Noninvasive Glucose Monitoring: In God We Trust—All Others Bring Data

Journal of Diabetes Science and Technology
2021, Vol. 15(6) 1211–1215

DOI: 10.1177/19322968211046326
journals.sagepub.com/home/dst
SAGE

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Keywords
noninvasive, optical, glucose, infrared, device

Introduction

There is great demand for a United States Food and Drug Administration (FDA)-cleared noninvasive glucose monitor. We define this term as a technology where the concentration of glucose is obtained without inserting a device into the body or puncturing the skin. When the measurement involves passing a type of radiation into the body, the technology is referred to as a noninvasive optical glucose monitor (NIO-GM).[1] The amount of interest in seeing the development of an accurate, viable NIO-GM and the amount of hyperbole by companies promising accurate NIO-GMs both far outstrip the amount of publicly available data actually generated by these potential products. This mismatch in the production of large amounts of claims and predictions compared to small amounts of actual data accounts for the title of our editorial.

The Appeal of Noninvasive Optical Glucose Monitoring

Access to an NIO-GM would be very appealing to people with diabetes who want to know their glucose concentrations before and after meals, as well as during other activities throughout the day, so they can titrate their activities and doses of medications without pain, inconvenience, or blood waste. Even people without diabetes are interested in the continuous glucose monitors (CGMs) currently on the market as a way to track dietary intake and improve fitness.[2] Many people who do not have diabetes and want to know their glucose concentrations on demand might prefer an NIO-GM to avoid the troublesome nature of an indwelling sensor or might object to being tethered to a CGM device.[3] From a medical standpoint, a significant fraction of people without diabetes can benefit from periodic use of an NIO-GM to (1) hasten an early diagnosis of prediabetes or reactive hypoglycemia, (2) avoid hypoglycemia induced by either extensive exercise or following a low carbohydrate diet, and (3) screen for improved general health as part of a "quantified self" personal tracking program.

Current Industry Interest

In the past few months, many companies have announced progress or interest in developing technology for an NIO-GM. On August 25, 2021, we conducted a Google search for articles published within the previous sixty days using the search phrase "noninvasive glucose." In the first ten pages (100 articles) we found stories about eleven companies developing NIO-GMs. These companies included Hagar[4] (Tel Aviv, Israel, August 12, 2021), Rockley Photonics[5] (Pasadena, California, July 19, 2021), Apple[5,6] (Cupertino, California, July 19, 2021), Samsung[6] (Seoul, South Korea, August 15, 2021), Integrity Applications[7] (Ashdod, Israel, August 12, 2021), Meta Materials Inc.[8] (Dartmouth, Nova Scotia, Canada, August 13, 2021), Movano[9] (Pleasanton, California, August 12, 2021), Lucid Diagnostics Inc.[10] (New York, New York, August 10, 2021), Nanoco[11] (Manchester, UK, August 12, 2021), Afon Technology[12] (Caldicot, UK, June 29, 2021), and GBT Technologies Inc.[13] (Santa Monica, California, August 24, 2021). We also found an article about a company with a noninvasive fluid sampling glucose monitor (NIFS-GM) device, which measures glucose concentrations in a fluid collected from the body in a noninvasive manner (*i.e.*, without the need to puncture skin). This company is Nemaura Medical (Loughborough, UK, August 12, 2021).[14] To our knowledge, only one of these twelve companies (Integrity Applications) has published noninvasive glucose data in a reviewed medical journal and the article by Integrity Applications appeared 3 years ago.[15] In a recently published review, 28 companies were identified as actively pursuing NIO-GMs.[1] Little clinical data have been reported by any of these companies.

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Table 1. Analytical Metrics for Evaluation of Noninvasive Glucose Monitors.

1. Bias
2. Precision
3. Effects of interfering substances
4. Effects of physiologic states
5. Effects of environmental or external conditions
6. Sensor stability
7. Sources of variability (physiology, instrument, or environment)

We anticipate that surprises will confront the early-stage companies in the noninvasive glucose space, both those described above and others that went peer unidentified in our searches. We predict difficulties when these entrepreneurial companies are ready to expand their (1) test populations to a wide demographic, (2) test sites from in-clinic to in-home, and (3) range of tested glucose concentrations to extreme levels like those that can occur in the real world. The data reported by these companies are generally too preliminary to justify the overhyped announcements commonly released from this industry.

Within these three wide ranges of populations, test sites, and measurement ranges, it is important for noninvasive glucose monitor manufacturers to report performance data in peer reviewed journals to achieve credibility in their appeals to investors and patients. We believe that measurements of noninvasive glucose monitor performance should begin with descriptions of monitor analytical results when performed by the company followed by more rigorous testing performed at independent research sites. The 7 analytical metrics listed in Table 1 must be reported, even if only partly for initial reports. We have not seen a report of a noninvasive glucose monitor in the medical literature that includes all 7 of these metrics.

Prior Regulatory Clearance of Products with Poor Performance

When publicity gets ahead of data, there can be a lot of disappointment and anger from patients, healthcare professionals, and investors. Two examples of former companies that manufactured NIO-GMs, which received regulatory clearance without published data and whose performances were oversold to the public are Pendragon Medical (Zurich, Switzerland), and C8 MediSensors (San Jose, California).[16] Pendragon introduced the Pendra system in 2003. This product used impedance spectroscopy and had received a CE mark, but it was not accurate and the company went out of business the same year.[17] In 2012, C8 MediSensors received a CE mark for their Optical Glucose Monitor System based on Raman scattering spectroscopy.[18] Because of poor accuracy, their product never appeared on the market and the company went out of business soon thereafter. Furthermore, Cygnus (Redwood City, California) developed a NIFS-GM, the GlucoWatch G2 Biographer, that received FDA clearance in 2001.[19] The users of this NIFS-GM found that it lacked clinical accuracy and had significant interface problems. The product was taken off the market in 2007.[20] Neither Pendragon nor C8 MediSensors published accuracy data in the peer-review literature. Cygnus did publish their accuracy data and it was well below the performance level for all blood glucose monitors or continuous glucose monitors cleared by the FDA from 2008 onward.[21] It is noteworthy that Cygnus introduced the idea of using error grid performance as a basis for clearance. No company with a glucose monitor had previously disclosed publicly that they were using error grid metrics to support clearance of their product. Therefore, even when a company receives regulatory clearance, that is not automatically a reason to be confident in the accuracy of their device, be it based on optical or fluid sampling methods. Peerreviewed performance data enhances one's judgment of a product's potential clinical viability.

Technical Barriers

Development of an NIO-GM requires overcoming several major technical barriers. Primarily, success demands accurate glucose concentrations reported in a timely fashion under real-world conditions. Such accuracy will require measurements that are insensitive to interferences associated with both exogenous environmental conditions and endogenous substances as well as physiological states that impact the distribution of glucose throughout the body. From a practical standpoint, commercially and clinically successful devices must operate free of inconvenient power interruptions, have reasonable calibration requirements, and couple to the body with a stable, comfortable, and nonobtrusive interface. Most prototype NIO-GM devices are built to provide an intermittent or spot reading any time a person touches the device with a designated body part, such as a wrist, fingertip, or earlobe. An additional challenge for a manufacturer of an NIO-GM is to create a portable wearable sensor that is in constant contact with the body in order to provide a continuous noninvasive signal.

Research and development will be greatly facilitated by establishing methods to collect representative samples of interstitial fluid (ISF). Because most of the analytical information used for measuring by an NIO-GM originates from ISF located within the skin matrix, the ability to harvest high quality ISF samples is paramount to understand and improve clinical performance. Clinical chemists, endocrinologists, and regulatory experts all recognize that it is virtually impossible to harvest representative samples of ISF for reference testing.[22]

Strategies for Advancing Technology

It turns out to be surprisingly simple to measure a noninvasive optical signal that tracks blood glucose concentrations

in the body. Many peer-reviewed papers published in the early 1990s demonstrated strong correlations between blood glucose concentrations and the intensity of light reflected from skin during oral glucose tolerance tests (oGTT).[23] It was ultimately determined that these results derive from glucose-dependent changes in the refractive index of skin, thereby altering the intensity of light scattered off the skin surface.[24] Such simple measurements were ultimately deemed clinically useless because changes in the refractive index of skin depends on many parameters, and not exclusively on the concentration of glucose. In 1995, Kohl and co-workers used a tissue phantom to illustrate how the light scattering properties of skin are impacted by a range of factors, including the concentrations of glucose and other endogenous substances, such as albumin, organelles, osmotic pressure, and temperature.[25,26] Overall, correlations between reflected or scattered intensities of radiation and glucose concentrations observed over a short time period, such as during an oGTT experiment, are not constant over time periods relevant to practical clinical use and therefore are incapable of serving as a basis for accurate *in vivo* glucose measurements.

A principal lesson learned in the 1990s is that successful noninvasive optical measurements require specificity between glucose and the analytical signal.[27] This realization drives the use of near infrared and Raman spectroscopic methods that have glucose-specific features which are capable of unique optical signatures in comparison to other chemical components in the skin matrix.[28,29] Other approaches which are gaining in popularity today, such as radiofrequency, dielectric, and impedance spectroscopies, must also have a glucose-selective signature or these approaches will likely be found to lack sufficiently stable measurement correlations for practical clinical measurements.

Although demonstrating a correlation between a measured noninvasive signal and blood glucose concentrations for a single oGTT is a relevant first step, it must not be considered proof of clinical viability for an approach. The key is to demonstrate that a specific calibration function can predict glucose concentrations accurately in a prospective manner. A proposed calibration function must be applied to independent data, that is data collected at a different time and ideally under different conditions. The period of time and the types of conditions over which the function provides accurate glucose concentrations must be understood and reported. Peer-reviewed papers must include such prospective concentration measurements for early, preclinical testing for any putative NIO-GM approach.

Applications of Artificial Intelligence and Machine Learning

Artificial intelligence (AI) through machine learning or neural network methods represents an innovative approach to identify a selective signature for glucose within noninvasive optical data.[30-32] Machine learning methods are capable of identifying analytical correlations embedded within complex datasets, thereby potentially improving clinical performance and measurement accuracy. These methods demand a large number of observations. Of course accurate reference blood glucose measurements are required for each of these many observations. As a guide, it is preferred to develop AI models from optical datasets known to possess a glucose specific signature, even if this signature is embedded within confounding variations created by the complexities of living tissue. Too strong of a reliance on AI approaches can lead to setbacks, however, particularly in situations where AI-identified calibration functions are based on spurious correlations associated within a particular dataset and are ultimately found to be not representative of a broader general population of users. This problem is known as overfitting and must be considered a principal concern for any machine learning method.[33,34]

Another approach is to couple machine learning methods with hybrid techniques, whereby noninvasive signals are obtained from two or more analytical methods. One example is the Glutrac device under development by Shutang Information Technologies (Shenzhen, China) that reports the uses of 4 different optical signals: (1) absorption spectroscopy, (2) electrocardiography, (3) photoplethysmography, and (4) dynamic metabolic heat.[35] Similarly, the combination of ultrasonic, electromagnetic, and thermal parameters is used by the GlucoTrack device by Integrity Applications for measurements in earlobe tissue.[36] Ideally, such hybrid methods should combine noninvasive information that provides unique glucose-dependent signals derived from different mechanisms. Individually, each method might be insufficient for reliable clinical sensing but together, and with the aid of machine learning, a clinically viable device might be possible.

Technological advances demand an understanding of glucose specificity coupled with sound experimental protocols. The method must demonstrate accurate glucose concentration measurements hours, days, weeks, and months following an established calibration procedure.

Conclusion

The need for NIO-GMs is well established for people both with type 1 and type 2 diabetes. More broadly, smart watch technology continues to become more sophisticated, particularly in terms of measurements related to patient-generated health data for people with diabetes and even for people without diabetes, such as athletes and members of the quantified-self movement. The wellness market for various physiologic monitors, including glucose, is a potentially huge revenue source for manufacturers of NIO-GMs. Certainly, the promise to determine the concentration of glucose in one's body without collecting a blood sample or without placing a needle under your skin is attractive for many types of people. This potentially large market for diabetes, wellness, and sports, is

fueling interest and investments in new startups as well as established companies that are developing NIO-GMs.

As outlined here, the challenges are substantial to produce a device that provides clinically relevant results. Knowledge of the basis of measurement sensitivity and selective are paramount, as is the establishment of effective calibration protocols. An over-reliance on machine learning algorithms must be avoided. Candidate technologies must be tested over an array of environmental and physiological conditions, including over a range of glycemic concentrations during periods of stable glycemia and rapidly fluctuating glycemia in diverse populations of users.

The most efficient path for the successful development of clinically viable NIO-GMs is to disseminate hypotheses, protocols, and data within the medical, scientific, engineering, regulatory, and business communities. Products with secret, unpublished data will ultimately not be embraced by the diabetes community. The publication of results can stimulate new ideas and approaches with the potential to overcome barriers that currently limit technological progress. The publication of data also has the potential to establish benchmarks that can be used to judge progress in the field and to develop established protocols that can be followed by all research teams, thereby permitting meaningful comparisons of findings between different research groups.

An iconic line from the movie Jerry Maguire was "Show me the money!" Our approach to noninvasive glucose monitoring, where we read every few weeks about a new breakthrough technology, is "Show me the data!"

Acknowledgement

We thank Annamarie Sucher-Jones for her expert editorial assistance.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: DCK is a consultant for EoFlow, Fractyl, Integrity Applications, Lifecare, Novo, Roche Diagnostics, and Thirdwayv. KTN and NYX have nothing relevant to disclose. MAA is a consultant for LifePlus, Inc. and Foundation for Innovative New Diagnostics.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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