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GLUCOSE MONITORING TECHNOLOGIES AND CHALLENGES: AN UPDATE

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ABSTRACT

The innovation of glucometer has set a benchmark to restrain the effects of diabetes. Diabetes is a scourging metabolic disorder, responsible for disabilities and anachronistic deaths among mass populations. The hyperglycemic condition creates physiological and psychological sufferings to the patients. These complications have led to drastic evolvement in the diabetes diagnostic technologies. The pioneer work in the field of glucose monitoring devices started with the development of blood-based sensing practices, extensively used by the patients but it is an invasive technique which induces trouble in the subjects. Thus, a non-invasive, painless method of glucose testing is a new advancement in the range of glucometers and would profoundly increase the compliance and overcome complications. Saliva-based glucometers is a non-invasive approach, has the potential to exceptionally overcome the discomfort brought up by the blood-based invasive methods. The objective of presenting this review is to provide the chronological series of events in the identification of the disease along with the technological advancements in the glucose monitoring devices.

Contribution/Originality: This study contributes in the existing literature about the glucose monitoring technologies available in current use as well as the upcoming technologies which will add the comfort and painless methods for glucose testing to support patient care.

1. INTRODUCTION

Diabetes is a Greek-derived term, which means "to pass through" and Mellitus means "sweet", collectively recognized as Diabetes Mellitus, the silent epidemic. Diabetes Mellitus is an ancient disease, proclaimed by Egyptians and Indians approximately 3000 years ago (Ahmed, 2002; Sami *et al.*, 2017). Diabetes Mellitus (DM) is defined by world health organization (WHO) as a chronic metabolic disorder which is characterized by elevated sugar level in blood, which eventually leads to the serious damage and malfunctioning of body organs, and contributes to 1.6 million deaths every year. According to the Global report on diabetes released by WHO, since 1980 a drastic rise in the count of diabetic patients (422 million adults) had been reported in 2014. The classification of hyperglycemic disorder can be determined on the basis of aetiology and pathophysiological stages and can be termed as type 1 Diabetes Mellitus, caused by the body's own immune system; type 2 Diabetes Mellitus caused by insulin resistance in the body; Gestational diabetes, elevated glucose concentration during pregnancy; and Diabetes Mellitus due to other specific mechanism or disease (genetic abnormalities, pancreatic disease) (Deshpande *et al.*, 2008; Seino *et al.*, 2010; Baynes, 2015). The degree and time of hyperglycemia determine the severity of symptoms

of DM from being asymptomatic to ketoacidosis or coma (Seino *et al.*, 2010; Kharroubi and Darwish, 2015). T2DM, being an epidemic disorder globally, is majorly developing in Asia, with India and China experiencing a hasten in the number of people suffering from this disorder, followed by United States (Mohan and Pradeepa, 2009; Kaveeshwar and Cornwall, 2014; Zheng *et al.*, 2018).

It has been reported by WHO that one in three adults (over the age of eighteen years) and one in ten individuals, resembles overweight and obese respectively, which are the major driving factors for T2DM and its prevalence, amongst other factors including age, lifestyle, diet which is acknowledged in many studies (Sami *et al.*, 2017; Zheng *et al.*, 2018). The raised blood glucose level causes severe damage to internal organs of the body due to which it has now become a leading cause of morbidity and fatality. Now a day's diabetes and related disorders are considered as the consistent burden on the health care system. The diabetes-induced complications are categorized on the basis of severity as Acute, Chronic and other complications. Acute complication includes hypoglycemia, hyperglycemic crises, Diabetes ketoacidosis and hyperglycemic hyperosmolar state (HHS), while the chronic complications consists of microvascular (diabetic retinopathy, nephropathy and neuropathy) and macrovascular complications and other complications comprises of hypothyroidism, limited joint mobility, impaired growth and infection among others (Henry, 1987; Deshpande *et al.*, 2008; Baynes, 2015). Figure 1 illustrates the complications induced by diabetes.
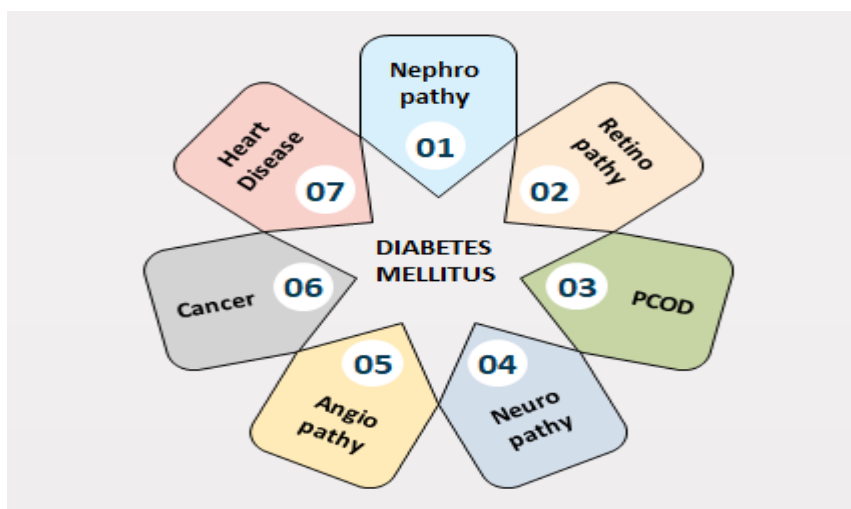

Figure-1. Relation of Diabetes with other Diseases
Source: Deshpande *et al.* (2008); Xu *et al.* (2012); Palomba *et al.* (2015); Giovannucci *et al.* (2010)

Diabetes Mellitus is diagnosed by various series of tests like Random plasma test, Fasting plasma glucose test, Oral glucose tolerance test and Fructosamine test, in order to determine the type of diabetes so that proper treatment can be provided to control the disorder (Seino *et al.*, 2010; Baynes, 2015). Since a diabetic patient requires frequent glucose concentration monitoring per day, researchers introduced a hassle-free technique termed as self-monitoring of blood glucose (SMBG). SMBG is a potential advancement developed for diabetic patients to manage the blood glucose concentration so that diabetes-related complications can be prevented before time. Glucometer or Glucose meter is an extensively used analytical device that instantly measures the glucose level of the body by taking blood as analyte (Tonyushkina and Nichols, 2009; Yoo and Lee, 2010). Blood sampling is an invasive process that requires skin pricking which is quite painful for many patients especially at the time of multiple pricking. Thus important advancements have been made by the scientists in the recent years that avoid invasion or pricking inside the skin. Non-invasive glucometer is an advancement in the range of glucometers that do not invade the skin. The working principle of non-invasive glucometer is based on three techniques: spectroscopy, transdermal and other techniques (Losoya-Leal *et al.*, 2012; Todd *et al.*, 2017; Nawaz *et al.*, 2018). A saliva-based non-invasive glucometer

is an imminent glucometer which uses saliva as an analyte to help diabetic patients to succumb to various difficulties.

2. DIABETES MELLITUS HIGHLIGHTS

There have been significant events of the contribution made by the physicians in the history of Diabetes to understand the disorder and develop various diagnostic tools in order to control the disease. The following list includes chronologically arranged milestone years of Diabetes, before 1st century till 21st century, in order to understand the emergence of the disease and various diagnostic devices launched in the market to manage it (Eknoyan and Nagy, 2005; Poretsky, 2010; Yoo and Lee, 2010; Clarke and Foster, 2012; Lakhtakia, 2013; Karamanou *et al.*, 2016; Bruen *et al.*, 2017).

Table-1. The Chronological events in Diabetes (Eknoyan and Nagy, 2005; Poretsky, 2010; Yoo and Lee, 2010; Clarke and Foster, 2012; Lakhtakia, 2013; Karamanou *et al.*, 2016; Bruen *et al.*, 2017).

Year	Highlights
1500 BC	Ebers Papyrus, a manuscript referred a condition "too great emptying of the urine" for Diabetes
230 BC	Apollonius of Memphis first time used the term "Diabetes"
1st century AD	Galen described diabetes as a disease specific to the kidneys
2nd century AD	Aretaeus of Cappadocia provided the first accurate description of diabetes and introduced diabetes into the medical nomenclature
5th century AD	Sushruta and Charaka, differentiated two types of Diabetes Mellitus
11th century AD	Avicenna provided the description of diabetes in detail
1674	Thomas Willis noticed the sweet taste of urine and coined the term "Mellitus"
1776	Matthew Dobson proved the presence of sugar in the urine
1815	Michel Eugene Chevreuil identified sugar in the blood and urine as glucose
1855	Claude Bernard showed the glycogenic properties of the liver
1889	Oskar Minkowski and Joseph Von Mering experiment concluded the role of the pancreas in the maintenance of glucose homeostasis by internal secretions
1922	Frederick Banting and Charles Best isolated insulin hormone
1923	Banting and Macloed received Nobel Prize for insulin discovery
1957	Miles-Ames Laboratory introduced 'dip and read' urine reagent strip
1962	Clark and Lyons provided the description of biosensors
1965	Dextrostix, the first blood glucose strip
1970	Ames Reflectance Meter, the first blood glucose meter, developed by H. Clemens
1987	MedisenseInc launched ExacTech (first electrochemical SMBG)
1999	Cygnus launched a non-invasive device, Glucowatch Biographer

3. SAMPLES USED IN DIABETES DIAGNOSIS

Diabetes diagnosis involves the identification and quantification of various disease-specific molecular markers resembling the occurrence of changes due to the incidence of the complication, glucose is the biomarker estimated to confirm Diabetes Mellitus. Blood testing has been used for years to detect the presence of diabetes in an individual, it provides most significant, sensitive and accurate results as compared to the other available samples but it is an invasive method causing troubles to the patients. Hence non-invasive means of detection using other alternative physiological fluids were identified in the early 1950's but due to lack of technology, efficiency did not match the required standards. Now with the advent of nanotechnology, they are able to produce the required efficiency and authenticity. Urine is one such fluid, with an easy non-invasive collection. Glucose is found in urine when the person is suffering from diabetes and can be amperometrically measured. Interstitial fluid can also be used for glucose monitoring with a minimally invasive process as the tissues exchange biological analytes with the blood. Sweat is another biofluid having the capability to measure the glucose concentration with enormous advantages such as easiest access and availability. Ocular fluid, the fluid surrounding the eyes and ocular tissue released in the form of tears can also determine the glucose content. This is done by the use of contact lenses having the ability to

measure the glucose concentration in ocular humour developed by the Google [X] lab (Mountain View, CA, USA) and Novartis (Basel, Switzerland). Breath-based sensors have the potential to detect the acetone content in the exhaled human breath, producing fruity odour resembles presence of Diabetes Mellitus. Saliva-based analysis is the most profound method enabling non-invasive detection of alterations, occurring because of the changes in the biological functioning of the body such as in case of diabetes, elevation in the amount of glucose happens which can be estimated using salivary glucometers (Makaram *et al.*, 2014; Bruen *et al.*, 2017).

4. GLUCOSE MEASURING TECHNIQUES

Glucometers are the devices utilized worldwide by humans for managing the appropriate glucose level in the body, such as in case of hypoglycemic and hyperglycemic disorders. The doctors require a certain level of authenticity in the body glucose concentration provided by the glucometer in order to initiate the treatment of the patient. The working principle of glucose measurement device includes two major parts: the reaction due to enzyme present and the detector. The glucometer consists of the reaction cuvette or the disposable strip carrying the enzyme in the dehydrated state which when reacts with the glucose in the patient's blood or fluid sample produces a detectable product after rehydration which is measured by the meter (Tonyushkina and Nichols, 2009). There is a remarkable evolution of the glucometers since the emergence of first blood-based glucometer device in late 1960, which is influenced the extensive growth of glucometers because of their small and compact size, easy to use and variability in design with inbuilt software memory to store and access the stored results (Clarke and Foster, 2012). Maintenance of glucose level in the body is the priority for treating diabetes and hence the technological advancements in this field have resulted in a series of glucose biosensors that gives the more authentic results. A biosensor is a unit that incorporates a sensitive biological recognition element that is associated with a physio-chemical transducer for producing a measurable signal. Clark and Lyons in 1962 were the first to give biosensor principle based on which the first generation of glucose biosensor devices came into existence. The biosensor mechanism worked upon the utilisation of natural oxygen as the substrate along with measuring an amperometric signal of the product hydrogen peroxide. The yellow springs instrument company analyser Model 23A, the first Biosensor to measure the glucose level based on Clark and Lyons principle, became accessible successfully in the market in 1975 (Yoo and Lee, 2010; Kesavadev *et al.*, 2017).

The second generation of the biosensor was produced as the need for improvement in the first-generation biosensors. The Non-physiological electron acceptors were used instead of oxygen from which electrons were mediated to the working electrode surface. The result was obtained by amperometric sensing of the oxidised form of mediator. In 1987, ExacTech produced by Medisence Inc. was the first electrochemical blood-based Biosensor. It was also the first self-monitoring device for diabetic patients (Yoo and Lee, 2010; Kesavadev *et al.*, 2017).

The third generation of the biosensor was the further advancement in the sensing technology in which the electrons were transferred without any mediator. The organic conducting materials were used to directly transfer the electrons and hence this improvement made the biosensor implantable for measuring glucose level continuously. It was the late 1990s when first in vivo glucose monitoring system was made available in the commercial market, launched by Medtronic Minimed Inc (Yoo and Lee, 2010; Bruen *et al.*, 2017).

On the basis of method of monitoring glucose level, the measuring techniques can be divided into Self-Monitoring of Blood Glucose(SMBG) based on the monitoring of glucose level by the patient himself, Continuous glucose monitoring(CGM) based on the principle of continuous measurement of interstitial glucose levels, Flash glucose monitoring system(FGMS), recently introduced in Europe, the monitoring system in which the sensor is introduced into the subcutaneous tissue for 14 days before disposal which provides the measured value on the scanner (Bailey *et al.*, 2015; Heinemann and Freckmann, 2015; Kesavadev *et al.*, 2017). On the basis of the interaction with the patient's body, the glucometer is classified into three categories, the first category contains Invasive monitors, Ames reflectance meter and BioRadioTransmitter are some devices based on invasive

measurement (Clarke and Foster, 2012; Bruen *et al.*, 2017). These are based on blood drawing procedure from the body which reacts with the chemically active disposable test strip and displays the glucose level in the connected monitor. Another invasive method includes the Implantable glucose microchips that detect and quantify changes in glucose level within the body. These are implanted with the glucose sensor based on the electrochemical principle which is powered wirelessly to give an accurate amount of glucose. But due to the implanting technique, the patients refuse and follow the non-implantable options (Losoya-Leal *et al.*, 2012; Todd *et al.*, 2017). The second group consists of minimally invasive devices, like small sub-dermal implants that rely on measuring the Interstitial Fluid (IF). The glucose concentration from the interstitial fluid is converted into an electronic signal by these implants (Losoya-Leal *et al.*, 2012). Another method of minimal invasion involves Microdialysis techniques that also extracts the interstitial fluid for analysis. Glucose measurement by Microdialysis involves the extraction by insertion of a fiber in the adipose tissue of the abdominal region (Krogstad *et al.*, 1996). Eirus Intravascular Microdialysis system monitors glucose level based on minimal invasion of skin (Schierenbeck *et al.*, 2014).

The third group comprises sensors based on Non-invasive glucose monitoring such as GlucoWatch G2 Biographer by Cygnus Inc, Pendra by Pendragon Medical Switzerland, C8 Medisensors, Gluco Wise by MediWise Ltd among some others (Lin *et al.*, 2017) which work on the principle of methods like spectroscopic techniques, transdermal glucose extraction techniques and some other techniques. The Spectroscopy involves the study of emersion or absorption of light by the substance based on their wavelength spectrum. Spectroscopic techniques are further divided into near Infrared Spectroscopy, Mid Infrared Spectroscopy, Raman Spectroscopy, Bioimpedance Spectroscopy and Thermal Emission Spectroscopy. In Transdermal Glucose Extraction Technique, the physical energy is used so that we can access the interstitial fluids and extract glucose levels. These techniques include Sonophoresis, Reverse Iontophoresis and Dead skin ablation, Polarimetric method, Fluorescence method and Electromagnetic Field Variation methods are some other techniques for the measurement of glucose level in the body (Losoya-Leal *et al.*, 2012; Nawaz *et al.*, 2018). The blood is the most studied body fluid for glucose measurements but other more accessible biological fluids such as interstitial fluid, ocular fluid, sweat, breath, saliva and urine have also been inspected as other samples for non-invasive glucose monitoring techniques (Bruen *et al.*, 2017). The following chart displays the various technologies used for glucose monitoring (Fig.2)
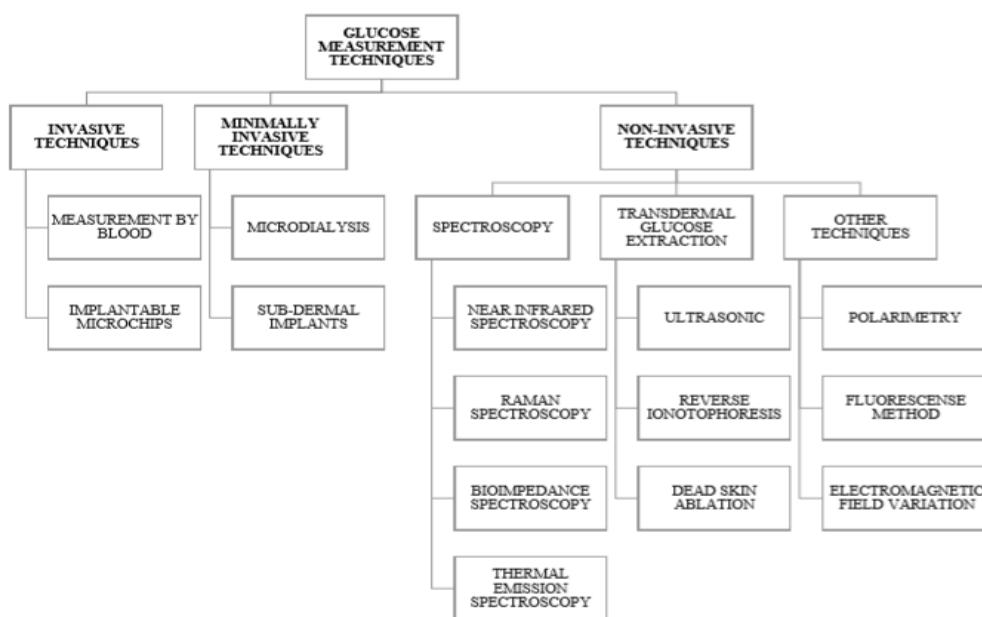

Figure-2. Types of Glucose Measuring Techniques

Source: Lin *et al.* (2017); Losoya-Leal *et al.* (2012); Todd *et al.* (2017)

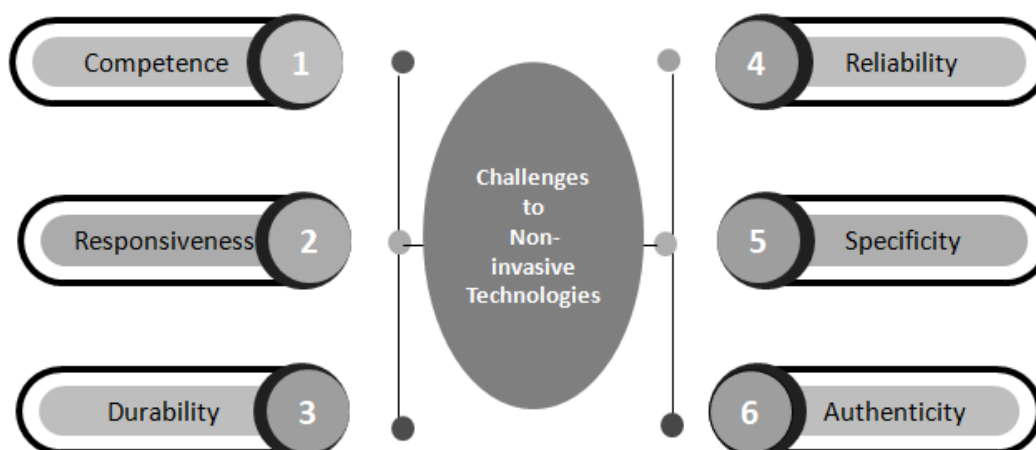Non- invasive technologies face various challenges as mentioned below (Fig.3):

Figure-3. Challenges of Non-Invasive technologies

Source: Tamar *et al.* (2017)

5. CHALLENGES OF NON-INVASIVE TECHNOLOGIES

Non-invasive glucose monitoring devices have paved the way for the future of diabetes research. However, these still face a combination of accuracy, usability and applicability challenges majorly and are currently under research to specify ways to overcome them. Accuracy challenges mainly include glucose specificity and sensitivity along with physiological time lag with usability and applicability challenges comprising of calibration of the device and suitability with different users (Lin *et al.*, 2017). Some other minor challenges include non-robustness of the device, non-portability, inconsistent functionality etc (Losoya-Leal *et al.*, 2012).

6. SALIVA BASED GLUCOMETERS

Saliva, a visibly transparent, watery, multiconstituent oral biofluid with a slightly acidic pH(6-7) secreted by the acinus cells present within the salivary glands mainly the parotid, sublingual and submandibular glands along with several minor salivary glands (Greabu *et al.*, 2009; Yoshizawa *et al.*, 2013; Proctor, 2016). Acinus cells are capable of absorbing molecules from blood via passive diffusion and releasing them along with the saliva, one of the reasons why blood and saliva share similar characteristic profiles thus rendering its potential to act as an astounding diagnostic biofluid for numerous metabolic disorders (Malamud and Rodriguez-Chavez, 2011; Tiwari, 2011). Major constituent of saliva is water along with some inorganic components such as sodium, calcium, phosphate, bicarbonates, nitrogenous molecules(e.g. urea and ammonia) and organic components like enzymes, glucose, hormones, glycoproteins, mucous and fatty acids (Humphrey and Williamson, 2001; Greabu *et al.*, 2009) facilitating it to perform several essential functions in digestion, mastication, lubrication, buffering, taste facilitation, remineralisation, maintaining oral hygiene, protection and defence (antimicrobial) mechanisms (Lee and Wong, 2009; Pink *et al.*, 2009; Yeh *et al.*, 2010; Wong, 2012). Apart from this, saliva comprises various biological constituents serving as biomarkers helpful in recognizing diseased conditions. This peculiarity about saliva, a biofluid makes it an important subject for research as it can be used for distinctive diagnosis of the unhealthy state of the human body. Saliva-based glucometers are under investigation as these can render real-time Diabetes monitoring without the need for invasive painful puncturing by traditional blood-based methods. Salivary glucometers allow simplistic sample collection without the necessity of phlebotomists as many times as required by the patients to keep track of their glucose levels. Saliva when compared to blood, the extensively used biofluid for diagnosis of diseases since ages, possess numerous advantages namely, non-invasive accessibility, easy procurement, safer handling, easy storage, economical, reduced discomfort, higher sensitivity, easy shipment, minimal exposure to blood-borne pathogens, reduced chances of contamination and no need of specialised personnel to collect the sample

(Kaufman and Lamster, 2002; Greabu *et al.*, 2009; Tiwari, 2011) but above all saliva presents a painless procedure for testing, much required in case of haemophiliacs and haemophobiacs, since it is the non-invasive diagnostic process which also increases compliance with the subjects requiring frequent sampling as in the case of Diabetes (Yoshizawa *et al.*, 2013) Numerous studies have been conducted to investigate the relation between the serum glucose and salivary glucose among the diabetic and non-diabetic patients which concluded that there is a compelling analogy between the above-mentioned parameters in case of diabetic subjects and hence saliva can be significantly used for the screening of diabetes and provide reliable outcomes (Reuterving *et al.*, 1987; Belazi *et al.*, 1998; Amer *et al.*, 2001; Abikshyeet *et al.*, 2012).

Saliva rightly cited as the "Window on health status" since it has most of the biomarkers present in it which can prove to be the reflector indicating the healthy and unhealthy state of a body. This happens due to the existence of various disease-specific biological markers contributing molecular information of the person. Biomarkers are the characteristic molecules or structures providing quantifiable information about the biological processes or the physiological changes taking place inside the body, capable of predicting the presence or incidence of diseases, pathogenic processes and pharmacological responses to drug therapies (Strimbu and Tavel, 2010). These help in the prognostication, cause identification, risk estimation, diagnosis, progression, regression, dose-response establishment and effects of treatment of diseases. They can help in the prognostic interpretation of existence or reoccurrence of diseases, disease mechanism can be identified, contribute more sensitive and precise results. These can be categorised into two, first biomarkers used for disease diagnosis helpful in screening and monitoring and second, biomarkers for risk prediction which can indicate the susceptibility of an individual to a particular disease hence regarded as prognostic biomarkers identifying the factors which can modify the extent of disease in future (Mayeux, 2004). Biomarkers occur in multiple forms such as DNA, RNA, proteins and metabolites, detected in different elements of the body including saliva, interstitial fluids, blood, urine, etc. Saliva being non- invasive, its biomarkers prove to be remarkable for easy monitoring hence are largely explored to detect the onset and severity of various types of diseases. Salivary biomarkers study can be classified broadly into two, transcriptomics and proteomics. Salivary transcriptomics is concerned with studying the transcribed RNA molecules released into the saliva during the cellular functioning while salivary proteomics entails the study of proteins present in the saliva resembling metabolic and immunological regulatory pathways. Saliva possesses several locally secreted proteins dissimilar from blood and their profiling can be a valid indicator of complications (Wong, 2012). Salivary biomarkers include various disease-specific and non-specific analytes such as hormones, steroids, immunoglobulins, nucleic acids, proteins, drugs, growth factors, cytokines and chemokines (Malamud and Rodriguez-Chavez, 2011). These are valuable in the identification of infectious diseases by recognizing the antibodies produced against the pathogens present within saliva such as HIV, Hepatitis virus, Herpes virus, Poliovirus, Influenza virus, Mycobacterium tuberculosis, Candida albicans, Plasmodium falciparum and Ebola virus using the PCR or saliva-based ELISA test. In case of Renal diseases, biomarkers found include cortisol, nitrite, uric acid, sodium, chloride, amylase and lactoferrin while for Cardiovascular diseases, C-reactive protein, Myoglobin, Free fatty acid, B-type natriuretic peptide, Myeloperoxidase, Low-density lipoprotein and Ischemia modified albumin are found in elevated amount in saliva samples (Miller *et al.*, 2010). In Systemic diseases such as Cancer, levels of different salivary biomarkers have been reported to increase such as the cancer antigen, CA15-3 and the oncogene c-erB2 in breast cancer patients. Several salivary transcriptomic biomarkers are found where DNA or RNA present is used to detect autoimmune disorders such as Sjogren's syndrome and Scleroderma. For psychological studies, markers identified include salivary amylase, serotonin, lysozyme, secretory IgA, calcitonin, cortisol, substance P and salivary testosterone levels proving to diminish pain and anxiety a person underwent during testing processes (Malamud and Rodriguez-Chavez, 2011). Diabetes biomarkers comprise the salivary glucose, whose concentration is affected in case of diabetic subjects hence it can be employed to diagnose diabetes as serum glucose and salivary glucose share comparable characteristics and fluctuation inclination. This can yield a better pre-diagnostic health intimating

system proving to be more convenient than the previously available procedures but the requirement is to standardize the methodology according to the salivary perspectives.

7. UPCOMING PRODUCT

Dr. Ron Clark, co-founder of the device iQuickIt Saliva Analyzer, put his tremendous efforts to develop a saliva-based glucose monitoring device, that is set to launch the device that would enable the measurement of the blood glucose levels without pricking or stabbing the finger of the patients. The product is not yet available to the public, it will soon be within the reach of them and provide freedom from the daily based inconvenience faced by all the diabetic patients. According to Dr. Ron Clark, the main aim for the development of the iQuickIt Saliva Analyzer was to create an opportunity for simple non-invasive testing and to develop a type of technology that makes life easier and comfortable for the diabetic people. Dr. Clark explained that the barrier to accurately calibrate and measure saliva glucose has been removed by developing technologies that utilize high but more practical methods, connecting the dots on proven technologies with some modifications to use saliva for the glucose reading. He stated that the device provides a comparable level of accuracy and further trials are being carried out to refine and provide a higher level of accuracy. Currently, a crowd funding program is being carried out to help support the next phase of product refinement and clinical trials. Even though the process to achieve FDA approval long, the product is supposed to be consumer available within 24 months and will be released into the hands of a diabetic patient/person to provide a better solution (Vieira, 2013).

Kiss & Tell is another award-winning product that tests for high blood glucose levels using saliva instead of blood. The product is best suited for monitoring the hyperglycemic conditions of Type II diabetic patients. It is mainly for health screening and high blood glucose monitoring but not for diagnostic purpose. Kiss & Tell has been tested with thousands of samples in the laboratory and with people and has demonstrated the high percentage of accuracy in the detection of normal to high glucose levels. But the product is not suitable for testing glucose levels below normal and hence is not intended for either Type I diabetic patients or patients using insulin. It has also been tested to show that other types of sugars (non-glucose) do not interfere with the test results unless the concentration is exceptionally higher than the normal physiological levels. For using the product the patient has been instructed to follow the steps mentioned below:-

1. First, the patient has to rinse his/her mouth completely.
2. Then the saliva has to be delivered to the collection well.
3. After that, a pause for 5 minutes has been instructed.
4. Then, the device is checked for colour (dark pink colour indicates high glucose level) (eNano Health, 2016).

Indiegogo (2018) has also developed a glucose measuring device which is painless, faster, simpler and more accurate. The glucose meter that is to be released by Adour has been named SalivaTest and is said to be a revolutionary new, painless way of testing glucose levels by using saliva instead of blood. SalivaTest is close to final testing and prototyping. SalivaTest is being claimed to be the first painless diabetic device. SalivaTest's groundbreaking technology is easier, more convenient, less painful and very accurate. The handy SalivaTest device has been designed to have an attractive design. It can also be linked to the SalivaTest Smartphone App to save data and provide a regular, "at-a-glance" diabetes monitoring. And also, the technology used in the SalivaTest device is said to be highly innovative and groundbreaking (Indiegogo, 2018).

8. CONCLUSION

The review provides the highlights of the Diabetes Mellitus over centuries that incorporate the recognition of the disease as well as the endowment of the glucose measuring devices. The establishment of the glucose meter accuracy and integrity is a challenging and very demanding task that requires tremendous investigation and efforts in the research field. Traditional blood-based devices possess above mentioned properties and are commonly used

by the majority of the population but the reoccurring invasion of skin along with other difficulties create discomfort to the subjects. This necessitates the scientist to discover such technologies that can. Conquer these problems. The non-invasive methods mentioned in our review have been advancements in the field of glucose sensing technologies that use various easily accessible biofluids that can be used as the sample instead of blood. The saliva-based glucometer is one such technology that has proven to be used effectively in the place of traditional blood-based glucometer and develops a better future for diabetic patients.

REFERENCES

Abikshyeet, P., V. Ramesh and N. Oza, 2012. Glucose estimation in the salivary secretion of diabetes mellitus patients. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy, 5: 149-154. Available at: https://doi.org/10.2147/dmso.s32112.

Ahmed, A.M., 2002. History of diabetes mellitus. Saudi Medical Journal, 23(4): 373-378.

Amer, S., M. Yousuf, P. Siddqiui and J. Alam, 2001. Salivary glucose concentrations in patients with diabetes mellitus–a minimally invasive technique for monitoring blood glucose levels. Pakistan Journal of Pharmaceutical Sciences, 14(1): 33-37.

Bailey, T., B.W. Bode, M.P. Christiansen, L.J. Klaff and S. Alva, 2015. The performance and usability of a factory-calibrated flash glucose monitoring system. Diabetes Technology & Therapeutics, 17(11): 787-794. Available at: https://doi.org/10.1089/dia.2014.0378.

Baynes, H., 2015. Classification, pathophysiology, diagnosis and management of diabetes mellitus. Journal of Diabetes and Metabolism, 6(5): 1-9. Available at: https://doi.org/10.4172/2155-6156.1000541.

Belazi, M.A., A. Galli-Tsinopoulou, D. Drakoulakos, A. Fleva and P.H. Papanayiotou, 1998. Salivary alterations in insulin-dependent diabetes mellitus. International Journal of Paediatric Dentistry, 8(1): 29-33. Available at: https://doi.org/10.1046/j.1365-263x.1998.00057.x.

Bruen, D., C. Delaney, I. Florea and D. Diamond, 2017. Glucose sensing for diabetes monitoring: Recent developments. Sensors, 17(8): 1-21. Available at: https://doi.org/10.3390/s17081866.

Clarke, S. and J. Foster, 2012. A history of blood glucose meters and their role in self-monitoring of diabetes mellitus. British Journal of Biomedical Science, 69(2): 83-93. Available at: https://doi.org/10.1080/09674845.2012.12002443.

Deshpande, A.D., M. Harris-Hayes and M. Schootman, 2008. Epidemiology of diabetes and diabetes-related complications. Physical Therapy, 88(11): 1254-1264. Available at: https://doi.org/10.2522/ptj.20080020.

Eknoyan, G. and J. Nagy, 2005. A history of diabetes mellitus or how a disease of the kidneys evolved into a kidney disease. Advances in Chronic Kidney Disease, 12(2): 223-229. Available at: https://doi.org/10.1053/j.ackd.2005.01.002.

eNano Health, 2016. Kiss & tell: A non-invasive glucose test using saliva. Available from http://www.enanohealth.com/products/kissfaq.php [Accessed September 17 2018].

Giovannucci, E., D.M. Harlan, M.C. Archer, R.M. Bergenstal, S.M. Gapstur, L.A. Habel, M. Pollak, J.G. Regensteiner and D. Yee, 2010. Diabetes and cancer: A consensus report. CA: A Cancer Journal for Clinicians, 60(4): 207-221. Available at: https://doi.org/10.3322/caac.20078.

Greabu, M., M. Battino, M. Mohora, A. Totan, A. Didilescu, T. Spinu, C. Totan, D. Miricescu and R. Radulescu, 2009. Saliva—a diagnostic window to the body, both in health and in disease. Journal of Medicine and Life, 2(2): 124-132.

Heinemann, L. and G. Freckmann, 2015. CGM versus FGM; or, continuous glucose monitoring is not flash glucose monitoring. Journal of Diabetes Science and Technology, 9(5): 947–950. Available at: https://doi.org/10.1177/1932296815603528.

Henry, W.L., 1987. The complications of diabetes mellitus. Journal of the National Medical Association, 79(6): 677–680.

Humphrey, S.P. and R.T. Williamson, 2001. A review of saliva: Normal composition, flow, and function. The Journal of Prosthetic Dentistry, 85(2): 162-169. Available at: https://doi.org/10.1067/mpr.2001.113778.

Indiegogo, 2018. Adour:The first painless glucometer using saliva. Available from https://www.indiegogo.com/projects/adour-the-first-painless-glucometer-using-saliva#/ [Accessed September 17 2018].

Karamanou, M., A. Protogerou, G. Tsoucalas, G. Androutsos and E. Poulakou-Rebelakou, 2016. Milestones in the history of diabetes mellitus: The main contributors. World Journal of Diabetes, 7(1): 1–7. Available at: https://doi.org/10.4239/wjd.v7.i1.1.

Kaufman, E. and I.B. Lamster, 2002. The diagnostic applications of saliva—a review. Critical Reviews in Oral Biology & Medicine, 13(2): 197-212. Available at: https://doi.org/10.1177/154411130201300209.

Kaveeshwar, S.A. and J. Cornwall, 2014. The current state of diabetes mellitus in India. The Australasian Medical Journal, 7(1): 45–48. Available at: https://doi.org/10.4066/amj.2014.1979.

Kesavadev, J., L. Ramachandran and G. Krishnan, 2017. Glucose monitoring technologies - complementary or competitive? Role of continuous glucose monitoring versus flash glucose monitoring versus self-monitoring of blood glucose. Journal of Diabetology, 8(3): 61-67. Available at: https://doi.org/10.4103/jod.jod_14_17.

Kharroubi, A. and H. Darwish, 2015. Diabetes mellitus: The epidemic of the century. World Journal of Diabetes, 6(6): 850-867. Available at: https://doi.org/10.4239/wjd.v6.i6.850.

Krogstad, A.L., P.A. Jansson, P. Gisslén and P. Lönnroth, 1996. Microdialysis methodology for the measurement of dermal interstitial fluid in humans. British Journal of Dermatology, 134(6): 1005-1012. Available at: https://doi.org/10.1046/j.1365-2133.1996.d01-893.x.

Lakhtakia, R., 2013. The history of diabetes mellitus. Sultan Qaboos University Medical Journal, 13(3): 368-370.

Lee, Y. and D. Wong, 2009. Saliva: An emerging biofluid for early detection of diseases. American Journal of Dentistry, 22(4): 241-248.

Lin, T., A. Gal, Y. Mayzel, K. Horman and K. Bahartan, 2017. Non-invasive glucose monitoring: A review of challenges and recent advances. Current Trends in Biomedical Engineering & Biosciences, 6(5): 001-008. Available at: https://doi.org/10.19080/ctbeb.2017.06.555696.

Losoya-Leal, A., S. Camacho-León, G. Dieck-Assad and S. Martínez-Chapa, 2012. State of the art and new perspectives in non-invasive glucose sensors. Mexican Journal of Biomedical Engineering, 33(1): 41-52.

Makaram, P., D. Owens and J. Aceros, 2014. Trends in nanomaterial-based non-invasive diabetes sensing technologies. Diagnostics, 4(2): 27-46. Available at: https://doi.org/10.3390/diagnostics4020027.

Malamud, D. and I.R. Rodriguez-Chavez, 2011. Saliva as a diagnostic fluid. Dental Clinics of North America, 55(1): 159–178. Available at: https://doi.org/10.1016/j.cden.2010.08.004.

Mayeux, R., 2004. Biomarkers: Potential uses and limitations. NeuroRx, 1(2): 182–188. Available at: https://doi.org/10.1602/neurorx.1.2.182.

Miller, C.S., J.D. Foley, A.L. Bailey, C.L. Campell, R.L. Humphries, N. Christodoulides, P.N. Floriano, G. Simmons, B. Bhagwandin and J.W. Jacobson, 2010. Current developments in salivary diagnostics. Biomarkers in Medicine, 4(1): 171-189.

Mohan, V. and R. Pradeepa, 2009. Epidemilogy of diabetes in different Regions of India. Health Administrator, 22(1-2): 1-18.

Nawaz, A., P. Ohlckers, S. Saelid, M. Jacobsen and N.M. Akram, 2018. Review: Non-invasive continuous blood glucose measurement techniques. Journal of Bioinformatics and Diabetes, 1(3): 1-27. Available at: https://doi.org/10.14302/issn.2374-9431.jbd-15-647.

Palomba, S., S. Santagni, A. Falbo and G.B. La Sala, 2015. Complications and challenges associated with polycystic ovary syndrome: Current perspectives. International Journal of Women's Health, 7: 745-763. Available at: https://doi.org/10.2147/ijwh.s70314.

Pink, R., J. Simek, J. Vondrakova, E. Faber, P. Michl, J. Pazdera and K. Indrak, 2009. Saliva as a diagnostic medium. Biomedical Papers of the Medical Faculty of the University of Palacky Olomouc, Czech Republic, 153(2): 103-110.

Poretsky, L., 2010. Principles of diabetes mellitus. US, United States: Springer.

Proctor, G.B., 2016. The physiology of salivary secretion. Periodontol, 70(1): 11-25.

Reuterving, C., G. Reuterving, E. Hägg and T. Ericson, 1987. Salivary flow rate and salivary glucose concentration in patients with diabetes mellitus influence of severity of diabetes. Diabete & Metabolisme, 13(4): 457-462.

Sami, W., T. Ansari, N.S. Butt and M.R.A. Hamid, 2017. Effect of diet on type 2 diabetes mellitus: A review. International Journal of Health Sciences, 11(2): 65–71.

Schierenbeck, F., M. Nijsten, A. Franco-Cereceda and J. Liska, 2014. Introducing intravascular microdialysis for continuous lactate monitoring in patients undergoing cardiac surgery: A prospective observational study. Critical Care, 18(2): R56-R56. Available at: https://doi.org/10.1186/cc13808.

Seino, Y., K. Nanjo, N. Tajima, T. Kadowaki, A. Kashiwagi, E. Araki, C. Ito, N. Inagaki and Y. Iwamoto, 2010. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. Journal of Diabetes Investigation, 1(5): 212-228. Available at: https://doi.org/10.1111/j.2040-1124.2010.00074.x.

Strimbu, K. and J.A. Tavel, 2010. What are biomarkers? Current Opinion in HIV and AIDS, 5(6): 463–466.

Tamar, L., G. Avner, M. Yulia, H. Keren and B. Karnit, 2017. Non-invasive glucose monitoring: A review of challenges and recent advances. Current Trends in Biomedical Engineering & Biosciences, 6(5): 555696. Available at: https://doi: 10.19080/CTBEB.2017.06.555696.

Tiwari, M., 2011. Science behind human saliva. Journal of Natural Science, Biology, and Medicine, 2(1): 53–58. Available at: https://doi.org/10.4103/0976-9668.82322.

Todd, C., P. Salvetti, K. Naylor and M. Albatat, 2017. Towards non-invasive extraction and determination of blood glucose levels. Bioengineering, 4(4): 82. Available at: https://doi.org/10.3390/bioengineering4040082.

Tonyushkina, K. and J.H. Nichols, 2009. Glucose meters: A review of technical challenges to obtaining accurate results. Journal of Diabetes Science and Technology, 3(4): 971–980. Available at: https://doi.org/10.1177/193229680900300446.

Vieira, G., 2013. Personal interview with Dr. Ron Clark. Diabetes Daily. Available from https://www.diabetesdaily.com/blog/2013/12/testing-your-blood-sugar-with-your-saliva/.

Wong, D.T.W., 2012. Salivary diagnostics. Operative Dentistry, 37(6): 562-570.

Xu, L., K. Kanasaki, M. Kitada and D. Koya, 2012. Diabetic angiopathy and angiogenic defects. Fibrogenesis & Tissue Repair, 5(1): 1-9. Available at: https://doi:10.1186/1755-1536-5-13.

Yeh, C.-K., N.J. Christodoulides, P.N. Floriano, C.S. Miller, J.L. Ebersole, S.E. Weigum, J. Mcdevitt and S.W. Redding, 2010. Current development of saliva/oral fluid-based diagnostics. Texas Dental Journal, 127(7): 651–661.

Yoo, E.H. and S.Y. Lee, 2010. Glucose biosensors: An overview of use in clinical practice. Sensors, 10(5): 4558–4576. Available at: https://doi.org/10.3390/s100504558.

Yoshizawa, J.M., C.A. Schafer, J.J. Schafer, J.J. Farrell, B.J. Paster and D.T. Wong, 2013. Salivary biomarkers: Toward future clinical and diagnostic utilities. Clinical Microbiology Reviews, 26(4): 781-791. Available at: https://doi.org/10.1128/cmr.00021-13.

Zheng, Y., S.H. Ley and F.B. Hu, 2018. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nature Reviews, Endocrinology, 14(2): 88-98. Available at: https://doi.org/10.1038/nrendo.2017.151.