Calibrating Non-Invasive Glucose Monitors Facts and Factors

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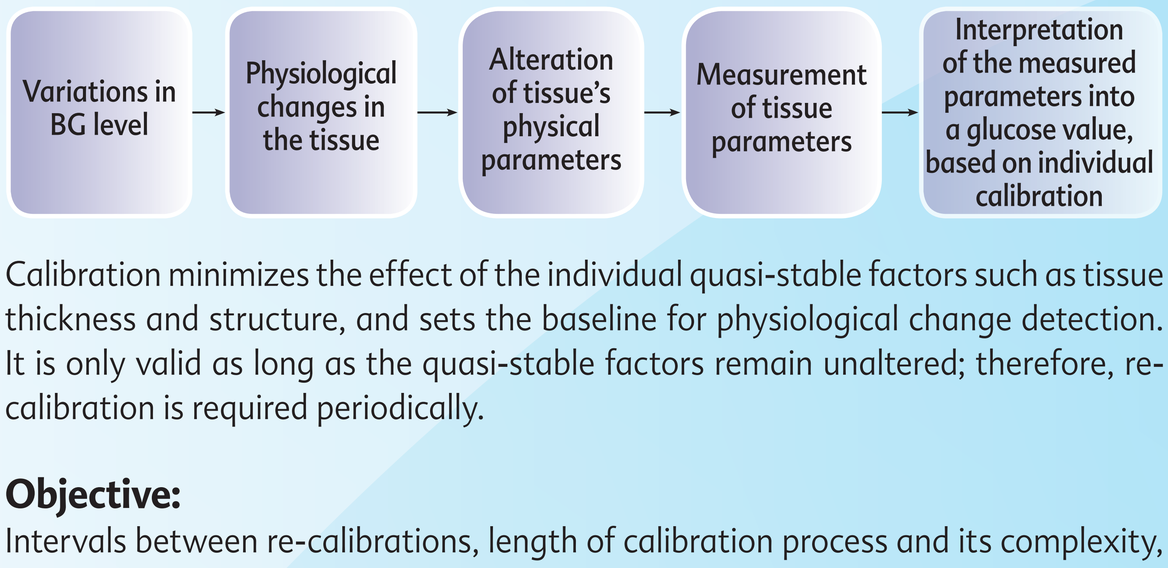
Background:

Since Non-Invasive (NI) glucose monitoring devices use indirect measurement and are usually based on tracking physiological phenomena, correlated with Blood Glucose (BG), rather than direct reading, calibration is a must (Figure 1).

Figure 1: Basis of Indirect and Non-Specific NI Glucose Monitoring

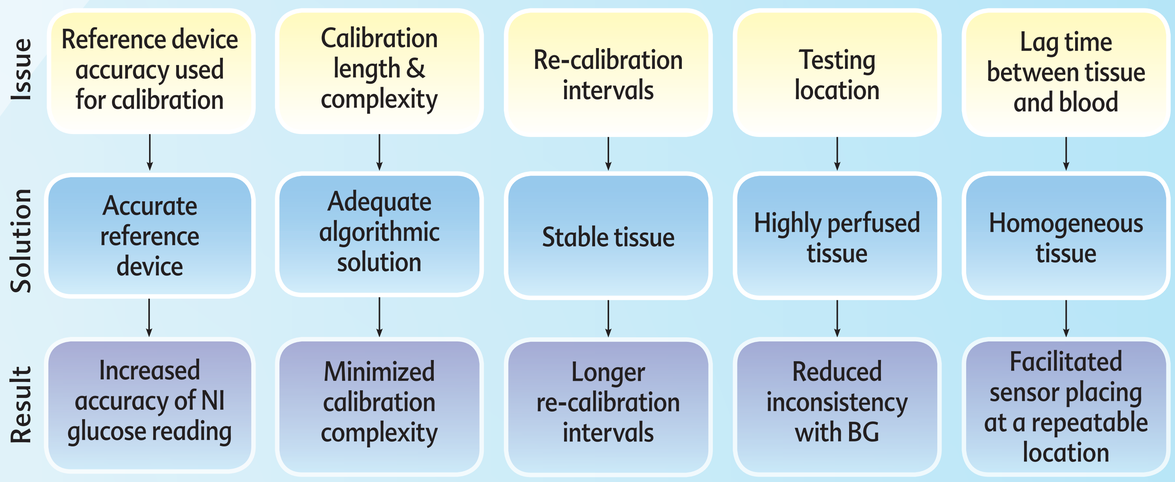


Calibration minimizes the effect of the individual quasi-stable factors such as tissue thickness and structure, and sets the baseline for physiological change detection. It is only valid as long as the quasi-stable factors remain unaltered; therefore, re-calibration is required periodically.

Objective:

Intervals between re-calibrations, length of calibration process and its complexity, number of finger-pricks required and choice of invasive reference device strongly affect NI device usability and utilization. The coping approach of the above issues is summarized in Figure 2.

Figure 2: Coping with Calibration Issues



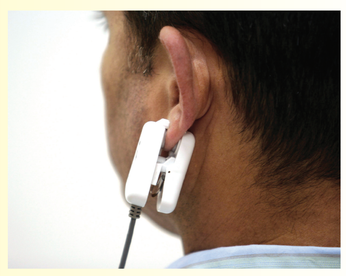
Methodology:

The above approach was considered in calibrating ***GlucoTrack®*** glucose monitor.

The earlobe was chosen to be the measurement location, due to:

- Large blood supply;
- Ear and finger capillary BG concentrations are well correlated;
- Fairly homogeneous tissue;
- Relatively slow blood stream;
- Easy to approach;
- Doesn't disturb regular activities.

Figure 3: Performing a Spot Measurement

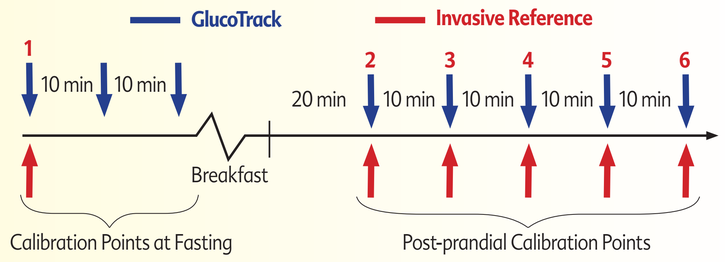


The Personal Ear Clip (PEC), where the sensors are located, is clipped externally to the earlobe (Figure 3) for the duration of a spot measurement (less than a minute), and is removed afterwards. Prior to calibration, PEC is adjusted individually for a firm fit to the user's tissue thickness. This process is guided by the device to reduce user derived inconsistencies.

Post PEC adjustment, a calibration is individually performed against invasive basal and post-prandial blood glucose references, producing an individual calibration model for each user. The procedure is easy, fully guided by the device and takes less than 2 hours (Figure 4).

Figure 4: Calibration Process

Duration	~1.5 ÷ 2 hours
Current Validity	Over a month
Requirements	Start at fasting
Invasive reference points required	6



A variety of clinical trials, with ~2 hours calibration procedure (6 invasive points), were conducted to validate the above approach. In these trials, the calibration procedure was performed by the medical team, in the clinic. HemoCue® 201+ analyzer was used as the reference for calibration, as well as to evaluate measurements. Each individual trial from the 110 subjects (Table 1) was performed in 2 to 3 different days:

- During **Day 1**, calibration was individually performed using HemoCue® as an invasive reference, followed by 6 measurement pairs.
- On **Days 2** and **3**, a full-day measurement session was conducted (including two meals and snack), with same reference device.

Table 1: Subjects' Demography

Diabetes Type	12 type 1 ; 98 type 2
Gender	47 F ; 63 M
Age (Years)	51 ± 30
BMI (Kg/m^2)	30.1 ± 10.0
Total subjects	110

The intervals between day 1 and days 2 and 3 were 1 ÷ 30 days, according to subjects' availability. Thereafter, all the post calibration readings were divided according to 4 time intervals (1 weak each): ≤ 6 days, 7 ÷ 14 days, 15 ÷ 22 days and 23 ÷ 30 days post calibration.

Results:

During a full month, weekly analysis of potential degradation in accuracy level as a function of elapsed time from calibration was performed on the 110 subjects (2695 data points). Clarke Error Grid (CEG) analysis and Absolute Relative Difference (ARD) values for each week were evaluated. No increment in the degree of error was observed as a function of days post calibration (Table 2).

Table 2: Relationship Between the Degree of Error and Time After Calibration (110 subjects)

	≤ 6 days post calibration	7 ÷ 14 days post calibration	15 ÷ 22 days post calibration	23 ÷ 30 days post calibration	Total
# of Points	1776	755	117	47	2695
CEG A Zone (%)	59	58	59	58	
CEG A+B Zones (%)	96	97	97	97	
Mean ARD (%)	23.1	22.7	23.1	21.9	22.5 ± 0.6
Median ARD (%)	16.4	16.8	15.1	21.7*	18.4 ± 3.3

* Not indicative due to small data set

Conclusions:

- Combining the above methods increases the feasibility of a simple, NI glucose monitoring device, which requires not frequent re-calibrations.
- No degradation in performance was observed as a function of elapsed time after calibration. This indicates that the intervals between re-calibrations indeed may be increased.
- Further activity to increase the calibration validity period for up to 6 months is currently in process.
- It's believed that long intervals between re-calibrations are essential for a NI device to become a useful home and home alike environment SMBG solution for diabetics.
- An algorithmic solution without the pre-fasting requirement, to enable higher flexibility and convenience of the calibration procedure, is currently being developed.

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