# Cross-sectional investigation on the accuracy of alternate site glucose testing using the Soft-Sense® glucose meter

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# **Summary**

Questions under study: The aim of this study was to evaluate possible differences in the results of blood glucose testing with the Soft-Sense® blood glucose monitoring system (Abbott MediSense, Wiesbaden, Germany; not yet available in Switzerland) using different sites for drawing whole blood samples.

Methods: In total, 66 patients participated in the study. Blood glucose measurements were performed with the Soft-Sense® device taking capillary blood from the forearm and the fingertip. The results were compared with blood glucose measurements by means of a laboratory reference method using blood from the fingertips.

Results: 276 blood glucose data sets could be obtained and were used for the examination of the accuracy of blood glucose measurements at both different sites. Blood glucose results obtained from the arm with Soft-Sense correlated well and were nearly parallel with the results achieved from the fingertip with a laboratory reference method (regression analysis: slope = 0.981; intercept = 0.045 mmol/l (0.819 mg/dl); correlation coefficient r = 0.943). Error grid analysis showed 99.2% of the measurements within clinically acceptable zones A and B. In addition, finger stick measure-

ments done with the Soft-Sense device and the reference method revealed a strong correlation (regression analysis: slope = 0.959; intercept = -0.042 mmol/l (0.748 mg/dl); correlation coefficient r = 0.972). Error grid analysis showed 98.9% of all blood glucose readings within clinically acceptable zones A and B. Mean absolute percent deviations were 9.3±8.1% for the finger tests and 11.2±8.7% for the arm tests. If blood glucose values exceeded 11.1 mmol/l (200 mg/dl), measurements revealed from the forearm were slightly lower than the measurements obtained from the fingertips.

Conclusions: The results indicate that the automated blood glucose monitoring device Soft-Sense provides accurate results independent of the measuring site. As with other alternate site testing devices, nearly painless blood collection at the forearm might help to increase patients readiness to perform more frequent measurements by self blood glucose monitoring, which is a known prerequisite of improved blood glucose control.

Key words: blood glucose self monitoring; alternate site measurements; blood glucose control

#### Introduction

Daily self-injecting of insulin and frequent self-monitoring of blood glucose (SMBG) are essential prerequisites for adequately managing insulin-dependent diabetes mellitus [1, 2]. Devices used for SMBG must be accurate and reliable to allow correct calculations of required insulin doses for regular treatment or treatment adjustments. The principle barriers to effective SMBG are operator errors and decreased compliance because of discomfort or inconvenience [3, 4]. There is evidence suggesting that fear of blood and injury

is associated with less frequent self-testing and consequently with poor glycaemic control [5, 6]. Since the establishment of SMBG and especially as pen injection devices now allow almost pain-free application of insulin, it is a desire of patients also to be able to measure blood glucose painlessly. Painful measurement of blood glucose is therefore one of the major daily burdens for patients on insulin. Like other recently introduced glucose meters (Freestyle, Therasense/Disetronic; One-Touch Ultra, Lifescan, and At Last, Amira), Soft-

This work was supported by a grant from Abbott Medisense, Wiesbaden, Germany. Sense (Abbott Medisense) is a blood glucose monitoring system for alternate site blood glucose testing at the forearm, upper arm, or ball of the thumb. Compared with the fingertips, the arm has a lower density of sensory nerve endings [7]. Blood glucose self measurements at the forearm have been shown to be less painful than blood glucose measurements at the fingertips [8]. With the development and introduction of the new almost pain-free blood glucose meter Soft-Sense, it is expected that fear of SMBG will become a less important issue in the treatment of patients with diabetes mellitus.

An important question requiring evaluation is whether there are differences in the results of blood glucose testing at different sites and what the extent of these differences is, in particular as regards detection of hypoglycaemic or hyperglycaemic events.

The goal of this study was to compare the results obtained from parallel measurements at two different sites (fingertip and forearm) using the Soft-Sense meter with values obtained from a standard reference method in three different ranges of glucose concentrations.

### Patients and methods

The study was performed in accordance with Good Clinical Practice and the Declaration of Helsinki. The patients were recruited from the inpatient and out-patient department of the Diabetes Research Institute and Academy, Bad Mergentheim, Germany. After approval of the institutional review board was obtained, 66 Patients were enrolled into the study. There were 20 female and 46 male participants with a mean age of 47.8  $\pm$  15.3 years. The mean duration of diabetes in these 28 Type 1 and 36 Type 2 patients (on oral treatment) was 11.4  $\pm$  10.3 years. All patients gave their written informed consent before participation in the trial.

The patients were allowed to perform up to five test procedures with blood measurements at the fingertip and the forearm. The measurements were performed with the Soft-Sense glucose meter (figure 1) using the appropriate glucose strips at both testing sites. The glucose measurement range of the device is 1.7–25 mmol/l (30–450 mg/dl). Precision studies showed a coefficient of variation between 2.9% and 5.9% [8]. The Soft-Sense glucose meter device has two different blood glucose test ports where the glucose test-strips can be loaded. Port 1 is equipped with an automated vacuum system which allows measuring at the arm or the ball of thumb. The device is gently pressed to the skin. After activation by pushing the start button, the device produces the vacuum and a lancet pricks the

Figure 1
Picture of the SoftSense device in use.



skin. If enough blood is collected under this vacuum on the strip, the measurement procedure automatically starts and a value is given within 20 seconds. Port 2 can be used for conventional glucose testing at the fingertip and calibrating the meter with calibration strips. In this study, blood glucose measurements were performed with the Soft-Sense at the upper side of the forearm (port 1) and the fingertip (port 2) and with the EBIO® Plus glucose analyser (Eppendorf, Hamburg) as the laboratory reference method with capillary whole blood obtained from the fingertip. EBIO Plus is based on enzymatic amperometry (Glucoseoxidase/Hydrogensuperoxide; CV <1.5% at 12 mmol/l [216 mg/dl]) and meets all requirements for internal and external quality control.

The order of measurements was randomly assigned. The randomisation was performed in such a way as to ensure that both fingertip measurements were performed consecutively, ie, no forearm measurement was performed between the two fingertip measurements. The blood sample for the laboratory value was thus always drawn as second sample. Each patient had to wash and dry the hand and forearm before each measurement series. Adverse events observed by the investigator or reported by the subject were documented. The goal was to create 200 Data Sets with 50 data sets in the 1.1–5.6 mmol/l range (20–100 mg/dl), 10 data sets below 2.8 mmol/l (50 mg/dl), 100 data sets in the 5.6–11.1 mmol/l range (100–200 mg/dl), and 50 data sets in the >11.1 mmol/l (200 mg/dl) range with 10 data sets above 13.9 mmol/l (250 mg/dl).

Error-Grid-Analysis was used to evaluate the accuracy from a clinical point of view. This type of analysis was developed by clinicians and statisticians for the interpretation of blood glucose meter comparisons. The zones were defined according to the rules and recommendations of insulin treatment. Values within zones A and B would lead to comparable therapeutic decisions and are, therefore, considered to be clinically acceptable. Values in zones C, D, and E would lead to different decisions by using the different meters and are thus considered to be clinically unacceptable [9, 10]. Parametric statistical approaches were used for the validation of analytical accuracy [9, 10]. Since the precision of blood glucose measurements could be different in several blood glucose ranges [11], data were also individually analysed in three different blood glucose ranges (<5.6 mmol/l [100 mg/dl), 5.6-11.1 mmol/l (100-200 mg/dl), >11.1 mmol/l (>200 mg/dl]). In addition, the analysis was also performed with values in the hypoglycaemic range <3.5 mmol/l (63 mg/dl) and hyperglycaemic range >13.9 mmol/l (>250 mg/dl). The two-sided student's T-test was used in case of comparison of mean values.

#### Results

276 complete data sets were obtained. Measurements with the Soft-Sense monitoring system revealed a highly significant correlation between results obtained from the arm (Port 1) and from the fingertips (Port 2) (regression analysis: slope = 0.990; intercept = 0.360 mmol/l (6.480 mg/dl); correlation coefficient r = 0.938).

In addition, a significant correlation was found between results obtained from the arm using the Soft-Sense device and the results obtained from the fingertips with the reference method (regression analysis: slope = 0.981; intercept = 0.045 mmol/l (0.819 mg/dl); correlation coefficient r = 0.943). Error grid analysis shows 99.2% of all values within clinically acceptable zones A and B (80.4% zone A; 18.8% zone B), whereas 2 (0.7%) were within zone D (figure 2). The Bland-Altmananalysis of this comparison is given in figure 3, that also gives the ranges of acceptance according to the new ISO/DIS 15197 guideline. The mean absolute percent deviation was  $11.2 \pm 8.7\%$ .

Regression analysis of the finger-stick Soft-

Figure 2

Error grid analysis of the comparison between Soft-Sense measurements at the arm and the reference method.

## Error-Grid-Analysis SoftSense Fingertip vs. EBIO Fingertip

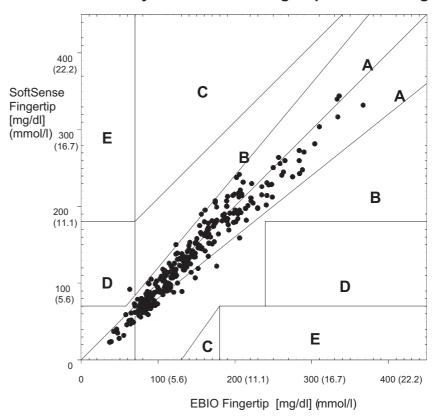
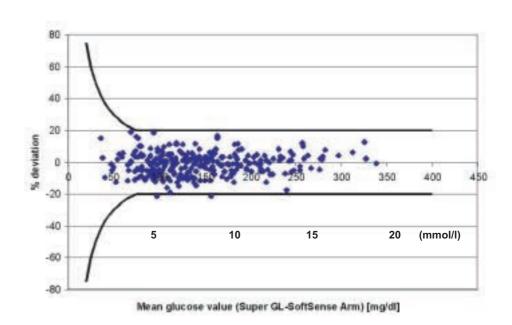


Figure 3

Bland-AltmanAnalysis of the
Soft-Sense measurements at the
arm compared
with the reference
method. The black
lines frame the
area of acceptance
as given by the
new ISO/DIS 15197
guidelines.



Sense (Port 2) vs. fingerstick EBIO Plus reference system revealed a strong agreement between the two methods (slope = 0.959; intercept = -0.042 mmol/l (-0.748 mg/dl); correlation coefficient r = 0.972). Error grid analysis is given in figure 4. In total, 273 of 276 measurements (98.9%) were within zones A and B (90.9% zone A; 8.0% zone B), whereas 3 (1.1%) were within zone D. Bland-Altman-analysis of this comparison is shown in figure 5. The mean absolute percent deviation was  $9.3 \pm 8.1\%$ .

All correlations were in an acceptable range. The best correlation was seen between the refer-

ence method and the Soft-Sense measurement at the fingertip. The best mean agreement in the Bland-Altman-analysis was seen between the reference method and the measurement at the forearm.

There were 76 data sets in the range <5.6 mmol/l (<100 mg/dl), 149 data sets in the range of 5.6–11.1 mmol/l (100–200 mg/dl), and 51 data sets in the range >11.1 mmol/l (>200 mg/dl). The mean differences for these stratification groups revealed no clinically important differences between the different ranges. Measurements on the forearm showed slightly lower values in the high measure-

Figure 4
Error grid analysis of the comparison between Soft-Sense measurements at the fingertip and the reference method.

# Error-Grid-Analysis SoftSense Foremarm vs. EBIO Fingertip

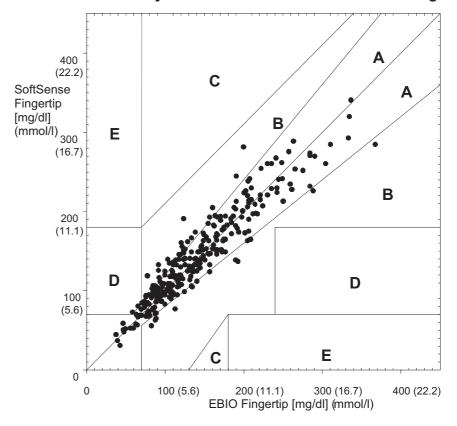
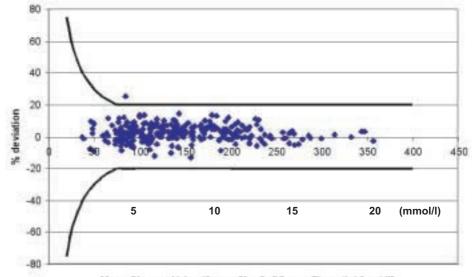


Figure 5
Bland-Altman-analysis of the Soft-Sense measurements at the fingertip compared with the reference method. The black lines frame the area of acceptance as given by the new ISO/DIS 15197 guidelines.



Mean Glucose Value (Super GL - SoftSense Fingertip) [mg/dl]

Table 1
Mean deviations
after the stratification
into the three measurement ranges
and for the hypoglycemic (<3.5 mmol)
and hyperglycemic
(>13.9 mmol) range.

Range	EBIO vs. Fingertip	EBIO vs. forearm	forearm vs. fingertip
<3.5 mMol/l (<63 mg/dl) n = 12	0.12 ± 0.31 mmol/l (2.28 ± 5.59 mg/dl)	0.13 ± 0.42 mmol/l (2.42 ± 7.65 mg/dl)	$0.01 \pm 0.57 \text{ mmol/l}$ $0.14 \pm 10.32 \text{ mg/dl}$
<5.6 mmol/l (<100 mg/dl) n = 76	0.26 ± 0.58 mmol/l (4.68 ± 10.45 mg/dl)	0.29 ± 0.76 mmol/l (5.22 ± 13.69 mg/dl)	0.03 ± 0.89 mmol/l (0.54 ± 16.03 mg/dl)
5.6–11.1 mmol/l (100–200 mg/dl) n = 149	0.56 ± 7.94 mmol/l (10.09 ± 143.05 mg/dl)	0.22 ± 1.12 mmol/l (3.96 ± 20.18 mg/dl)	$-0.34 \pm 1.19 \text{ mmol/l}$ (-6.13 ± 21.44 mg/dl)
>11.1 mmol/l (>200 mg/dl) n = 51	0.10 ± 1.04 mmol/l (1.80 ± 18.74 mg/dl)	-0.47 ± 1.47 mmol/l (-8.47 ± 26.48 mg/dl)	-0.57 ± 1.53 mmol/l (-10.27 ± 27.56 mg/dl)
>13.9 mmol/l (>250 mg/dl) n = 27	-0.22 ± 0.83 mmol/l (-3.96 ± 14.9 mg/dl)	-0.88 ± 1.48 mmol/l (-15.81 ± 26.64 mg/dl)	-0.66 ± 1.50 mmol/l (-11.85 ± 26.99 mg/dl)

ment range (mean difference 0.56 mmol/l (10 mg/dl) in comparison to the reference and to the Soft-Sense fingertip measurements. The data sets from the clinically extreme ranges (hypoglycaemic range: <3.5 mmol (n = 12) and hyperglycaemic range: >13.9 mmol/l (n = 27)) also showed good

performance of both, arm and fingertip measurement (see table 1). In the lower range of blood glucose, there was a high agreement between the different methods. No significant differences could be seen for the mean differences of the two EBIO vs. Soft-Sense comparisons.

#### Discussion

Self monitoring of blood glucose has become an important tool in the management of patients with diabetes mellitus [12, 13]. Intensive diabetes management includes multiple SMBG to adjust the dosage of insulin and oral hypoglycaemic agents [14, 15]. Fear of SMBG with finger prick methods can be a source of distress and may seriously hamper self management of blood glucose control. Non-compliance with home SMBG occurs in up to two third of adolescents and young adults with type 1 diabetes [16, 17]. Alternative site testing has shown to reduce pain and to cause less discomfort than a finger stick and thus may increase measurement frequency with SMBG.

Until now, three devices are commercially available (Soft-Sense, Abbott Medisense; Freestyle, Therasense/Disetronic; and One Touch Ultra, Lifescan). In almost all of the clinical studies published so far, alternate site testing has shown acceptable accuracy performance under different circumstances and in different populations In these studies a large majority of this subjects preferred the alternate site devices over the finger stick meters they were using before [8, 18, 19], however this preference did not lead to an increase in the measurement frequency or in the long-term glucose control.

In the presented study, measurements obtained in parallel from the forearm and fingertip using the Soft-Sense device were in good agreement with the reference method. For both measuring sites (arm and fingertips) more than 98% of the glucose values were in the A and B zones of the error grid analysis, which are considered to be clin-

ically acceptable. These values are comparable to those obtained with other commercially available devices using fingertip measurements [10, 20]. Less than 2% of the data was observed in the D zone. In a recent study comparing six different devices measuring blood glucose at the fingertip, values within the D zone were up to 8% [21].

The quality of agreement was equally distributed for the fingertip measurements over the entire measurement range from 2.1-20.4 mmol/l (37–367 mg/dl), except at very high glucose values. The same result was obtained with the alternate site testing in the range of 2.1–11.1 mmol/l (37–200 mg/dl). If the blood glucose values were above 11.1 mmol/l (200 mg/dl), the measurement at the forearm revealed slightly lower glucose concentrations than the other two methods with capillary blood from the fingertips. Due to high number of data points analysed, this difference reached statistical significance. However, given the high variability of blood glucose testing with commonly used home meters of about 15%, a mean -0.56 mmol/l (-10 mg/dl) difference does not represent a clinical issue in daily practice. The observed correlation of the two Soft-Sense testing methods with the reference method is in any case comparable to the results with other home glucose monitoring devices measuring at the fingertip [20, 21].

A recent letter and the corresponding following full paper report have indicated that in case of artificially induced rapid blood glucose changes, the use of alternate site testing might show a delayed response of the arm testing as compared to fingertip testing [22, 23]. These results were sup-

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ported by a paper from Ellison and co-workers using the OneTouch Ultra device [24]. Their findings have been reflected in the recommendations about alternate site testing at low glucose concentrations of the American Food and Drug Administration [25]. However, exact repetition of the experiment from Jungheim and Koschinsky in our group with the Soft-Sense device revealed different results. There was no risk for example of overseeing a hypoglycaemic episode in the artificial experimental setting with OGT and consecutive intravenous insulin treatment and no differences at all were observed when the experiment was performed under practical daily treatment situations with a meal and consecutive subcutaneous insulin lispro treatment [26]. Results published by Lock and co-workers about comparable experiments using the Soft-Sense device also showed that the device provides clinically acceptable results from the arm in situations including periods of rapidly changing glucose concentrations [27]. Whether these contradictory results are due to different patient populations, the different devices used, or due to changes in the experimental conditions needs to be elucidated in further studies. A practicable recommendation about how to solve this issue is given in a recent report by Peled and co-workers [28]. Using a comparable high glucose load study design, they confirmed our result, but also showed that when using the palm of the hand as a testing site under these circumstances the data is more accurate as compared to the forearm measurements. All these experiments are of an artificial nature and comparable increases or decreases are rather unlikely to occur under daily treatment conditions. In this cross-sectional field study, the values in the hypoglycaemic range (<3.5 mmol/l, 63 mg/dl) showed a very high level of agreement. However, the small number of data points (n = 12) deriving from our practical setting is not sufficient to allow statistically significant interpretations.

It should be emphasised that overall accuracy of home blood glucose meters depends not only on

the analytical performance of the instrument but also on the proficiency of the operator. To avoid user error in our study, all measurements were done by trained health care practitioners. Hence in every day SMBG by the patients themselves, total error might influence the results to a larger extent than shown in our study. Thus, appropriate training of the patients and the development of devices with a minimum dependence on the operators skills are keystones of adequate performance of SMBG [29]. The automated device (Soft-Sense), described in this study combines lancing the skin and transferring blood to the test strip. When sufficient blood reaches the trigger electrode, the test is started automatically. Therefore, the device reduces operator errors to a minimum. There were no adverse events during the entire study, which demonstrates the tolerability of the measurement procedures in our study.

It can be concluded that the measurements with the Soft-Sense device at both possible testing sites are suitable in daily practice. The device meets the requested standard specifications with regard to accuracy and precision. The alternate site testing feature of the device allows almost pain-free testing at the forearm. It may thus be used to prevent chronic pain and skin lesions at the fingertips and improves the testing performance of many patients who are afraid of painful testing at the fingertip. It can be expected that the device, like other alternate site testing devices, may be able to encourage these patients to perform more frequent measurements at the alternate site. Improved testing performance is known to be a prerequisite of a better long-term diabetes control.

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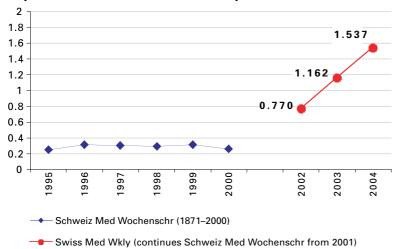
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