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An Analysis of the SEVEN® System: Have We Reached the Summit of Needle-Type Sensor Accuracy?

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Abstract

In this issue of *Journal of Diabetes Science and Technology*, Zisser and colleagues show improved sensor accuracy with the newest generation of needle-type sensors as compared to first generation sensors. Can we expect further improvement? It is unknown what the future holds, but there certainly seems much to be gained from improved calibration procedures. In addition, sensor operating times are increasing and it is hoped that this will translate into improved sensor use and thereby into improved glycemic control.

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Introduction

In ancient times, the Chinese determined glycemic status by counting the number of ants attracted by patients' urine.[1] Since then, the technology of glucose monitoring has made huge leaps forward via urine sticks and blood glucose meters to the introduction of continuous glucose monitors some 10 years ago. The results published by Zisser and colleagues[2] revealing ongoing improvement, departing from the early continuous glucose monitoring (CGM) technology to current state of the art, are very promising. Have we reached the summit of needle-type sensor accuracy? Also, more importantly, does current technology really contribute to significant clinical benefits for patients with diabetes?

Accuracy

Taking together the median and mean absolute relative differences (ARD) compared to reference values for all currently available CGMs, they seem to stagnate with ARD varying from 12 to 17%.[2] Until now, no ARD below 10% have been reported for any prospectively calibrated system. Zisser and associates[2] revealed significantly better accuracy for the newer version of the DexCom sensor compared to the previous version, with improvement of the overall median ARD from 23 to 13.2%. They attributed the improved accuracy to the modified algorithm. Improvement of CGM technology is indeed continuously ongoing, but can accuracy get even better in the future? Increased competition is likely to promote this, but there may be limits to needle-type sensors.

Brauker and colleagues[3] explained sensor inaccuracy as partly due to time lag error and sensor noise error. They divided the latter into elevating noise, e.g., a higher nonglucose signal in the first few hours after sensor implantation as a consequence of the wound-healing

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Abbreviations: (ARD) absolute relative differences, (CGM) continuous glucose monitoring, (HbA1c) hemoglobin A1c, (SMBG) self-measured blood glucose, (YSI) Yellow Springs Instrument

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process, and suppressing noise, e.g., current leakage and biological responses to the subcutaneous sensor. However, up to 50% of sensor inaccuracy was suggested to be caused by the calibration procedure.[3] This is supported by a recent study comparing the accuracy of CGM readings calibrated against self-measured blood glucose measurements (SMBG) by the patients themselves, to CGM readings calibrated retrospectively against glucose values obtained with the Yellow Springs Instrument (YSI) at a hospital, and to CGM readings calibrated against SMBG obtained under clinical supervision.[4] Results showed median ARD compared with YSI of 13.5% for CGM readings calibrated against SMBG by patients themselves, whereas median ARD were 5.0 and 6.8%, respectively, for CGM readings calibrated against YSI values and SMBG under supervision. With a more than 50% improvement of ARD when changing the calibration procedure, Garg and Jovanovic attributed half of the sensor inaccuracy to the calibration procedure and emphasized the importance of a good calibration teaching program for patients and clinicians.[4]

The accuracy of the CGM itself is still in need of further improvement, especially in the hypoglycemic area, not only to improve reliability and confidence among patients, but also to enable realization of a closed loop in the future.[3] Although Zisser and colleagues[2] reveal stable and even improved accuracy over a 7-day period for the DexCom SEVEN system, 25% of the sensor readings in the hypoglycemic range still end up being erroneous, according to continuous glucose error grid analysis, whereas this accuracy assessment method can be characterized as relatively forgiving.[5]

Operating Period

Remarkably, as reported by Zisser and associates,[2] the sensor readings on day 7 were more reliable than those on day 1 after insertion. An explanation for this finding may be extinction of the subcutaneous inflammatory reaction over time. Although histological investigations on this subject are lacking, the historical fear of inflammation prohibiting glucose sensor wear longer than 2 or 3 days seems obsolete.

However, there may be more factors in determining the operation period of the sensor. The introduction of more biocompatible sensor material may play a role in the extended sensor wearing time. The more biocompatible the material, the less chance of a foreign body response and the resulting biofouling phenomenon.[6] McGarraugh[6] elegantly clarified several chemical aspects of the reduction–oxidation reaction that takes place subcutaneously on the sensor needle. Understanding this process brings up two more factors that may influence the needle-type sensor performance and operation period.[6] The first is the mediator chosen by the manufacturer. This electron bridge between oxidized glucose and the working electrode is eventually oxidized on the working electrode with the resulting current being converted into a glucose concentration through calibration. The magnitude of the current depends on the chemical properties of the mediator and the enzyme. Some manufacturers use oxygen/hydrogen peroxide as a mediator, whereas others use an alternative mediator substituting for oxygen to avoid the risk of glucose concentrations exceeding those of oxygen, which disturbs the linearity of the reduction–oxidation reaction. Another factor that influences the operation period more predominantly is the applied method used to immobilize the mediator and the enzyme, i.e., glucose oxidase, on the sensor electrode. Every immobilization technique is accompanied by a certain risk of denaturing of the enzyme, which has an impact on the duration of the reduction–oxidation reaction and thus on the operation period. Several techniques have been mentioned, although most manufacturers keep their technique undisclosed.[6]

Clinical Consequences

As we all know, an important advantage over single-point monitoring is that CGM enables the use of derivative information to predict glucose excursions in the near future, enabling early intervention.[3] What about the clinical benefits of extending the sensor wearing period?

First of all, one might expect the patient's compliance with respect to sensor use to become better, as patients do not have to change the sensor needle as often as every 3 to 5 days. Another benefit of extending the sensor wearing period is a reduction in health care costs.

Many patients use their sensors as long as possible. One of our patients at the outpatient clinic wore the sensor for a period up to 1 month, with acceptable accuracy. The willingness to wear a sensor uninterruptedly is promoted by the user-friendliness of the device. Results of a Juvenile Diabetes Research Foundation study demonstrated that sensor use correlated with glycemic control at the end of the study. The adults—who wore the sensor 6 days per week on general—had lower hemoglobin A1c (HbA1c) values compared to the control group, but not so for the two younger groups who wore the sensor substantially less frequently.[7] These results not only suggest that there is still a lot to win in the field

of user-friendliness, but also that extending the wearing period might contribute to a better HbA1c.

Until now, no data on patient preference regarding sensor use have been published. The issue of negligence regarding alarms should be addressed as well. Daily practice shows experienced patients adjusting the alarm settings to prevent bothersome false alarms, which will be at the cost of decreased sensitivity for hypo- or hyperglycemia. The impact of continuous exposure of glucose data on patient quality of life has not been investigated thoroughly enough and should be embedded in future clinical studies.

As mentioned previously, many patients tend to wear the sensor longer than the approved period. However, this practice is prohibited by manufacturers because sensor performance in this overtime period cannot be guaranteed. For example, a software adjustment was made in one of the sensors for an automatic stop of continuous glucose monitoring after 5 days. Because of this adjustment, there is no option to wear the sensor for more than 5 days. This seemingly protective adjustment might be tempting but also carries a risk for the manufacturer. For economic reasons, patients may either switch to another company that does enable more prolonged use of a sensor or even try to hack the software to undo this restriction.

In conclusion, the extended use of disposable sensor needles is a positive development. It may lead to reduced health care costs, better compliance, and, in the end, better glycemic control. Although sensor accuracy has improved over the years, according to the results by Zisser and colleagues,[2] it still needs further improvement. Optimizing the calibration procedure and teaching both patient and clinician how to do so may contribute considerably to better accuracy. More insight into the biochemical processes at the needle site, such as the immobilization technique and the mediator chosen, may help us to prolong sensor use even further, but these data will likely stay within companies. The endurance of patients, clinicians, and scientists, in combination with a healthy competition between companies, will allow us to reach even further in the field of CGM.

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