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Diabetes and noninvasive glucometers: status review
Cukrzyca i nieinwazyjne glukometry: przegląd stanu wiedzy

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Abstract

Diabetes is growing in scope and numbers globally. Early screening, education, lifestyle interventions and easy to use and painless glucose levels monitoring systems are of necessity. The challenge is to invent a noninvasive glucometer that provides personalized information, is highly accurate and easy to use also by an aging population. The paper presents the state of art related to the current work on the topic of noninvasive glucometers. *Geriatria 2018; 12: 198-203.*

Keywords: Diabetes, glucometer, non-invasive, regulations, blood glucose level

Streszczenie

Cukrzyca jest chorobą, której częstość i związane z nią zagrożenia intensywnie wzrastają na całym świecie. Dlatego też niezbędne jest upowszechnienie badań przesiewowych, edukacja, interwencje związane ze stylem życia, a także łatwe w użyciu i bezbolesne systemy monitorowania stężeń glukozy. Wyzwaniem jest wynalezieniu nieinwazyjnego glukometru, który dostarcza spersonalizowanych informacji, jest dokładny i łatwy w użyciu także przez osoby starsze. Artykuł przedstawia stan wiedzy w temacie nieinwazyjnych glukometrów. *Geriatria 2018; 12: 198-203.*

Słowa kluczowe: Cukrzyca, glukometr, nieinwazyjne, przepisy, stężenie glukozy we krwi

Background

Diabetes is growing in scope and numbers globally. The World Health Organization (WHO) has reported an increased incidence from 108 million in 1980 to 422 million in 2014 and the trend continues [1]. According to Frost & Sullivan, a leading market researcher, the U.S. incidence of more than 30 million diabetics is projected to grow and the existing revenue of $10.71 billion should increase to $14.68 billion by 2022 [2]. In Europe, 66 million people are diagnosed with some form of diabetes and among the adult population, 1 in 11 are diabetic. This statistic further increases among the elderly adult sub-population to 1 in 5. Europe spends $208 billion or 25% of the worldwide diabetes expenditure annually on treatment.

A similar incidence is found in Poland which ranks 38 out of 57 countries for prevalence of diabetes. The WHO reported that in Poland in 2016 alone, 6,340 deaths of people aged 30 and older were due to diabetes and an additional 25,880 deaths were attributed directly to high blood glucose levels. The combination of these two figures represents over 10% of all mortality in Poland in 2016. With 64% of the Polish population classified as overweight and an additional 27% obese, an astounding 1 in every 11 Polish adult (9.5%) has some type of diabetes and the risk increases with age, mirroring the global incidence of 1 in 5 among the elderly population. This statement is in agreement with the PolSenior study (national wide study of aging in Poland) [3] which show that 18% of elderly population in Poland have diabetes.

This global trend is likely to continue resulting in increased incidence of mortality and a huge global economic burden for treatment. A twofold approach to impact this trend would have to involve (1) Early screening coupled with lifestyle interventions for those with identifiable risk factors and (2) Education and strict maintenance and monitoring for those who are currently diagnosed as diabetic.

Technology and Diabetes

Technology can help to improve maintenance and monitoring of the diabetic population. In the emerging technology of this generation that produces

efficient, smaller and highly complex components and processing hardware, it is now feasible to develop accurate and simple medical devices for home testing and monitoring. In fact, this trend is seen, not just as a feasible option for the future, it is ascending into the mainstream market and presenting a viable option to traditional medical health screening. The popularity of this approach is evident in the investment companies are making in both the clinical and technical challenges to develop relevant home medical devices for health screening, monitoring and treatment.

This significant market elicits great opportunity for investment in an improved technological solution to replace the current invasive glucometer that requires a finger prick to provide a blood sample for testing. In fact, dozens of companies have attempted to develop a noninvasive glucose monitoring device for home use which has resulted in the glucometer challenge described as the 'holy grail' of home medical devices [4]. To date, there has not been a proved successful noninvasive solution and a number of companies have dropped out of the challenge to develop one due to lack of funding. The latest array of experimental products utilizes technologies ranging from infrared spectroscopy that measures glucose concentration though the skin, to skin patches designed to monitor sugar levels in sweat. However, it remains to be seen whether a clinically acceptable alternative to the traditional finger prick will successfully emerge in the home testing market.

Home Medical Device

A home medical device is defined as "a device intended for use in a nonclinical or transitory environment, that is managed partly or wholly by the user, requires adequate labeling for the user, and may require user training by a health care professional in order to be used safely and effectively" [5]. Medical devices used in the home need to be easy to use and read, accurate for the condition they are monitoring and fit into the environment in which they are used. Consumers who use home medical devices may be professional caregivers or lay users and will exhibit diversity in knowledge, experience, physical dexterity, sensory and cognitive perception and emotional state. The testing environment may be the home, but it could also be the workplace or another location in the community or even a remote area across the globe. Environments vary in the quality and accessibility of resources such as electrical power and internet access, in the amount of space available, light and noise levels, temperature and humidity and occupants that may include children, pets, or vermin. All of these 'interfering' environmental factors must be considered when developing a medical device to ensure the safe and effective delivery of accurate home test results.

There are several types of glucometers on the market today; the most common and readily available are self-monitoring glucometers. Most likely the first regulatory approved home testing device historically, along with simple reagent test strips, its home use has assisted diabetics for many years. Continuous and noninvasive glucose monitors are also emerging on the market with many providing additional medical management (such as dietary guidance) by utilizing phone apps or PC software to store and manage personal data. This data, in some cases, can be shared online with remote physicians via a Bluetooth/Wi-Fi/USB connection for remote analysis.

Noninvasive Glucose Meters

The "holy grail" of home testing devices, the noninvasive glucometer, is still an elusive technology. For years now, repeated attempts have been made to bring such a medical device to the home, yet most designs are still in development. The optimal profile for a noninvasive blood glucose monitor should include a disruptive technology that requires 'no pain or discomfort when performing the test, no blood or other body fluid obtained by piercing the skin and does not require or cause any tissue damage, injury, or deterioration' [6]. Based on this definition, alternative technologies such as low-power radio wave detectors and others that sense glucose levels in the blood, without any invasive method of obtaining a sample, are the focus of the current technological challenge.

Additional categories of devices that are noninvasive or minimally invasive are excluded from the definition sited above. To continuously monitor and detect glucose levels, these devices may employ tiny needles or other body fluid extraction methods or utilize alternative fluids that are normally secreted by the body. One example of a minimally invasive glucometer is the GlucoWatch G2 Biographer [2], manufactured by Cygnus Inc, which draws glucose from interstitial fluid just under the surface of the skin into an "auto sensor". Although this device was FDA cleared, it was later pulled from the market due to multiple safety issues.

Sensitivity: The Technical Challenge

The complexity of measuring blood glucose levels cannot be understated. The glucose molecule is small, colorless and present in miniscule concentrations. Mark Rice, MD specializing in diabetes at Vanderbilt University, describes the technical and analytical challenges of detecting glucose in the blood with this analogy: "If you're standing next to a railroad track, and you're trying to sense the movement of a bug crawling on the other side of the track, well, you might be able to sense that. Now sense that bug crawling on the other side of the track while a train is going between you. That's the kind of signal-to-noise [ratio] you're looking at" [2]. More frustrating still, this very low signal to noise ratio for blood glucose detection gets more complicated when glucose levels drop to dangerously low levels. While an industry ± error standard for an over the counter device of 20% might be acceptable for measuring the upper end of a patient's glucose range, this broad sensitivity at low glucose levels could prove to be fatal.

Emerging market of non-invasive devices

Currently the products on the market that claim to be noninvasive home glucose monitoring devices utilize direct and indirect methods for detecting glucose. Extensive research identified the following most promising noninvasive devices which are either on the market or in an advanced developmental stage:

GlucoVista (GlucoTrack): CE approved device, which uses three independent technologies delivered simultaneously via an ear-clip device: Ultrasonic, Electromagnetic and Thermal – glucose level in the blood is measured by capturing the natural thermal infra-red radiation emitted from the glucose in the blood of a human body in specific wave-lengths. An advanced algorithm then clusters the data into a glucose level report [7].

LighTouch Medical: An experimental device that uses near-infrared spectroscopy to measure blood glucose in human fingertips [8].

Glucosense Technologies: A spinoff of research conducted at the University of Leeds in the U.K., developed a device that measured near-infrared fluorescence triggered by a Low-Powered Laser directed at the skin. When the LPL emitter's glass is in contact with the user's finger, the reflected fluorescent signal changes in relation to the concentration of glucose in the blood, resulting in a measurement in less than 30 seconds [9].

MediWise, GlucoWise: Utilizes radio waves to detect glucose levels across thin sections of tissue. Relies on a specially designed nanocomposite film that that make the skin "transparent" to radio waves. Having recently published data from a 10-person trial on the ability of "GlucoWise" to detect glucose spikes in healthy humans, the product may enter the market (pre-orders only) in 2019 in the U.K. [10].

Cnoga, TensorTip: Multiple pain-free glucose readings can be conducted daily using the same disposable components. Device lifecycle ~ 2 years making it cost effective. Requires one week of calibration of blood glucose using standard methods. Following the calibration cycle, the patient inserts his finger into the device for 40 seconds. An array of light-emitting-diodes (LED) shines visual to infrared wavelengths of light through the fingertip. As the light waves pass through the fingertip, some of it is absorbed and some reflected. A camera sensor, similar to that found in professional digital cameras, detects the changes in the reflected light signal in real time. The product is already on sale, via the firm's website. The end user price is as high as $1,000-$1,500 [2,11].

Abbott Diabetes Care - FreeStyle Libre: A small sensor patch is placed on the arm and can be worn for up to 14 days. The patch measures glucose levels in the interstitial fluid between the cells right under the skin. Although the measurements are not as accurate as using a blood test, the device allows patients to monitor their glucose levels continuously and wirelessly, either using a reading device or downloading an app to their phone [12].

NovioSense: A Dutch startup working on a glucose sensor that is placed under the lower eyelid, from where it can wirelessly send glucose measurements directly to a smartphone. The device consists of a flexible metal coil of just 2cm in length that contains nano-sensors. The coil is covered by a protective layer of soft hydrogel. The coil measures minute-to-minute changes in the glucose levels of tears by using the same enzyme technology as glucose test strips. The device has been tested in animals and the company is now planning clinical trials [13].

DiaMonTech: The company has now patented technology whereby an invisible infrared light beam is placed into the skin, enabling the beam to calculate glucose molecules non-invasively. An optic lens guides

the infrared laser beam to a sensor crystal, burying the laser further into the skin. At the heart of the measurement system is a state-of-the-art quantum cascade laser, which emits the infrared light in a spectral range, which is then absorbed by the glucose [14].

Google's/Novartis smart contact lens: In 2014, Google and Novartis' eye care division partnered to develop a smart contact lens that could measure glucose levels. The lens would incorporate a thin microchip to measure glucose and an antenna to send the information to a smartphone [15].

Apple: Rumors are flying that Apple is developing some kind of wearable that would continuously track the user's blood sugar without breaking their skin. No further data are available to date [4].

Considering both the technical and clinical challenges to date and factoring in past experience, the overall chance that both FDA and CE cleared, safe and effective, easy to use, accurate and completely noninvasive (with no need to use prick calibration) home glucose monitoring device will become available soon seems to be uncertain at this point in time. But the good news is that the best and biggest companies in the world are taking up the challenge and seeking a solution (Google, Apple, Abbot, Novartis) which looks to be focused on a combination of methods that will also rely on large data bases (on clouds, IoT) to utilize quick inter and intra comparisons to produce highly accurate results. Until then, we wait until technology and innovation catches up with ideas and need.

Regulatory Pathway

Glucose home monitors are regulated by both CE (Europe) and FDA (U.S.) based on a slightly different classification system and standard for clearance. The differences between the two approaches stem from a central divide: the U.S. approach assesses the device's effectiveness as well as its risk of harm; the CE mark, on the other hand, affirms simply that the product "meets high safety, health and environmental protection requirements" (European Commission 2015) [16]. It follows that FDA clearance would ensure not only that the product poses no harm to consumers, but that it also performs according to its claims. Critics of the FDA system argue that this framework adds time and unpredictability to the approval process without really establishing the effectiveness of the device [16].

CE and FDA also vary in risk classification. The FDA classifies noninvasive glucometers as Class II and implanted ones as Class III [17] while CE follows in most cases Class IIb for the non-invasive glucometers [18]. Both regulatory agencies require that device validation and approval involve success driven multi-center clinical trials to prove efficacy and establish clinical performance claims versus a known and previously cleared predicate. Below is an overview of the classification criteria for FDA and the European CE standards.

FDA Device Classification:

- Class I: These are devices that present minimal potential for harm to the user. Examples include enema kits and elastic bandages. 35% of medical devices are classified as Class I and 93% of these are exempt from pre-market review.
- Class II: These are devices that generally present a moderate risk of harm to the user. Examples of Class II devices include powered wheelchairs and some pregnancy test kits. 53% of medical devices are classified as Class II and most require FDA review through premarket notification (510(k) and CE review by a notified body.
- Class III: These are devices that sustain or support life, are implanted, or present potential high risk of illness or injury. Examples of Class III devices include implantable pacemakers and breast implants. 9% of medical devices are Class III and require FDA review through premarket approval (PMA) or humanitarian device exemption (HDE). An additional category: Unclassified/Not classified, are devices that the FDA has not yet classified. 3% of devices are currently in the category of unclassified/not classified [19]. Noninvasive glucometers are classified as minimally invasive devices and are subjected to class III FDA clearance and regulations [4,20]. Due to the high risk to the consumer, the FDA requires extensive multicenter analytical and clinical studies to support the intended claims for these devices. Companies have attempted to dispute the Class III requirement without success.

CE Classes

According to the European framework, there are four classes of medical devices:

- Class I**:** Includes three differentiations; Sterile Medical Devices, Measuring Medical Devices and Other Medical devices.

- ❖ Class IIa**:** All medical devices or Only Non-Sterile Medical Devices – Low to medium risk of harm and for short-term (less than 30 day) use.
- ❖ Class IIb: All Medical device or Only Non-Sterile Medical Devices - Medium to high-risk of harm and for longer term (greater than 30 day) use.
- ❖ Class III: Is the highest risk category with additional rules that may apply to the specific medical device. It includes all Medical devices or Only Non Sterile Medical Devices [21].

In addition to the classes above of the Medical Device Reporting establishes in Annex VIII, of different classifications for devices, there are also 22 rules for devices additional classifications [22].

Currently there is no evidence of FDA clearance for a 100% noninvasive over-the-counter glucometer in the market. CE approved noninvasive over-the--counter glucometer have lately emerged, but they are prick calibration dependent yet to be accepted in the market (price, safety, efficiency). Because of the complexity and high risk for accurately detecting and reporting blood glucose levels, both CE/FDA clearance could be a long and arduous process. However, when considering the high risk to the health of the diabetic consumer from a clinical and technical perspective this rigorous regulatory clearance path imposed by both CE/FDA makes sense.

Summary

- The occurrence and mortality resulting from diabetes is increasing globally underscoring the need for close monitoring at home, so treatment will be safe, effective, immediate and controlled.
- The global increasing population of diabetics has a significant and increasing impact on world health and economics.
- The complexity to correctly detect and utilize the signal to noise ratio demonstrated by the small, colorless glucose molecule that is present in miniscule concentrations in the blood, has made product development highly challenging.
- The challenge of inventing a noninvasive glucometer becomes even more complex when the solution must be (1) easy to use by an aging population who make up a majority of the user base, (2) highly accurate and (3) provide professional and personalized information.
- There is a great need for a 100% noninvasive (prick free) home glucometer test that is both FDA and CE approved. The emerging CE approved devices require routine calibration necessitating a finger prick which makes them partially invasive devices.
- A complete free of pain, noninvasive, FDA and CE approved device, which mitigates the high risk to the consumer for accurate results, and which is suitable for use by the elderly population (most of the potential users) – is not yet available.

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