TAS Journal, vol. 6, n. 2, p. 111-121
ISSN 2595-1521
JUNE 2022
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NON-INVASIVE METHODS OF HOME BLOOD GLUCOSE MONITORING.

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Abstract. Diabetes is a worldwide health problem, a metabolic disorder that can lead to serious complications and damage to all vital organs. The resulting complications can be prevented with regular monitoring and maintenance of blood glucose level. The present review study aims to gather information on current methods for monitoring capillary blood glucose. Scientific articles were consulted in national and international journals, in addition to the Guidelines of the Brazilian Society of Diabetes and 9th Edition of the Diabetes Atlas of the International Diabetes Federation, American Diabetes Association, Ministry of Health and Brazilian Institute of Geography and Statistics (IBGE) data. Non-invasive methods include impedance spectroscopy, optical coherence tomography, photoacoustic spectroscopy, mid and near infrared spectroscopy, photoplethysmography. The advantages, in general, of non-invasive methods, seek ease of implementation and use, cost, accuracy in blood glucose measurement. The main disadvantages are physical parameters that can interfere with glucose measurement, as well as environmental variations. Interferences due to physiological factors can be eliminated using filtering processes, which suppress noise and increase effective information. With the present study, it is possible to conclude that there is a need to develop a non-invasive, painless, easily accessible method, without tissue damage, providing cost savings for the health system, considering quality of life, functional limitations, social and financial stress, emotional discomfort and depression in individuals with diabetes mellitus.

Keywords. Diabetes Mellitus. Home Care. Non-invasive monitoring.

Introduction. Diabetes Mellitus (DM) is a chronic disease that occurs when the pancreas is no longer able to produce insulin, or when insulin is insufficient for the body (SBD, 2015).

DM comprises a long-term metabolic pathological condition in which the blood glucose level fluctuates outside normal range (90-120 mg/dL). Glucose is the main source of energy in biological cells. Insulin, a hormone secreted by the pancreas, helps in the absorption of glucose by cells, which in turn regulates the blood glucose level (YADAV et al., 2015).

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It is currently considered a growing global health problem. The latest data published by International Diabetes Federation (IDF) in the 9th IDF Diabetes Atlas, are 463 million people living with DM in the world. In 2019, Brazil ranked 5th in the number of adults (20 to 79 years old) with diabetes, with a total of 16.8 million people. It is estimated that in 2030 this number will rise to 21.5 million and in 2045 to 26 million people.

According to the Brazilian Diabetes Society, WHO (World Health Organization) estimates that one in ten adults in the world has diabetes (SANTOS, 2014).

DM and its complications, if not well monitored and treated properly, can lead to frequent hospitalizations, worsening complications and even premature death (IDF, 2019).

Social inequalities are present all over the world, making it difficult to monitor risk factors, symptoms, diagnosis and also access to medicines and tests, even today insulin remains inaccessible and unavailable for many people (IDF, 2019).

With rapid and accurate diagnosis and access to adequate care, DM can be well managed and its complications avoided. In the case of type 2 diabetes, it is often preventable and there is evidence to suggest that it can, in some circumstances, be reversed (IDF, 2019).

After the diagnosis of diabetes is established, patients start several treatment modalities to correct the hyperglycemia, seeking to achieve the best possible metabolic control, that is, fasting glucose levels <110µg/dl or postprandial glucose levels <140 mg/dl or glycohemoglobin below the maximum limit of the method used (GROSS et al., 2002).

The control of glycemia significantly reduces the complications of DM, thus, the methods that assess the frequency and magnitude of hyperglycemia are essential for monitoring this pathology, aiming at adjustments in the treatment (GROSS et al., 2002).

Diabetic patients are advised to check their glucose level at least four to five times a day to avoid hyperglycemic/hypoglycemic events. Frequent glucose monitoring plays a crucial role in improving the quality of life as well as the life expectancy of a diabetic individual (YADAV et al., 2015).

Continuous glucose monitoring provides the advantage of measuring interstitial glucose every 5-15 min, thus providing a comprehensive 24-h glycemic profile, with better assessment of nocturnal and/or asymptomatic hypoglycemia and pattern recognition after each treatment intervention (GALINDO et al., 2020).

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Blood Glucose Monitoring

In the 1970s, the assessment of glycemic control was performed with home measurement of glucosuria and occasional fasting glucose measurements. With the advancement of methods, there was the development of tests that assess long-term glycemic control, such as glycated hemoglobin (HbA1c), as well as those that detect blood glucose fluctuations throughout the day, such as self-monitoring of capillary glycemia (SMBG). and the continuous interstitial fluid glucose (SMCG) monitoring system (SBD, 2019).

The development of home self-monitoring of capital glucose (SCGA) is very useful for assessing glycemic control, in a complementary way to the HbA1c measurement, and allows patients to identify capillary blood glucose (GC) at different times of the day and can act to correct it. rapidly hyperglycemic spikes or hypoglycemic episodes (SBD, 2015).

This method is recommended for patients with type 1 DM (DM1) and those with DM2 using insulin. In these individuals, the method allows a reduction in the risk of hypoglycemia and a better understanding of the effect of different foods, stress and exercise on blood glucose. In addition, it can be used to make decisions about the insulin dose to be used in real time (SBD, 2015).

SMBG is performed by inserting a drop of capillary blood into a disposable biosensor strip containing glucose dehydrogenase or glucose oxidase coupled to a medical device (glucometer) that, for the most part, quantifies plasma glucose, seen in Figure 1. (SBD, 2015).

Figure 1: Self-monitoring of capillary glycemia system.

Despite the improvements of glucometers, they are inconvenient because they are invasive and painful, require intermittent use, and cause expense for disposable parts and their proper disposal, in this way, a non-invasive method is driven by factors such as painless operation, without the need for samples. biological or chemical reagents and production of waste of any kind, resulting in greater convenience and cost reduction for the health system (SILVA, 2017).

Non-invasive methods are technologies for measuring blood glucose concentrations that do not cause any pain or discomfort to the patient and do not cause any tissue damage.

Individuals with DM suffer from psychosocial discomfort, which has a negative impact on their ability to maintain basic self-monitoring recommendations. Pain is often one of the factors that

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make it difficult to perform capillary blood glucose on a “fingertip” due to the nerve endings in this location (FERRAZ et al., 2004).

Yadav et al. (2015) reported various non-invasive glucose detection techniques, their advantages and disadvantages, such as Raman Spectroscopy, Polarimetry, Optical Coherence Tomography, Photoacoustic Spectroscopy, Impedance Spectroscopy, Middle Infrared Spectroscopy, Near Infrared Spectroscopy. Glucose is a polarizable molecule that has the isomers: Alpha-D-Glucopyranose and Beta-D-Glucopyranose, Figure 2.

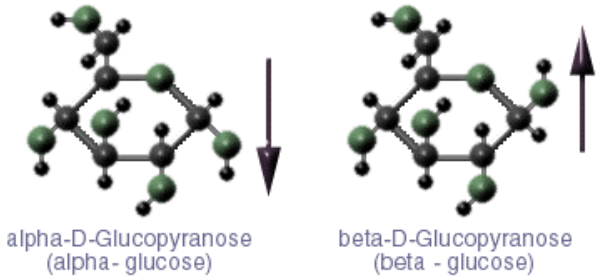

Figure 2: Alpha-D-Glucopyranose and Beta-D-Glucopyranose.

Santos et al. (2014) defined that the blood glucose measurement techniques adopted for the development of non-invasive methods were obtained after analyzing several techniques available in the literature, among those that presented the most positive points, considering the ease of implementation, cost and precision., in the measurement of blood glucose, were Photoplethysmography and Metabolic Heat Conformation.

In Photoplethysmography (PPG) the non-invasive measurement of glucose can be performed by focusing a beam of light on the finger and analyzing the light transmitted through it. The glucose concentration can be determined by analyzing the change in wavelength, using spectroscopy techniques, or in the intensity of transmitted light, at different wavelengths, usually from 700 to 2500 nm (SANTOS, 2014).

Its application is consolidated in different clinical segments, from monitoring physiological parameters to assessing oxygen saturation, cardiac frequency and output, pulse and blood pressure; as well as in specific studies to assess vascular function and autonomic function. Being carried out according to the technical guidelines of the equipment, its use is safe, has good reproducibility, but its results can be influenced by factors such as ethnicity, epidermis thickness and age group (SOUZA, 2016).

The principle of PPG is to measure the amount of infrared light absorbed or reflected by the blood, as a function of volume changes in the microvascular bed caused by variations in blood pressure in the vessels. Given the relationship between vascular blood flow and the amount of absorbed or reflected light, it is possible to observe the volume variation based on the measurement of detected light (SOUZA, 2016).

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Glucose is an optically active substance, when light passes through it, the plane of polarization is rotated by some angle, which is correlated with the concentration of glucose in the solution (YADAV et al., 2015).

This method is based on the light scattering properties caused by glucose present in the blood. The increase in glucose decreases the misalignment of the beam that passes through the tissue, as the refractive index is decreased by its presence, thus providing a better path for the passage of light, as a result, less light is absorbed and the intensity of the light that passes through. the fabric is bigger (BRINCE, 2012).

The device that performs PPG is basically composed of two components: an optical one, a light source that will be directed to the tissue, and an electronic one, a photodetector, which will measure and record minimal variations in light intensity associated with changes in blood perfusion; converting these variations into electrical signals, graphically represented by pulsatile waves (SOUZA, 2016).

Another non-invasive method is the use of radiation emitted by the human tympanic membrane, which is also an indicator of blood glucose. Measuring glucose across the tympanic membrane has shown some promising results but needs regular calibration (YADAV et al., 2015).

Impedance spectroscopy measures the resistance offered by the skin to alternating currents of different frequencies. The impedance spectrum is determined by the frequency range from 100 Hz to 100 MHz. The dielectric characteristics of blood change with blood glucose level, which further affects blood impedance. Changes in plasma glucose concentration decrease Na ions and increase K+ ions, which further alters the membrane potential of red blood cells. The dielectric spectrum can be used to estimate membrane potential (YADAV et al., 2015).

Optical coherence tomography (OCT) enables accurate and non-invasive real-time glucose monitoring. TCO uses a low intensity light source, an interferometer and a photodetector to measure the interferometric signal. The interferometer consists of a reference arm, a sample arm and a moving mirror. The light returned from the reference part of the interferometer is combined with the backscattered light from the tissue. The resulting interferometric signal is detected by a photodetector. Delay in stray light back or changes in stray light due to variation in glucose concentration are used for measurement (YADAV et al., 2015).

Near Infrared spectroscopy was considered by Yadav et al. (2015) the best and most promising method as it provides simple, economical, safe and convenient online monitoring, currently on the market it has become popular for monitoring many physiological parameters.

This method allows the measurement of glucose under the skin within a few minutes. The penetration of light into the skin decreases with increasing wavelength, as light interacts with tissue, it is partially absorbed and scattered due to interaction with chromophores within the tissue (YADAV et al., 2015).

Among the advantages presented by this study are the penetration of light into the skin from 1 to 100 mm, the high sensitivity of photoconduction detectors, high energy signals compared to mid-infrared spectroscopy, low cost and wide variety of commercial products available.

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The disadvantages are that physical parameters (variation in pressure, temperature and chemical parameters, triglycerides and albumin) can interfere with glucose measurement, as well as environmental variations such as changes in temperature, humidity, skin hydration, carbon dioxide and atmospheric pressure. (YADAV et al., 2015).

Interferences due to physiological factors can be eliminated by volume of blood subtracted spectrometry (EVSS), where two spectra of blood measured are subtracted over a short period. In order to improve the performance of EVSS, decomposition in empirical mode (DME) filtering can be used.

DME filtering suppresses noise in subtracted spectra and increases effective information. It is suitable for non-linear and non-stationary data sets. It is a fully data-driven adaptive method that does not need predetermined information about the signal. The remarkable repeatability of glucose spectra can be improved if the measurement is performed under well-controlled physiological and environmental conditions.

Zanon et al. (2013) proposed a multi-sensor device considering the sweat event for non-invasive glucose measurement. The author noted that updating the calibration parameter after the sweat event significantly improves performance.

Using a proper spectral preprocessing technique before building multivariate calibration models also helps to improve results. Mathematical pre-treatments to improve information search in the study and reduce the influence of secondary information contained in the spectra. It removes artifacts due to instrumental and environmental variations, baseline drift, temperature fluctuation, path length change, and other nonlinearities due to scattering. It also removes unwanted variances or clusters and increases the relevant variance (YADAV et al., 2015).

Some of the common pre-processing techniques are: moving average filter, spectral differentiation, bandpass filter, Savitzky-Golay filter, digital filters, Classic Least Square and Hybrid Linear Analysis.

Methods. Research was conducted at the national and international levels, guidelines published by the International Diabetes Federation, Brazilian Diabetes Society, American Diabetes Association, Ministry of Health and International Diabetes Federation, American Diabetes Association, Ministry of Health and Brazilian Institute of Geography and Statistics (IBGE). The databases consulted were SciELO, Capes Periodicals, Virtual Health Library with the keywords Diabetes Mellitus, Home Glucose Monitoring, Non-Invasive Glucose Monitoring. Throughout the present study, eleven scientific articles were consulted, in addition to the Guidelines of the Brazilian Society of Diabetes and the 9th Edition of the Diabetes Atlas.

Results and Discussion. We currently have the FreeStyle® Libre which is a device already available in the Brazilian market from the company Abbott Brazil, it is composed of a sensor and a reader. It can be considered a minimally invasive method since there is the introduction of a "catheter" in the dermis. The sensor is painlessly applied to the triceps region, it captures blood

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glucose levels through a 0.4 mm wide by 5 mm long microfilament. It is under the skin, in contact with the interstitial fluid, measuring the glucose present in the bloodstream every minute. The reader is scanned over the sensor and shows the measured glucose value (Abbott Brasil, 2015).

Each sensor can remain on the patient's arm for up to 14 consecutive days, requires no calibration, is water resistant and disposable. The average price of the sensor is R$ 240.00, however, to start using it, it is necessary to purchase an initial kit consisting of a sensor and a reader, with an average value of R$ 540.00.

The reading of the device on the sensor presents a result in real time, bringing a history of the last 8 hours and the blood glucose trend, whether it is rising, falling or remaining stable, it has a capacity to store data for up to 90 days.

Galindo et al. (2020) performed a prospective study in adult patients with type 2 DM admitted to general and surgical wards. Patients are monitored with capillary glucose testing (GCT) before meals and before bed and with continuous glucose monitoring (CGM) during hospitalization. Study outcomes included differences between GCT and MCG in mean daily blood glucose, hypoglycemia <70 and <54 mg/dL, and nocturnal hypoglycemia. Mean daily glucose was significantly higher by TGC. Hypoglycemia with nocturnal GCM was 26% and prolonged 12%.

The conclusion of the study was that Compared with the TGC, the FreeStyle Libre CGM had lower mean daily glucose and greater detection of hypoglycemic events, particularly nocturnal and prolonged hypoglycemia in hospitalized patients with type 2 DM. The accuracy of the MCG was lower in the range of hypoglycemia.

Although it is a minimally invasive method, the use of FreeStyle® Libre is painless as reported by the manufacturer, but it is the only one available on the market.

Taking into account that in Brazil there are still people without access to information, basic health and even basic sanitation, access to this equipment, and its high cost, taking into account the use of two sensors per month, a cost of approximately R$ 480.00 per month, equivalent to 43.93% of the minimum wage in force in Brazil, without taking into account the value of the reader that must be acquired in the first use, this equipment becomes unfeasible for part of the diabetic population.

According to the Ministry of Health, to treat diabetes, the Brazilian Unified Health System (SUS) offers medicines for free. There are six medicines financed by the Ministry of Health and released in accredited pharmacies. In addition, patients with the disease are followed up by Primary Care and obtaining the medication for the treatment has been essential to reduce the more serious outcomes of the disease.

In this way, patients are guaranteed comprehensive treatment in SUS, which provides the population with NPH human insulin – injectable suspension 1 and regular human insulin, in addition to three other medicines that help control the blood glucose index: Glibenclamide,

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Metformin and Gliclazide. For monitoring the glycemic index, reagents and syringes are also available at Basic Health Units.

To receive insulin and capillary blood glucose monitoring supplies, users with type 1 diabetes, insulin-dependent type 2 diabetes and Gestational Diabetes must be registered in the Pharmaceutical Assistance Management System - SIGAF.

The glucose measuring device, test strips and lancets are only provided to patients with Type 1 Diabetes, Insulin Dependent Type 2 Diabetes and Gestational Diabetes.

Taking into account that the SUS provides the equipment to monitor the blood glucose level, the vast majority of people do not have the capital to invest in an expensive method, which commits a good part of their monthly salary, given that currently the second quarter of 2020 recorded a record in the 9.6% reduction in the number of employed persons in Brazil. In total, 8.9 million people lost their jobs from April to June, compared to the period from January to March, according to IBGE data (2020).

Non-invasive methods are technologies for measuring blood glucose concentrations that do not cause any pain or discomfort to the patient and do not cause any tissue damage.

In individuals with DM, there is a significant impairment of quality of life, including functional limitations, social and financial stress, emotional discomfort and even depression, estimating that the reduction in quality of life in diabetics is due to multiple long-term complications and of inadequate glycemic control (FERRAZ et al., 2004).

In a study carried out by Ferraz et al. (2004) it was demonstrated that there is no significant difference in the value between the conventional invasive test with application of a lancet applied to the fingertip and to the ear lobe, with the second being preferred by 70% of the individuals submitted to the study, who report being the painless spot. Although the region is painless, it is not at all simple, as the region is out of the field of vision, requiring third parties, or remaining in front of the mirror, making the whole process difficult and inconvenient.

Faced with this situation, a non-invasive, cheap, effective method, with no monthly investment and easy to use, is necessary.

Among non-invasive technologies, the literature indicates that near-infrared spectroscopy is a promising technique because it contains more advantages than disadvantages, which are easy to solve (YADAV et al., 2015).

Final Thoughts: With the present study, it was possible to assess that there is a need to develop a method of monitoring blood glucose in a non-invasive way, but that also does not compromise part of the monthly income, considering the current situation of the Brazilian population.

According to Silva (2017), the conventional method of monitoring capillary glucose with a glucometer, despite its improvement over the years, is still inconvenient, as in addition to being invasive, they are painful, requiring intermittent use and incurring expenses with disposable parts for its proper disposal.

According to the study conducted by Galindo et al. (2020), we can verify that continuous monitoring of capillary glucose prevents spikes, as well as nocturnal and prolonged hypoglycemia, preventing secondary problems from this adverse event.

Among the researched methods, near-infrared spectroscopy was the method that presented more advantages than disadvantages, and the items that were pointed out as disadvantages are factors that can be filtered by other technologies such as the filters mentioned above.

This method has the advantages of easy penetration of light into the skin, sensitivity of photoconductors, which are responsible for the detection of parameters, low cost and wide variety and applicability of commercially available products (YADAV et al., 2015).

A non-invasive method has a painless operation, does not cause discomfort or tissue damage, without biological samples, without chemical reagents, without the production of waste of any kind, reducing costs for the health system (SILVA, 2017; SMITH, 2015).

In this way, it is possible to conclude that further research with pilot projects is necessary for the development of devices that are really accessible to the less favored population, with better cost benefit and a real possibility of implementation in the SUS program.

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