technical issues. May this non-invasive technology reach the common man in the near future.

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