



Evaluation of the Non-Invasive Glucose Monitoring Device GlucoTrack® in Patients with Type 2 Diabetes and Subjects with Prediabetes

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Abstract

Background: GlucoTrack is an approved (CE-mark) non-invasive glucose monitoring device for home use. The device measures three physiological conditions at the earlobe known to be indirectly correlated with tissue glucose concentrations. It employs ultrasound, electromagnetic and thermal measurement technologies and is intended for use in adult type 2 diabetic patients and pre-diabetic patients. We evaluated the performance of the device during a standardized meal test.

Methods: A total of 27 participants was enrolled into this prospective, open-label trial (20 type 2 patients, 4 women, age: 68±8 yrs; HbA1c: 7.2±1.0%, BMI: 32.1±4.7 kg/m²), 7 pre-diabetic subjects, 2 women, age: 64±9 yrs; HbA1c: 5.8±0.3%, BMI: 30.4±5.9 kg/m²). After calibration of the device during the day before using a HemoCue blood glucose meter, the patients ingested a standardized breakfast at the site during the next visit. Blood glucose was measured every 30 min over 180 min with HemoCue, AccuChek Performa and YSI Stat2300plus. Mean Absolute Relative Difference (MARD) was calculated and a Consensus Error Grid Analysis was performed (vs. YSI). Precision was determined with 5 patients using two devices in parallel.

Results: In the Consensus Error Grid, 100 % of the non-invasive results were within the clinically accepted zones A and B (62.4 % and 37.6 %). MARD was found to be 19.7 % vs. YSI (17.5 % vs. HemoCue®). Precision was determined with 9.5±5.5 %. There was no difference between type 2 diabetes patients and prediabetic subjects.

Conclusions: The results confirm a stable GlucoTrack device performance among its intended users, including prediabetic patients, for frequent pain-free non-invasive monitoring of glucose levels.

Introduction

Diabetes mellitus is an epidemic disease affecting more than 422 million people around the world. In case current morbidity trends continue, it will be the seventh leading cause of death worldwide in the next ten years [1]. Glucose monitoring is an essential part of diabetes management. Maintaining Blood Glucose (BG) levels within the physiological range is crucial to reduce the long term complications of the disease [2,3], including kidney failure, stroke, heart attack, high blood pressure, blindness and coma [4,5]. For most people with type 1 diabetes or insulin-treated type 2 diabetes, Self-Monitoring of Blood Glucose (SMBG) is recommended three or more times daily [6-8] and even 6-10 times daily in the course of an intensive insulin regime [8]. The benefits of more frequent SMBG have also been demonstrated in subjects

with prediabetes deteriorating to type 2 diabetes [9]. Moreover, even if glucose levels are stable, SMBG is a useful surveillance tool if patients are undergoing adjustments in medication, nutrition, physical activities or entering a new life experience. In summary, frequent BG measurements may improve glycemic control and may lower overall costs of diabetes management, if the incidence and progression of diabetes complications can be prevented [10]. Furthermore, glucose monitoring can alert patients of impending glycemic excursions, thus helping to avoid the occurrence of hypoglycemia along with its associated complications [11]. However, self-monitoring of glucose is often under-utilized [2,3,9, 12-19] due to the pain, expenses and inconvenience of current invasive self-monitoring systems [20,21]. Minimally invasive devices for Continuous Glucose Monitoring (CGM) have only a

limited time span and stability [22], and they are more expensive than portable glucose meters and strips [23].

Consequently, new solutions for glucose monitoring are substantially needed. Ideally, alternative technologies should be painless and easy to operate, while at the same time provide reasonably accurate estimations of glucose concentration. If possible they should be sufficiently accurate for clinical decision making. Non-invasive glucose monitors for home use are aimed to overcome the barriers of current glucose monitoring methods by offering a simple, painless and cost-effective way to measure glucose. Their increasing use in routine care is also based on improvements in sensitivity and better patient compliance contrary to invasive methods [24].

A device largely meeting these needs is the non-invasive GlucoTrack® device (Integrity Applications, Ashdod, Israel), which measures three different glucose-related physical conditions at the ear-lobe and has been shown to work with stable accuracy over a period of 6 months after one calibration procedure [25-27].

The translation of the measured signals into glucose readings is done by individual calibration, which also reduces the impact of quasi-stable components in the earlobe tissue. The measurement is conducted by three independent technologies, which act sequentially to avoid interfering with each other: ultrasound (phase shift as a function of speed of sound change within the tissue), electromagnetic properties (conductivity of the tissue), and thermal changes (heat capacity of the tissue). The three independent readings are combined by a proprietary algorithm, which calculates their weighted average and provides the related tissue glucose value [25, 26].

The purpose of this study was to evaluate the performance of this device with respect to accuracy and precision in comparison to a standard point-of-care reference method for assessment of capillary blood glucose concentrations (YSI Stat 2300 plus) when tested during a standardized meal experiment in patients with type 2 diabetes and in subjects with prediabetes (impaired fasting glucose or impaired glucose tolerance).

Material and Methods

Study Device

GlucoTrack Model DF-F (see Figure 1) is a CE-mark approved non-invasive glucose monitoring device for people with type 2 diabetes or prediabetes, to be used at home and in an in-door environment. This device measures tissue glucose in the range of 70-500 mg/dl (3.9-27.8 mmol/L) in a discrete (spot) manner without drawing blood or extracting any other body fluid. The device is composed of two units: the main unit, containing a color touch screen display and control, transmitter, receiver and processor, and a Personal Ear Clip (PEC), containing sensors and

calibration electronics, which is attached (externally clipped) to the earlobe to perform non-invasive monitoring. The main unit displays the reading results, provides high and low alerts (set at individual thresholds), history data, configuration, and personalization options. To perform a real-time spot measurement, the PEC is clipped externally to the user's earlobe for the duration of the measurement (~60 sec.). Glucose readings are displayed and may also be verbally announced by an integrated speaker. The device does not require sterilization. The Ear Clip life span is 6 months from first use, after which it must be replaced. As a monitoring device, it is neither meant for diagnosis, nor for providing the information as the basis for medication intake. Treatment decisions cannot be taken based on a single non-invasive result.

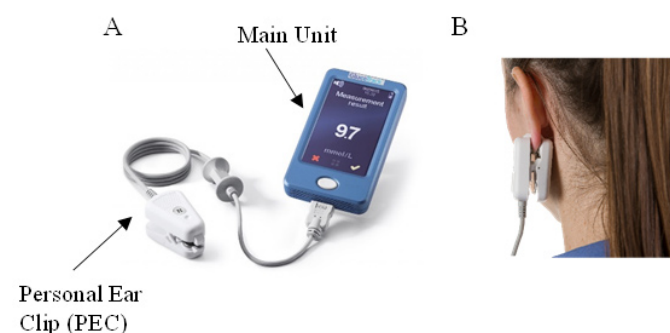


Figure 1: The GlucoTrack device consists of two sub-units (A), the ear clip which contains the sensing elements and the main control unit which is used to control device operations and to display the result on a colored touch-screen. For the measurement with the device, the ear clip is conveniently attached to the ear lobe (B).

Study Conduct and Objectives

This study was conducted as an open label, prospective, comparative, single-center trial. It was performed in accordance with the ICH-GCP guidelines, the German Medical Device Act (Medizinproduktegesetz, MPG), and local ethical regulations. The responsible Ethical Review Committee of the State of Rheinland-Pfalz approved the study conduct. Participants were recruited and enrolled by the study site and signed informed consent prior to any study procedure.

All participants were men and women who were older than 18 years, and who were known to suffer from type 2 diabetes or prediabetes (impaired fasting glucose >110 mg/dL or impaired glucose tolerance 2 hours postprandial >140-200 mg/dL). Patients were excluded if they were on intensive insulin treatment or pre-mix insulin treatment, or any other treatment involving regular human insulin or a short-acting insulin analog. Patients were also excluded, if they had any anatomical abnormality at the earlobe or carried major metal items in the earlobe, as determined by the investigator.

During the first visit, a calibration procedure was performed by the investigators. For calibration, the patients were measured with the study device and the Hemocue device three times with 10 min intervals between each assessment. At each time-point, the Hemocue reading was entered into the GlucoTrack device.

For the meal test, the patients came to the study site after an overnight fast for at least 8 h. After an initial capillary blood sampling and glucose measurement with YSI, Hemocue, and AccuChek Performa, and an additional glucose measurement with the study device, they ingested a standardized breakfast, which was composed of two pieces of rye bread roll with cream cheese and water (water ad libitum, total carbohydrate uptake: 24 g). Further blood glucose assessments with all four methods were performed at postprandial time-points 30 min, 60 min, 90 min, 120 min, 150 min, and 180 min. Thereafter, patients were allowed to leave the site, if their blood glucose levels were below 180 mg/dL.

Precision was assessed on 5 subjects. At visit 1, each subject simultaneously calibrated two non-invasive devices with the respective ear clip to be placed at each ear lobe in parallel. A device was applied to each earlobe and calibrated by using the same invasive reference glucose values obtained from the HemoCue meter. At visit 2, the investigators conducted all 7 measurements with 30 minutes' intervals with both non-invasive devices, which were again applied in parallel.

The primary endpoint of this study was the evaluation of the performance and accuracy of GlucoTrack Model DF-F in monitoring glucose levels by the consensus error grid analysis and by using the proportion of non-invasive measurements falling within ± 15 mg/dL of the measured values of the YSI device (YSI 2300 STAT Plus™) at glucose concentrations < 100 mg/dL and within $\pm 15\%$ of the YSI measurements at glucose concentrations ≥ 100 mg/dL.

Secondary Endpoints of this study included the evaluation of the non-invasive device performance in comparison to the HemoCue Glucose 201 RT system (Radiometer, Willich, Germany) and of the Accu Chek Performa device (Roche Diagnostics, Mannheim, Germany). Another secondary endpoint was the device precision,

assessed by computing the mean Precision Absolute Relative Differences (PARD) between the readings two simultaneously applied non-invasive devices in a subgroup of five patients.

Statistical Methods

The data from all patient was used for the accuracy analysis, while a subgroup of five patients was used for the precision analysis. Clinical accuracy was determined using the Type 2 Consensus Error Grid Analysis [27, 28]. Statistical accuracy was demonstrated by the mean and median Absolute Relative Differences (ARD) values. Precision was demonstrated by using the Precision Absolute Relative Difference (PARD).

Results

Twentyseven participants were included in this device evaluation (20 type 2 diabetes patients, 4 women, 16 men, age: 68 ± 8 yrs., HbA1c: $7.2 \pm 1.0\%$, BMI: 32.1 ± 4.7 kg/m², and 7 prediabetic subjects, 2 women, 5 men, HbA1c: $5.8 \pm 0.3\%$, BMI: 30.4 ± 5.9 kg/m²). One subject did not complete the trial, because the anatomical situation and thickness of both earlobes did not allow proper placement and replacement of the ear clip. This condition was detected after he had signed informed consent. The patient was considered a drop-out and an additional patient was enrolled to replace this subject.

All subjects in the performance verification underwent individual calibration during the first visit using the HemoCue as calibration device, followed by an experimental measurement day (visit 2) with consumption of a standardized meal. All measurements and calibration related actions were performed by the investigators. A total of 189 paired data sets were collected from 27 participants. YSI reference blood glucose levels were in the range of 82 to 274 mg/dL. In comparison to YSI, 50.3 % of the values ≥ 100 mg/dL (≥ 5.5 mmol/L) were within an error range of $\pm 15\%$ (55.0 % compared to HemoCue and 49.7 % compared to AccuChek Performa). For values < 100 mg/dL (< 5.55 mmol/L), the numbers within the ± 15 mg/dL range were 20 %, 20 % and 18 %, respectively. The results of the accuracy assessments with the Consensus Error Grid are provided in Figure 2 and further analyzed in Table 1.

| 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% | 189 | 100% | 189 | 100% |
| A | 121 | 64.00% | 130 | 68.80% | 120 | 63.50% |
| B | 68 | 36.00% | 59 | 31.20% | 69 | 36.50% |
| C | 0 | 0 | 0 | 0 | 0 | 0 |
| D | 0 | 0 | 0 | 0 | 0 | 0 |
| E | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 189 | 100 | 189 | 100 | 189 | 100 |

Table 1: Distribution of the GlucoTrack results in the consensus error grid analysis in comparison to the different reference methods.

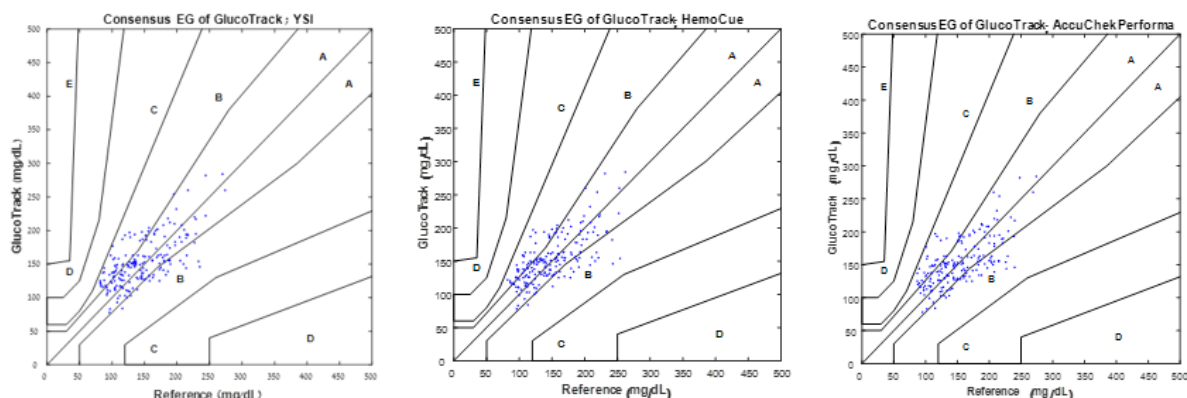


Figure 2: Consensus error grid analysis for GlucoTrack when compared to all other devices.

The ARD (Mean/Median) of the HemoCue-calibrated non-invasive devices was found to be 19.7%/15.9% vs. YSI, 17.5%/14.7% vs. HemoCue, and 18.1%/16.1% vs. AccuChek Performa. Cumulative percentages of absolute deviations below 10%/ 15%/20%/40% for values ≥ 100 mg/dL ($n = 169$) were 32%/50%/69%/94% vs. YSI (HemoCue: 39%/55%/69%/95%; AccuChek Performa: 31%/50%/68%/96%) and cumulative percentages of absolute deviations below 10 mg/dL, 15 mg/dL, 20 mg/dL, and 40 mg/dL for the values < 100 mg/dL ($n = 20$) were 0%/ 20%/30%/75% vs. YSI (HemoCue: 5%/20%/30%/90%, AccuChek: 6%/19%/38%/88%).

The mean glucose excursions during the test meal as assessed by the non-invasive device and the reference methods are provided in Figure 3. A lag time of 10-15 min can be seen between the non-invasive tissue glucose readings and the invasive capillary blood glucose readings with all reference methods, when the glucose values were increasing. This lag time was ~ 30 min when the glucose values dropped after reaching the postprandial maximum level.

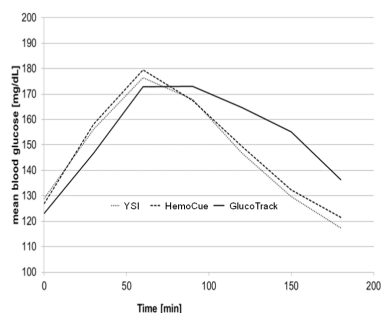


Figure 3: Mean glucose excursions during the test meal when assessed by GlucoTrack and the reference methods. The standard deviations were left out for better readability (the coefficient of variation was between 20-25 % for all devices and for all time-points).

For precision analysis, 35 GlucoTrack data pairs were acquired from 5 patients. The mean PARD was $9.5 \pm 5.5\%$.

In total, 224 non-invasive measurements (189 + 35) from 20 type 2 diabetes patients and 7 prediabetic subjects were collected and evaluated in this study. No device-related adverse events were observed during or after the use of the GlucoTrack. In particular, no injuries or appearance of complications at the ear lobe, such as skin irritation, burning or discomfort were reported.

Discussion

In this trial, we investigated the performance of a new non-invasive ear lobe tissue glucose monitor in comparison to several invasive point-of-care blood glucose measurement methods. The results show that 100% of the performance evaluation data points were within the clinically accepted zones A and B of the Consensus Error Grid, when compared to the YSI reference method. The same results were obtained in comparison to the HemoCue and the AccuChek Performa devices - both of which are acceptable blood glucose measurement methods for patient self-testing. The mean PARD between measurements with two separate devices was $9.5 \pm 5.5\%$ and median ARD was in the range of 15% to 19 %. These results are in line with the accuracy results obtained in previous clinical trials as reported by Horman, et al. and Mayzel, et al. (MARD: 18-22 %. [24,29]).

When interpreting the performance of a non-invasive device, it should be considered that unlike invasive devices, the non-invasive device does not measure blood glucose. Invasive devices are all operated with capillary blood samples obtained from the fingertip or the ear lobe. All three technologies employed by the non-invasive device indirectly measure changes in physiological conditions in the earlobe derived from changes in the local glucose concentrations, and are associated with the absolute levels of glucose in the earlobe tissue. It is thus expected that a tissue glucose reading from the ear lobe will represent a mixture of glucose

information from at least three different sources and compartments (interstitial fluid, arterial blood, venous blood). Yet, the observed time-lag indicates that the major component contributing to the non-invasive results is the interstitial glucose concentration and not capillary or venous glucose levels. The observed mean time-lag between the reference readings and the GlucoTrack readings in our study was 10-15 min when glucose was rising, and ~30 min, when glucose was dropping. These results are in line with results obtained from minimally invasive Continuous Glucose Sensor (CGM) experiments, measuring the time-lag between the interstitial fluid and blood glucose levels. These studies have shown that interstitial glucose is “Delayed” with respect to blood glucose, but it is not simply a shifted-in-time version of blood glucose. Type 1 patients in an overnight fasting state have been observed to have a time lag of less than 10 minutes between glucose appearance from the vascular compartment to the interstitial space. When the glucose levels go down after reaching the peak blood glucose excursion after a meal, a time lag of up to 45 min has been demonstrated in patients with type 2 diabetes with minimally invasive glucose sensors or by alternate site testing [24]. The lag time does in any case not compromise one of the main intentions for frequent non-invasive glucose measurement, which is to identify the right time for treatment initiation or intensification. Still, since there is a delay of real-time information detected by BG monitoring devices due to glucose being transported from the blood to the interstitial tissue, the reliability in glycemic emergency situations is limited [30]. Consequently, there is a need to further improve the accuracy of CGM devices and also of the non-invasive methods.

Our study has several limitations, which need to be considered before potentially drawing conclusions for daily routine care. As mentioned above, it is unclear whether capillary glucose is indeed the right reference method for this or any other non-invasive device that assesses physiological changes related to glucose tissue variations. However, YSI is a globally accepted standard reference method for invasive blood glucose meters for patient self-testing, and will therefore always be a considerable benchmark also for non-invasive devices. Secondly, we only performed one experimental visit one day after the calibration procedure to test the system accuracy in comparison to a capillary blood glucose reference method. In addition, all measurements were performed by health care professionals. It will be important to understand the long-term performance and validity of the applied calibration procedure under real-world conditions. Nonetheless, in a clinical and laboratory setting, GlucoTrack maintains its performance for six months [27]. Finally, our study has only a small cohort size and included only a specially selected patient population of subjects with prediabetes and early to moderate stage type 2 patients.

Conclusion

The current data suggests that non-invasive tissue glucose

information obtained from the ear lobe by using GlucoTrack, has an acceptable accuracy and precision. The device has an appropriate performance among its intended users, including type 2 and prediabetic patients, and is suitable for frequent trend glucose monitoring. The device offers a simple and painless way to encourage patients to perform frequent glucose assessments. By this more glucose information may be collected during the prediabetic period, which is known to be associated with insufficient frequency of self-glucose monitoring in clinical routine. This may ultimately lead to enhanced patient compliance and improved outcome.

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