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Research Article

Calibration of a Non-Invasive Glucose Monitoring Device Measuring at the Earlobe can be Performed using Different Invasive Glucose Monitoring Methods without Loss or Device Performance

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Abstract

GlucoTrack (GT) is a CE-approved non-invasive glucose monitoring device measuring at the earlobe for use at home or in in-door environment. A single calibration procedure is required before use for six months to minimize the effects of individual factors introduced by the user. We performed simulations on data previously obtained during a standardized meal test to evaluate potential differences in results when calibration is performed with different invasive glucose monitoring methods.

In the standardized meal test, 27 participants were enrolled (20 type 2 patients, 4 female, 68 ± 8 yrs (HbA1c: 7.2 ± 1.0%, BMI: 32.1 ± 4.7 kg/m^2), 7 prediabetic subjects, 2 women, (HbA1c: 5.8 ± 0.3%, BMI: 30.4 ± 5.9 kg/m^2)). Calibration was performed with HemoCue. YSI 2300 STAT+ (YSI) and AccuChek Performa (AP) results were obtained in parallel. The patients ingested a standardized breakfast with glucose measurements every 30 min over 180 min. We simulated calibrations with the three different invasive devices and retrospectively calculated the meal experiment results by employing a designated MATLAB code.

Simulated results of a calibration based on data obtained by the AP or YSI were comparable to the HemoCue-calibrated results. Specifically,100% of the data points were in zones A and B of the consensus error grid with all three calibrations. Median absolute relative deviation (vs. YSI) was 15.9% with YSI-calibration, 14.7% with HemoCue-calibration and 15.0% with AP calibration).

In conclusion, GT may be calibrated with accurate point-of-care devices for patient self-testing without loss of accuracy in comparison to calibration using accepted gold standard reference methods.

Keywords: *Calibration; Non-Invasive Glucose; Earlobe*

Introduction

Regular glucose monitoring is essential for effective diabetes management. Therefore, numerous devices have been developed in order to ensure accurate measurements of blood glucose (BG) levels to reduce the risk for long term diabetes complications [1,2], to alert patients of impending glycemic excursions [3] and to support patients in daily decision making related to food intake, insulin dosage or

physical exercise [4]. The different methods of glucose monitoring include invasive, minimally invasive and non-invasive (NI) technologies. Most commercially available devices make use of invasive principles of operation with capillary blood samples obtained by a finger prick method for glucose analysis. These BG meters yield measurements of capillary glucose via colorimetry, photometry or electrochemistry after applying a small drop of blood (< 1µl) on a customized test strip [5]. Advantages are high accuracy, low patient training requirements, the small amount of blood needed for analysis and optionally available device features like memory functions or software downloads [6,7]. However, test accuracy can be influenced by user errors [7] and the demanding requirement of several measurements each day cause pain and discomfort, consequently leading to poor patient compliance and impairing the associated cost effectiveness. Furthermore, only limited data is available as no BG trends can be displayed due to unique excerpts of the metabolic situation by each measurement.

Minimally invasive devices are aimed to replace current invasive portable meters to overcome these barriers. These devices measure trends of glucose fluctuation regularly during the day and hence are predestined for the detection and prevention of glycemic excursions. This technology is based on tiny needle sensors commonly placed in the subcutaneous tissue [8]. Limitations include high costs and limited life span due to biofouling, fibrous encapsulation of the implanted sensors and inflammation affecting the accuracy of the glucose results [9].

Non-invasive devices for glucose monitoring are expected to improve patient compliance [10], by using different technologies like iontophoretic extraction of glucose through the skin, plasmon resonance, Raman spectroscopy, near-infrared spectroscopy, polarimetry, photo-acoustic probes and fluorescence methods [8]. Still, non-invasive devices need a periodically invasive calibration and similar to the minimally invasive needle sensors, the information yielded by the applied sensors can be delayed (15 - 20 minutes) as blood glucose needs to be shifted to the interstitial tissue first, which limits the accuracy of devices in emergency situations [8]. NI devices also suffer from additional sources of interferences, including differences in skin properties, alterations in microcirculation and individual blood supply, current medication and comorbidities [11]. For these and other reasons most of non-invasive technologies did not meet the required standard of accuracy and failed to run for a durable period of time [12].

The indirect nature of non-invasive technologies requires from these devices to be calibrated against concurrent blood glucose values that provide an estimation of glucose concentrations. The calibration process is conducted prior to device use, in order to minimize the impact of individual factors introduced by the user. Since calibration is considered a reason for discomfort [13], utilizing a simple calibration procedure with a familiar and suitable invasive device is expected to increase device usability and user satisfaction.

A CE-approved commercially available non-invasive glucose monitoring device is GlucoTrack (Integrity Applications, Ashdod, Israel) [14]. Three different indirect technologies for tissue glucose assessment (ultrasound, electromagnetic changes and thermal modulations) are combined by this device to determine the glucose information by sensing elements built into an ear clip, which is placed at the ear lobe. The measurements are conducted without a need for drawing blood or extracting any other body fluid. Device performance has been demonstrated in laboratory and clinical studies to be acceptable for frequent pain-free glucose measurement by patients with early to moderate stage of type 2 diabetes or in subjects with prediabetes [11,14-16]. In a previously performed standardized meal test, 100% of 235 data points collected from a meal test were in the clinically accepted zones of the Consensus Error Grid (A and B) when compared to YSI 2300 STAT Plus™ (YSI) as reference method [16]. In this trial, the required calibration procedure was performed a day before the meal experiment using the HemoCue device as reference method. Additional measurements were performed at the same time points with YSI STAT 2300 plus and AccuChek Performa.

In this manuscript, we used these alternative readings to simulate the study outcome when the calibrations would have been performed by any of the other two devices instead of HemoCue. Our goal was to demonstrate that the accuracy of the non-invasive device does not depend on the device used for calibration, which may have an important impact on device acceptance and applicability for home-use.

Materials and Methods

The new non-invasive device is intended for use by patients with type 2 diabetes and prediabetic subjects at home or in an in-door environment (See figure 1). This device measures blood glucose in the range of 70 - 500 mg/dl (3.9 - 27.8 mmol/L) non-invasively by means of a Personal Ear Clip (PEC) containing the sensors and calibration electronics. The PEC is externally clipped to the earlobe for about a minute to obtain real-time tissue glucose data. The device employs three different technologies (ultrasound, electromagnetic and thermal). Each technology measures different tissue parameters affected by the same change in glucose concentration. The three independent readings are performed sequentially to prevent potential interferences and are combined afterwards by a proprietary algorithm, which calculates a weighted average to increase the validity of the result. Measured signals are then translated into glucose values by individual invasive calibration, which also reduces the impact of practically stable conditions of the earlobe tissue, such as thickness and tissue structure. The result is displayed on a touch screen integrated in the Main Unit. In case of extreme values, the device additionally evokes visual and audible alerts. The device does not require sterilization while in use.

Figure 1: *Picture of the GlucoTrack device.*

An individual calibration is required prior to glucose measurements to assess individual glucose patterns and to reduce interference of personal factors of each user. In the course of the calibration, three invasive glucose readings are correlated to non-invasively measured tissue parameters. This individual calibration process is needed prior to every use of a new PEC, which has a lifespan of 6 months. During this usage time, a virtually unlimited number of glucose measurements may be performed. Reliable results are dependent on proper performance of the calibration.

The original study (registration number: DE/CA99/00010432) was performed as described recently (16). Briefly, 27 participants with diabetes or prediabetes were ingesting a standardized meal one day after device calibration with HemoCue® Glucose 201 RT system (Ängleholm, Sweden) as reference method. Glucose information was obtained in 30 min intervals at time-points -30 min to 180 min in the context of this meal experiment using four different methods 1. YSI STAT2300 Plus (YSI Inc., Yellow Springs, OH), 2. HemoCue Glucose 201 RT system, 3. AccuChek Performa (Roche Diagnostics, Mannheim, Germany) and 4. GlucoTrack. Performance of the non-invasive method in comparison to YSI and the other two methods was analyzed with appropriate statistical methods (consensus error grid, mean absolute relative difference [MARD] etc.).

For this calibration method analysis, the original physical signals derived from the meal experiment were integrated with a designated MATLAB code and the calculated glucose results were compared with the readings from the YSI 2300 STAT Plus™ glucose analyzer, which served as the standard reference instrument. While the original study analysis was based on the data derived from a HemoCue-based

calibration, we simulated two other calibrations, which were based on the YSI results and AccuChek Performa results also collected during the original calibration procedure.

Benchmark metrix parameters were calculated for each of the calibration methods in comparison to the meal study results with the respective device, i.e. HemoCue-calibrated non-invasive results were compared with the HemoCue results, YSI-calibrated non-invasive results were compared with the YSI results and AccuChek-calibrated non-invasive results were compared with the AccuChek results. Benchmark parameters were mean/median absolute relative difference and a consensus error grid analysis [17].

Results

In total, 189 paired data sets were obtained from 27 participants in this device evaluation study (20 type 2 diabetes patients, 4 women, 16 men, age: 68 ± 8 yrs., HbA1c: 7.2 ± 1.0%, BMI: 32.1 ± 4.7 kg/m^2 and 7 prediabetic subjects, 2 women, 5 men, HbA1c: 5.8 ± 0.3%, BMI: 30.4 ± 5.9 kg/m^2). All analyzed patients underwent the study protocol and completed the standardized meal experiment with all planned measurements. There were no device-related adverse events reported during this study [16].

The analysis of the different calibration simulations revealed comparable results. The calculation of mean and median ARD values is provided in table 1. There was no difference between the different analyses with results ranging from 17.5% to 18.6% for mean ARD and from 14.7% to 15.9% for median ARD.

Reference Method	Mean ARD [%]	Median ARD [%]
YSI 2300 STAT Plus™	18.6	15.9
HemoCue®	17.5	14.7
AccuChek® Performa	18.4	15.0

Table 1: *Mean and Median absolute relative deviations for all subject glucose readings with the non-invasive results derived from the online or simulated calibration in comparison to the results collected with the respective reference device during the meal experiment.*

The consensus error grid analyses after employing each calibration procedure are provided in table 2 and figure 2-4. All paired data sets were in the clinically acceptable zones A and B, irrespective of the calibration device used. According to the consensus error grid definition, these results would therefore not lead to wrong interventions in case of clinical decisions [17]. The data set obtained with AccuChek Performa appears to be more heterogeneous, which is confirmed by a coefficient of variation for the mean ARD of 92%, which is higher than the coefficients of variation observed with HemoCue (76%) and YSI (74%). However, all results were within the consensus error grid acceptance criteria.

Reference Method	YSI 2300 STAT Plus™		HemoCue®		AccuChek® Performa	
Consensus EG Zone	Number of Points	%	Number of Points	%	Number of Points	%
A+B	189	100.0	189	100.0	189	100.0
A	122	64.6	130	68.8	123	65.1
B	67	35.4	61	31.2	66	34.9
C	0	0.0	0	0.0	0	0.0
D	0	0.0	0	0.0	0	0.0
E	0	0.0	0	0.0	0	0.0
Total	189	100.0	189	100.0	189	100.0

Table 2*: Consensus Error Grid analyses of all subjects with the non-invasive results derived from the online or simulated calibration with the respective reference device.*

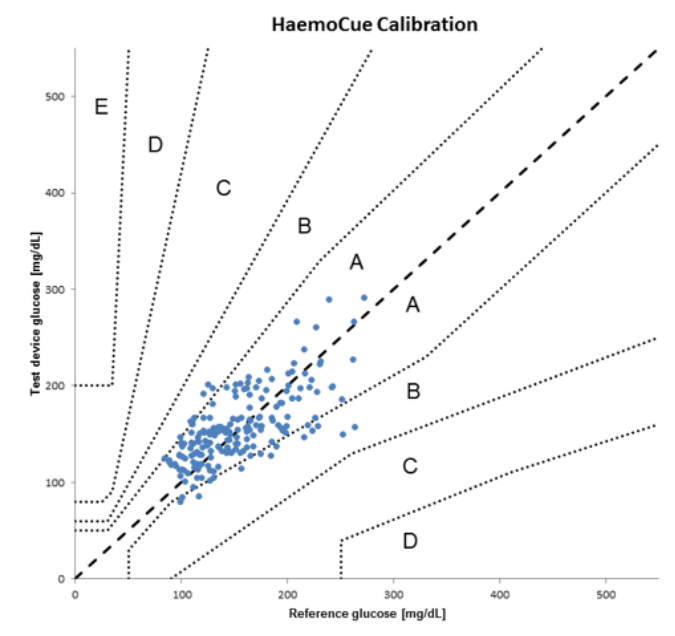

Figure 2: *Consensus Error Grid analyses for all subject readings using the non-invasive results derived from the online HemoCue-based calibration in comparison to the HemoCue results from the meal experiments.*

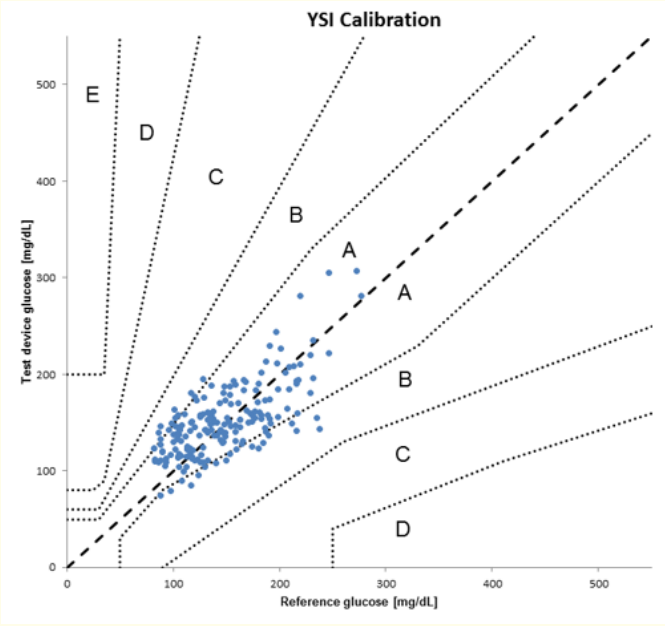

Figure 3: *Consensus Error Grid analyses for all subject readings using the non-invasive results derived from the simulated YSI-based calibration in comparison to the YSI results from the meal experiments.*

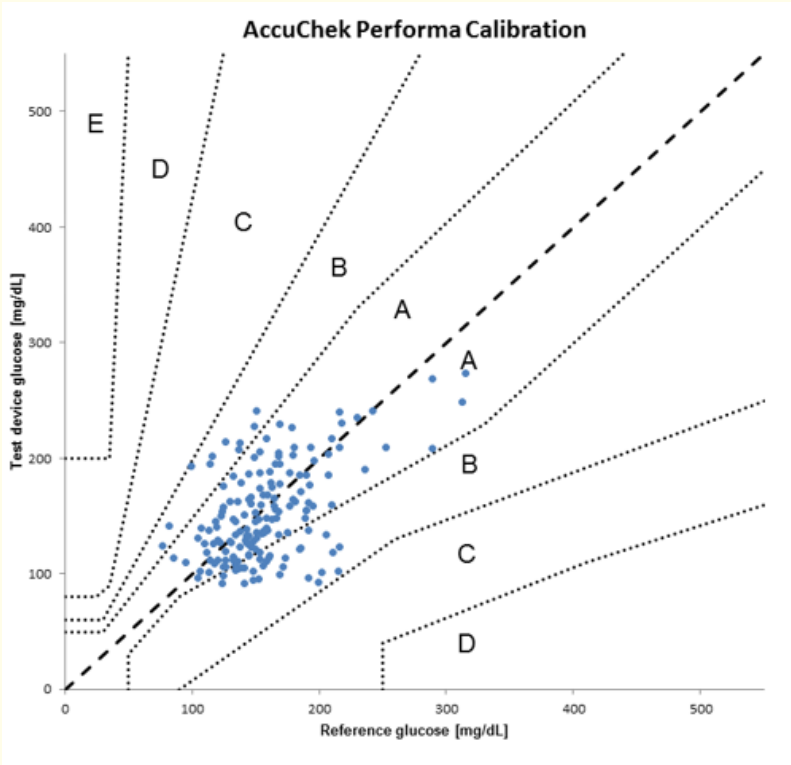

Figure 4: *Consensus Error Grid analyses for all subject readings using the non-invasive results derived from the simulated AccuChek Performa-based calibration in comparison to the AccuChek Performa results from the meal experiments.*

Discussion

The development of non-invasive methods for determination of blood or tissue glucose has become a major goal in diabetes technology during the last decades. The physical methods used to assess specific glucose signals in blood, tissue, saliva, retinal fluid and other organs include, but are not limited to (near/mid) infrared spectroscopy, photoacoustic spectroscopy, terahertz spectroscopy, Raman spectroscopy, radio impedance spectroscopy and optical rotation [18]. To note, devices typically utilize one of the aforementioned technologies and only very few devices with acceptable clinical accuracy have reached the market and have become a commercial success [19-22].

An attempt to obtain a valid glucose signal by combining several assessment methods has become reality with the new non-invasive device, which employs three different technologies to measure tissue glucose with a clip at the earlobe. The clinical performance was appropriate with mean absolute relative difference of around 18% to 23% in several clinical and laboratory investigations [11,14,15]. The results from our recent standardized meal experiment with the non-invasive device showed similar results when employing a HemoCue calibration and comparing to the YSI reference method (mean ARD: 19.7% [16]).

The simulation of using different reference devices for calibration reported here resulted in more or less similar results in the performance analysis of the non-invasive device, irrespective of the glucose source used for the calibration. When the non-invasive device was calibrated with YSI, the mean ARD calculated for the meal experiment was 18.6%, while it was 18.4% when using the AccuChek

Performa results for the calibration. Hence, there was no performance difference despite the well-established accuracy differences between both devices (mean ARD of AccuChek vs. YSI was 4.2% to 5.9% in a recent study [23]). How can such a finding be explained? When interpreting the performance of a non-invasive device, it should be considered that the device does not measure blood glucose but local tissue glucose concentrations, which represent a mixture of glucose information from at least three different compartments (interstitial fluid, arterial blood, venous blood). Based on the observed lag times between blood glucose readings and the non-invasive ear lobe readings [16], it can be concluded that the major component contributing to the non-invasive results is the interstitial glucose concentration and not capillary or venous blood glucose levels. Therefore, the errors associated with the use of different devices using capillary blood from the fingertip may have a very limited impact on the overall non-invasive device performance, as the error affects only a minor part of each of the entire measurement signal that is included from each of the three employed technologies into the device algorithm and that is used to calculate the tissue glucose result.

This consideration and our findings imply that the calibration of the non-invasive ear lobe device may be performed with an accurate point-of-care device for patient self-testing without losing major performance quality compared to calibration with accepted gold standard reference methods. In clinical routine, it is not decisive, which invasive device should be used for calibration of a non-invasive glucose monitoring device. Our results support the notion that any invasive device can be used for calibration. Furthermore, it is not essential for the calibration to be performed with a highly accurate laboratory reference method, like the YSI 2300 STAT Plus. This may result in greater flexibility and autonomy for the patient as he/she can decide which calibration option is the most suitable for him/her. This might also indicate that in the future the calibration process may be performed at home using a self-monitoring blood glucose device.

Conclusion

Non-invasive results, which were calculated based on different calibration simulations were comparable across the invasive devices used for calibration. This finding has the practical implication that calibration of the non-invasive ear lobe device may be performed with sufficiently accurate point-of-care devices for patient self-testing without reducing device performance in comparison to calibrating with a laboratory reference method.

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