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Prospective Analysis of Developing Noninvasive Blood Glucose Monitoring Biosensors for Diabetic Population

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Diabetes mellitus often referred as the metabolic disorder characterized by lack of insulin or existence of patho-physiological factors that resists the insulin action. Currently proper therapeutic cure for diabetes is not available. Supervision of increased blood glucose level without lowering below the normal physiological range is the ultimate goal of therapeutic protocols for managing diabetes mellitus. For achieving rational control over elevated blood glucose levels, frequent monitoring with invasive blood glucose monitoring techniques is mandatory for diabetic patients. Developing noninvasive glucose biosensors approaches will be pain free including reduction in complexities related to invasive techniques. This research article explains the principle methodologies of several developing noninvasive Blood Glucose Monitoring Biosensors for Diabetic population. The study reveals that these noninvasive glucose biosensors has a prospective future but numerous factors and obstacles are needed to be considered relating to signal acquisitions, accuracy and precision of the devices, design aspects, data management, risk benefit ratios, cost of the device, etc. In future, the noninvasive glucometer with user-friendly aspects, lower risk factors will be more popular as compared to present day invasive glucometers. Successful noninvasive glucose biosensors will be the primary diagnostic tool for diabetes management protocols in near future. All these new noninvasive technologies had increased expectations for better management of diabetes in near future.

Key words: Noninvasive, Invasive, Glucose Biosensor, Diabetes, Glucometer.

Diabetes mellitus is a medical emergency in which living body suffers from blood glucose imbalance and this state of body without treatment may lead severe vital organ damages associated with morbidity or mortality[1-3]. Diabetes related characteristic symptoms includes thirst, polyuria, vision abnormality, weight loss, and sluggishness, etc. Heart and blood vessel related diseases like atherosclerosis, coronary heart disease, strokes; etc precipitates due to diabetes related disorder consequences[3]. As of 2013, worldwide healthcare costs for diabetic population between 20-79 age groups had been 548 US dollars[2]. In near future if all projections related to diabetes epidemiology works out to be true, these health care expenditure figures will touch 627 US dollars during 2035 A.D[2]. At present complete cure from diabetes is not available. Tight control of abnormally elevated or

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decreased blood glucose is the major target area for proper diabetes management. Blood glucose meters are available for monitoring the blood glucose levels of the individuals and these technologies proves to be playing vital role in diabetes management and prevention from long term related complexities. In comparison to lab test for blood glucose levels, these glucose biosensors delivers results rapidly and user friendly also. The current world market for biosensors is dominated by the glucose biosensors, nearly above 85% of the biosensor market share[3]. At present more than 50 commercialized devices for monitoring blood glucose levels are available in the market. Out of which only few of them occupies the lion share in the biosensor multinational market. They are Roche Diagnostics, Life Scan, Abbott and Bayer[3]. This is an extremely competitive market with high profile entry barriers[3]. These competition yields a strategy, in which invasive glucose biosensor's technology is fully exploited to meet the customers demand regarding small size, quick response time, near to painless technology[3-5]. This painless and infection free approach generates the concept for noninvasive glucometer. At present various noninvasive glucose biosensors by few multinational companies are at the developmental stages[1-6]. A brief introduction about the noninvasive glucose bio-sensors those are in developmental stages and devices already withdrawn from the market had been discussed in this paper. Moreover, this paper focuses on the working principle of indigenously developed modulated ultrasound with infrared technique based noninvasive glucose biosensor.

Various Prominent Noninvasive Blood Glucose Monitoring Devices and their Techniques

Gluco Track by Integrity Applications

It utilizes the ultrasonic, electromagnetic, thermal techniques to detect the blood glucose in noninvasive style[1, 4, 5, 7]. The sensor modules were designed to utilize the ear lobes as its measuring site[7]. In the year 2009, CE (European Commission) had approved this device [4,5,7]. FDA (Food and Drug Administration) approval has been pending[4,5]. In the real life format, exhaustive clinically relevant experimental studies were required at different age, sex, race groups [1, 2, 4-6].

Noninvasive Glucometer by Glove instruments

It utilizes the patented optical bridge technology with infrared spectroscopy to detect blood glucose level within 20 seconds[4, 5, 8]. The approval status from CE and FDA is not mentioned[4, 5]. At present the company is focused on design innovation for miniaturizing the product[1, 4-6, 8].

Microwave based noninvasive Glucometer by Baylor University (Texas)

This device detects the pattern change in microwave propagation through living tissue to determine the blood glucose levels[9]. Microwaves can determine the inside objects characteristics in noncontact manner[4, 5, 9]. This phenomenon has been applied in noninvasive blood glucose detections[9]. The FDA and CE approval has been pending[4, 5].

Noninvasive glucometer based on near infrared optical spectroscopy and multivariate tools by Inlight Solutions

The optical technology and the multivariate tools were designed in such a manner to eliminate the background noise and focus on glucose molecules specially[4, 5, 10]. The FDA and CE approval has been pending[4,5].

Noninvasive glucometer based on LighTouch Technology by LighTouch

Based on Raman spectroscopy, the lights of different wavelength bearing different colors were directed over the subject's fingertip[4, 5, 11]. The output light signals were processed and analyzed for providing blood glucose levels[11]. The CE and FDA approvals were not mentioned[4, 5]. It has been in development status since 1999[4, 5, 11].

I-SugarX Noninvasive glucometer from Freedom Meditech

It measures the degree of fluorescence produced due to glucose molecules in the watery solution of human eye[4, 5, 12]. It provides faster and convenient results[12]. The FDA and CE approval has been pending[4, 5]. The proper projection of light is essential for this device[4, 5, 12].

Contact Lens based Continuous Glucose Monitoring by University of Washington

This device measures the glucose levels in tears through spectroscopy method with wireless technology for signal transmission facility[4, 5, 13, 14]. FDA and CE approvals are in initial submission stages[4, 5]. Design innovations and more human trials are required[4, 5].

Symphony tCGM system by Echo Therapeutics

This medical device had been divided into three components. Stratum corneum is removed from the skin layer by prelude skin preparation system. It increases the skin permeability for noninvasive device[15, 16]. Secondly, the Sensor part constitutes the electrochemical glucose unit and the small RF chip inbuilt on it. This part has been mounted on the skin area prepared by the prelude system previously[4, 5, 15, 16]. Third component refers to the remote receiver cum monitor for blood glucose display[15, 16]. It provides glucose readings in every 60minutes[15, 16]. Long term side effects prospects must be checked with cautions[4, 5]. The FDA and CE approval has been pending[4, 5].

Multisensory Glucose monitoring system by Biovotion AG

This device utilizes both the optical and impedance spectroscopy for providing information about blood glucose levels. FDA and CE approval not obtained[4, 5, 17, 18].

TensorTip CoG - Combo Glucometer by Cnoga Medical

It is a combo of both invasive and noninvasive glucometer. The invasive device had been used for primary glucose level reading calibrations for accuracy and precision purposes. Invasive part can be removed easily after automatic notification by the device. In noninvasive part of this medical device, four light emitting diodes in the range between 600nm to 1150nm wavelength had been used. When the light propagates through fingertips, the pattern of light changes which is detected by the camera like light sensor. The processor splits the light signal digitally into three hyper planes like red, green, blue. The obtained light pattern is correlated with the huge stored data sets for blood glucose level predictions[4, 5, 19]. The FDA and CE approval has been pending[4,5].

C8 Medisensors by California based firm

Raman spectroscopy techniques had been utilized here for glucose estimations transdermally[4 ,5]. The Raman specific signature signal for glucose were detected noninvasively and analyzed. The data can be transferred to the smart phone instantaneously[4, 5, 20]. The company had been working on this area for almost a decade[20]. This device had been operated as an investigational device[4, 5]. Both the FDA and CE approvals were not mentioned [4, 5, 20].

Easy Check Positive ID (Identification) by Positive ID Corporation an Israel based firm

During the breathing process, air inhalation and exhalation occurs. Various chemicals constituents in vapor forms were present in the exhaled breath air. Out of which the acetone level in the breath air is targeted here for blood glucose level determinations[4, 5, 21]. The exhaled air got reacted with the secret chemical compounds[21]. The outputs of this chemical reaction were calculated for glucose level predictions. It's still in developmental stage, so FDA and CE approvals were not available[4, 5, 21].

Eye sense by EyeSense GmbH

Eye sense developed continuous noninvasive glucose monitoring device based on fluorescent technology[22, 23]. Its measuring sites include upper limbs and abdomen parts of the human body[22, 23].Pump for insulin delivery had been projected for future[22, 23]. This device first appeared in the year 2008 and since then it had been in research and developmental stage[4, 5, 22, 23]. As predicted, it will hit the market in the year 2016[22, 23].

Glucoband by Calisto Medical Inc

This instrument applies bio electromagnetic resonance phenomenon for noninvasive blood glucose detections. The instrument resembles wrist watch type design in which all the electronic parts and required components were mounted[24]. This device emerged in the year 2005 and as off 2011 data it had been under pilot production stage[4, 5]. FDA and CE approvals were not mentioned[4, 5].

Occlusion spectroscopy based noninvasive Blood Glucometer by OrSense Ltd

This instrument applies over systolic pressures to produce occlusion on the measuring site like human finger[25 26].The blood flow cessation occurs due to occlusion applied to the finger base causes dynamic optical signal generations which facilities the noninvasive blood glucose measurements[25, 26]. This proprietary technology came into existence in the year 2008[4, 5]. The company declared that this instrument had been introduced to study the commercial responsiveness factor. FDA, CE approvals not mentioned, as it has been in developmental stages only[4, 5].

Noninvasive glucose monitoring device by Biosensor Inc

Bio-impedance spectroscopy technology (SEMP Technology) had been applied for noninvasive blood glucose determinations[4, 5 27]. It had appeared in the year 2010 and under developmental stage since then[4, 5, 27]. FDA and CE authorization not approved[4, 5].

ClearPath DS-120 by Freedom Meditech

Fluorescent Technology had been utilized in this medical device for noninvasive blood glucose predictions[28]. This device came into existence in the year 2007. During 2011, it had been forwarded to FDA for approval purposes[4, 5].

Regulatory body approved noninvasive blood glucometer devices

Diasensor, BICO Inc. distributed by EuroSurgical Ltd., UK

Near infrared spectroscopy forms the basis for this medical device. Infrared light band between 750-2,500nm of the spectrum had been focused on the measuring sites[1, 2, 6]. It measures glucose in tissues in the depth range between 1 to 100mm of length[1-6]. Here blood glucose levels were determined in less than 120 seconds[1, 2, 6]. This device focused largely over the self monitoring of glucose in noninvasive manner without removing the long-established invasive procedures[1, 2]. It had been marketed in the year 1998 to 1999 with price range per product approximately US $9,000[6]. Due to critical complications it had been withdrawn from the market afterwards[6]. At present Diasensor had been removed from the company website also and does not exist anymore[1, 2, 6].

Pendra by Pendragon Medical Ltd

The impedance spectroscopy had been applied as a technology for noninvasive blood glucose determination in this Pendra medical device[1, 2, 6]. When intensity of current is known then the impedance of a tissue can be measured[1, 2, 6]. A dielectric spectrum can be formed by applying current in an alternating mode at different wavelengths[1, 2, 6]. Usually 100Hz to 100 Mega Hz frequencies had been applied here[1, 2, 6]. The pattern change of cell membrane permittivity and conductivity due to blood plasma glucose level variation had been measured here[1, 2, 6]. The ion concentrations especially sodium ions plays the key role here[1, 2, 6]. After CE approval, it had been marketed in Europe in the year 2004 with 2,500 Euros per piece[1, 2, 6]. But withdrawn quickly, due to its little matched profile (around 35%) with the traditional glucometer[1, 2, 6]. After wards in 2005 February the company ended with bankruptcy issues[1, 2, 6]. Recently, after that a new company named as Solianis Monitoring AG emerged with same approach in technology[1, 2, 6]. Till then it had been under developmental stage only[1, 2, 6].The impact of body fluid content like water, dehydrated cells, diseases cells, etc needed to be considered here[1, 2, 6].

Glucowatch G2 Biographers by Cygnus Inc

The technology named as reverse Iontophoresis had been applied here for noninvasive blood glucose predictions[1, 2, 6]. Designed like wrist watch with pad of disposal in nature clipped behind the instrument[1, 2, 6]. The pad adheres to the skin to collect small electrical impulses which drives the reverse Iontophoresis processes[1, 2, 6]. This phenomenon attracts glucose molecules towards it and traditional meter type chemical reaction got initiated[1, 2, 6]. The result of the chemical reaction forms the basis for the blood glucose calculations[1, 2, 6]. Regulatory body like FDA and CE approved this device and Cygnus Inc sold it at a price of US $700 per piece[1, 2, 6]. In the year 2005, the company sold its all assets to Animas Corporation[1, 2, 6]. After certain year in 2007, Animas declared that they will not sell the current model named as GlucoWatch G2 Biographer[1, 2, 6]. But they had extended their customer support for next 1 year[1, 2, 6].

SCOUT DS system by Vera Light Inc

This medical device had been targeted for pre-diabetic and Type II diabetic subjects[4, 5, 29]. It utilizes the fluorescent technology to detect the biomarkers like Advanced Glycation End Products (AGEs) existence related to diabetic conditions in human skin tissue[4, 5, 29]. Approval for the market level distribution had been obtained from Health Canada[4, 5, 29]. European Union had approved the CE mark for this medical device[4, 5, 29]. However, the FDA approved it for investigational use only[4, 5, 29].

Indigenously Developed Noninvasive Glucose Biosensor Technology

In this technology, the amplitude modulated ultrasound and infrared techniques were collaborated to detect blood glucose in noninvasive manner. The amplitude modulated ultrasound provides vibrating pattern based standing wave on the focused area. Usually molecules vibrate according to their physical and chemical properties. The glucose signature specific vibrations were identified by the infrared light signal and its detector assembly. The signal obtained were processed and decoded for blood glucose level calculations. Here 940nm infrared LED (Light Emitting Diode) and ultrasound transmitter & receiver of 40 kHz had been utilized[30-38]. When modulated ultrasonic wave propagates through the medium, it causes series of vibrating pattern force generation over the molecules in that medium[30-38]. The impact of the radiating forces over the molecules were obtained from the gradient of the molecular acoustic potential energy and is represented as given below

$$F_r = -\left[\frac{\pi p_o^2 V_c \beta_w}{(2\lambda)}\right] \cdot \phi(\beta, \rho) . \sin(4\pi z/\lambda) \quad ...(1)$$

Where, the notations such as (F_r), (V_c), (z), (P_o) and (λ) represents nature of radiating force, molecular volumes, distance from the pressure nodes, peak amplitude of the acoustic pressure and the sound wavelength respectively[30-38]. When the influence of the compressibility factors (β_w) of the suspending medium were taken into considerations[30-38], the equation had been expressed as follows:

$$\phi(\beta, \rho) = \left[\frac{5\rho_c - 2\rho_w}{2\rho_c + \rho_w} - \left(\frac{\beta_c}{\beta_w}\right)\right] \quad ...(2)$$

Here the notation like (β_c), (ρ_c) and (ρ_w) represents the molecular compressibility, molecular densities of both the suspending molecules and the suspending medium respectively[30-38]. When light had been focused on this medium, its absorption pattern follows the Standard Lambert-Beer law[30-38]. This phenomenon had been expressed as follows:

$$A(v) = -\log I(v)/I_0(v) \quad ..(3)$$

The notations utilized here like (A), (v), (I_0) and (I) stands for absorption phenomenon, light wave number, background light intensity and the light intensity after propagating through the sample path length[30-38].

Description of the noninvasive glucose biosensor instrument

Light wavelength and ultrasound transducer selection criteria

The 940nm LED (Light Emitting Diode) had been applied here, as it had been under the tissue optical window region (700nm-1100nm)[30-38]. The other agents like oxy-hemoglobin, deoxy-hemoglobin, and water related interferences issues were much minimized in this zone of the light band[30-38]. The ultrasound transducer (transmitter and receiver) both were of 40 kHz as main operating frequency[30-38]. They are safe for utilization over human beings and commercially widely available[30-38]. All these factors play a major role in their selection for their respective experimental purposes.

Instrumental schematic

Figure.1. depicts the block diagram of the noninvasive glucose biosensor instrument called as MUS-IR unit (Modulated Ultra Sound-Infra Red Unit).

Subject's medical status

The adult subjects were total 09 in number. Out of which 03 of them are in normal health conditions (two male, one female, aged 26.5±3.5 years, of height 175±3.0cm, weight 76.2±11 kg). The other 06 subjects were all Diabetic subjects (four males, two female, aged 45.5±4.0 years, of height 170±2.0cm, weight 74.5±9 kg). Three (03) of them were with Type I Diabetic and next three (03) of them were Type II Diabetic subjects. The aim and objective of the experimental procedures were discussed with the subjects. They understood the same, and gave their written consent for the experimental purposes. The local ethical committee had approved the pilot study.

RESULT AND DISCUSSION

Diabetes Mellitus categorized as a metabolic disorder, indicates a physiological stage with high blood glucose levels. These elevated blood sugar indexes produces symptoms like polyuria, polydipsia, polyphagia. Based on various patho-physiological status Diabetes Mellitus had been broadly grouped into two main classifications like: (a) Type I Diabetes Mellitus (b) Type II Diabetes Mellitus[1-6].

Type I Diabetes Mellitus

This metabolic disorder condition often coined as Insulin-Dependent Diabetes Mellitus (IDDM). At this stage, the individual body ceases to produce insulin. Moreover, insulin injection required to maintain the normal blood glucose level[1-6].

Type II Diabetes Mellitus

These metabolic disorder phenomenon's had been termed as Non-Insulin-Dependent-Diabetes Mellitus (NIDDM). Physiological condition like insulin resistance, a condition in which inability to utilize body insulin properly or total deficiency of insulin occurs[1-6]. All this diabetic population needs to check Blood glucose levels repeatedly to maintain their respective glucose level homeostasis. In this respect, the noninvasive blood glucometer might be very helpful as compared to the invasive ones[1-6]. All this conditions had motivated us for choosing subjects from Normal healthy adults to Type I and Type II Diabetes Mellitus adults to predict their respective blood glucose levels at various stages of daily life through indigenously developed noninvasive Technology.

The blood glucose levels of all the subjects (Normal, Type I and Type II Diabetic) were obtained during fasting, post prandial and random stages by a standard invasive glucometer and indigenously developed noninvasive technology based MUS-IR unit respectively. All these invasive and the noninvasive method based blood glucose level values obtained during fasting, post prandial and random stages of the Normal, Type I and Type II diabetic subjects had been provided in the Table

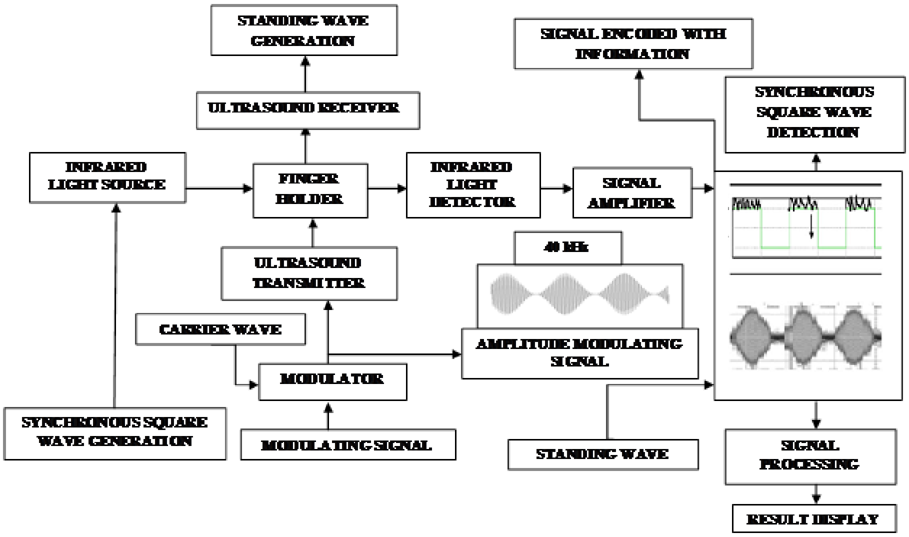
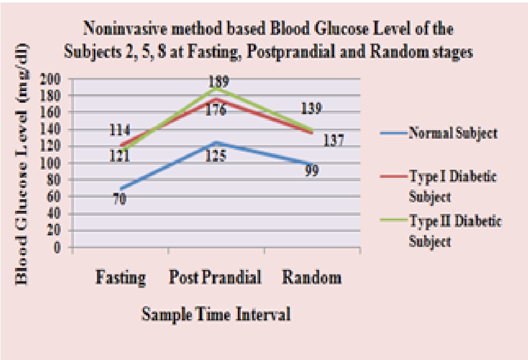
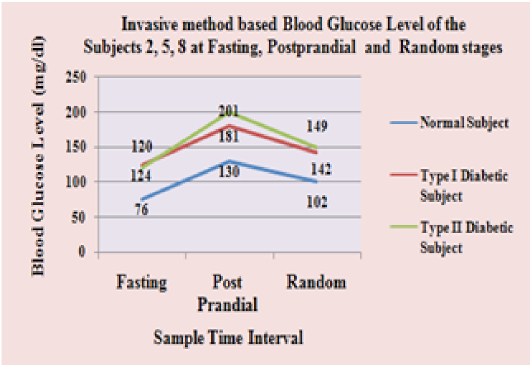


Fig. 1. Block diagram of the noninvasive glucose biosensor experimental setup (MUS-IR Unit).



Graph. 1. Shows the Noninvasive method based Blood Glucose Level values of the Subjects 2, 5, 8 at Fasting, Post prandial, and Random stages.



Graph. 2. Shows the Invasive method based Blood Glucose Level values of the Subjects 2, 5, 8 at Fasting, Post prandial, and Random stages.

No.1, 2, 3 respectively. The result from the Table No.1, 2, 3 and Graph No.1, 2 indicates that the blood glucose level values obtained from the MUS-IR unit changes in response to variations in blood glucose level of all the subjects (1-9) during fasting, post prandial and random stages. This observable fact proves that our indigenously developed MUS-IR unit had been sensitive in detecting the variations of blood glucose levels of all the subjects (Healthy, Type I and II Diabetic) at fasting, postprandial, random stages.

Table 1. Depicts noninvasive blood glucose levels and corresponding invasive blood glucose levels of the normal subjects during Fasting, Postprandial and Random stages respectively

Serial No.	Normal Subjects	Fasting Stage		Postprandial Stage		Random Stage	
		Noninvasive method based Blood Glucose Levels (mg/dl)	Invasive method based Blood Glucose Levels (mg/dl)	Noninvasive method based Blood Glucose Levels (mg/dl)	Invasive method based Blood Glucose Levels (mg/dl)	Noninvasive method based Blood Glucose Levels (mg/dl)	Invasive method based Blood Glucose Levels (mg/dl)
1.	Subject 1	74	88	130	128	89	80
2.	Subject 2	70	76	125	130	99	102
3.	Subject 3	84	79	137	142	91	89

Table 2. Depicts noninvasive blood glucose levels and corresponding invasive blood glucose levels of the Type I Diabetic subjects during Fasting, Postprandial, and Random stages respectively

Serial No.	Type I Diabetic Subjects	Fasting Stage		Postprandial Stage		Random Stage	
		Noninvasive method based Blood Glucose Levels (mg/dl)	Invasive method based Blood Glucose Levels (mg/dl)	Noninvasive method based Blood Glucose Levels (mg/dl)	Invasive method based Blood Glucose Levels (mg/dl)	Noninvasive method based Blood Glucose Levels (mg/dl)	Invasive method based Blood Glucose Levels (mg/dl)
1.	Subject 4	123	128	183	190	141	145
2.	Subject 5	121	124	176	181	137	142
3.	Subject 6	129	126	203	202	139	148

Table 3. Depicts noninvasive blood glucose levels and corresponding invasive blood glucose levels of the Type II Diabetic subjects during Fasting, Postprandial, and Random stages respectively

Serial No.	Type II Diabetic Subjects	Fasting Stage		Postprandial Stage		Random Stage	
		Noninvasive method based Blood Glucose Levels (mg/dl)	Invasive method based Blood Glucose Levels (mg/dl)	Noninvasive method based Blood Glucose Levels (mg/dl)	Invasive method based Blood Glucose Levels (mg/dl)	Noninvasive method based Blood Glucose Levels (mg/dl)	Invasive method based Blood Glucose Levels (mg/dl)
1.	Subject 7	127	132	202	192	136	143
2.	Subject 8	114	120	189	201	139	149
3.	Subject 9	136	141	223	230	146	150

CONCLUSION

In this paper, the nascent technologies and instruments for noninvasive blood glucose monitoring have been discussed. By the irony of fate, still almost all of these technologies were in their development or screening phase only. This indicates us in the way towards noninvasive technology in the near future. To establish correlation between blood glucose levels and readings were easy in the controlled laboratory environments. The problem arises in the real life scenario. From this we can conclude that, lots of unsolved factors were to be solved through rigorous clinical and scientific experimentations to achieve the goal of successful noninvasive blood glucose detection technology. Moreover, our noninvasive glucose biosensor technology had got the potentiality to evolve as a prominent noninvasive technology in near future.

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