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ORIGINAL ARTICLE

The Accu-Chek Mobile blood glucose monitoring system used under controlled conditions meets ISO 15197 standards in the hands of diabetes patients

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Abstract

Background. Self-monitoring of blood glucose is a cornerstone of diabetes management. The aim of this study was to evaluate the analytical quality and the ease of use of the Accu-Chek Mobile, a new glucose monitoring system designed for capillary blood testing by diabetic patients. ***Materials and methods.*** The performance of the Accu-Chek Mobile was evaluated both in the hands of a scientist and of diabetes patients. The designated comparative method was a hexokinase-based laboratory method (Architect ci8200). Diabetics ($N = 88$) with previous experience of self-testing were recruited for the study. Patient samples, containing glucose in concentrations mainly between ~4 and ~20 mmol/L, were analyzed in duplicates both on the Accu-Chek Mobile and with the comparative method. The patients answered a questionnaire about the ease of use of the meter. ***Results.*** The meter yields reproducible readings, with an imprecision CV <5% as required by the American Diabetes Association (ADA). Of the glucose concentrations obtained by both the scientist and the patients, more than 95% of the individual results were within ± 20% of the comparative method, meeting the ISO 15197 accuracy goal, but not the stricter ± 10% ADA goal. ***Conclusion.*** Accu-Chek Mobile is a user-friendly glucometer that in a normo- and hyperglycemic range fulfils the ISO 15197 accuracy requirement, also in the hands of diabetes patients.

Key Words: *Analytical quality, diabetes mellitus, plasma glucose, point-of-care, self-testing*

Introduction

Self-monitoring of blood glucose by patients (SMBG) was found to reduce the risk or slow the progress of diabetes-related complications as long as 30 years ago [1] and more recent studies confirm the beneficial effect of tight glycemic control [2–5]. However, the success of diabetes management depends on reliable blood glucose measurements, which in turn require methods that perform to specified standards [6,7]. Up until now self monitoring has been carried out by applying a small volume of blood to a coded test strip and inserting it into the measuring device. Roche (Roche Diagnostics GmbH, Mannheim, Germany) has recently introduced the Accu-Chek Mobile which replaces test strips with a cassette containing 50 test spots, thus simplifying the procedure by eliminating the handling, coding and disposal of strips. Together with the lancet pen this makes Accu-Chek Mobile a fully integrated blood glucose monitoring system.

The aim of the present study was to assess the analytical quality of Accu-Chek Mobile in the hands

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of both patients and laboratory scientists. The evaluation was carried out in line with the Scandinavian evaluation of laboratory equipment for primary health care (SKUP) and based on the Norwegian Quality Improvement of Primary Care Laboratories (NOKLUS) guidelines [8–10]. The purpose of SKUP is to improve the quality of patient testing in Scandinavia by providing objective and supplier-independent information on analytical quality and ease of use of laboratory equipment.

Material and methods

Analytical methods

The designated comparative method for quantitative determination of glucose in plasma was a photometric enzymatic method, utilizing hexokinase and glucose-6-phosphate dehydrogenase enzymes. Analyses were carried out on an Architect ci8200 system (Abbott Laboratories, Abbott Park, IL, USA) at the laboratory at Haraldsplass Deaconal Hospital in Bergen, Norway. The trueness of the comparative method was traceable to SRM 965a, a set of internationally accepted reference solutions supplied by the National Institute of Standards and Technology, Gaithersburg, MD, USA. It consists of human serum with certified concentrations of glucose at 1.9, 4.36, 6.92 and 16.2 mmol/L, and was used to calibrate the comparative method. The resulting factorization was then confirmed by analysis of two human serum controls (SERO AS, Billingstad, Norway) with glucose concentrations of 4.78 ± 0.09 and 11.80 ± 0.16 mmol/L, determined previously by isotope-dilution gas chromatography/mass spectrometry at the Laboratory for Analytical Chemistry, University of Gent, Belgium [11]. Throughout all analyses, internal quality control of the comparative method was performed by the use of the Autonorm Human Liquid Control Solutions (SERO AS, Billingstad, Norway) at levels 3.50 ± 0.21 and 14.92 ± 0.75 mmol/L.

The test method, i.e. Accu-Chek Mobile, is designed for capillary blood glucose testing performed by patients with diabetes. It consists of a meter, a test cassette containing a film with 50 test spots and the Accu-Chek FastClix lancet pen.

When whole blood is applied to the test spot, a glucose-oxidoreductase mediator reaction causes a color change that is detected reflectometrically. The result is reported as a plasma glucose value. The required sample volume is 0.3 µL and the measurement starts once the correct amount of blood is applied, yielding an answer within 5 seconds. According to the manufacturer the meter has a glucose measurement interval from 0.6–33.3 mmol/L and tolerates a hematocrit between 25 and 55%. It does not require calibration by the user. Due to the risk of patient-to-patient contamination, the Accu Chek Mobile is only recommended for single patient use.

Study protocol and sample collection

The protocol of the study is based on previous standardization efforts [8–10] and is outlined in Figure 1, employing a total of 176 Accu-Chek Mobile systems (glucometers). It was carried out at Moss Hospital in Norway. The biomedical laboratory scientist responsible for the study received practical training in the use of the glucometer from Roche representatives.

Subjects were recruited by advertisements in local newspapers and through the local branch of The Norwegian Diabetes Association. The characteristics of the patient group are shown in Table I and are assumed to be representative for the target population. One group of patients (the 'mail group') received their glucometer systems and instructions via mail; the other group (the 'training group') received their glucometers at the hospital and attended a standardized personal training program. Patients were randomly

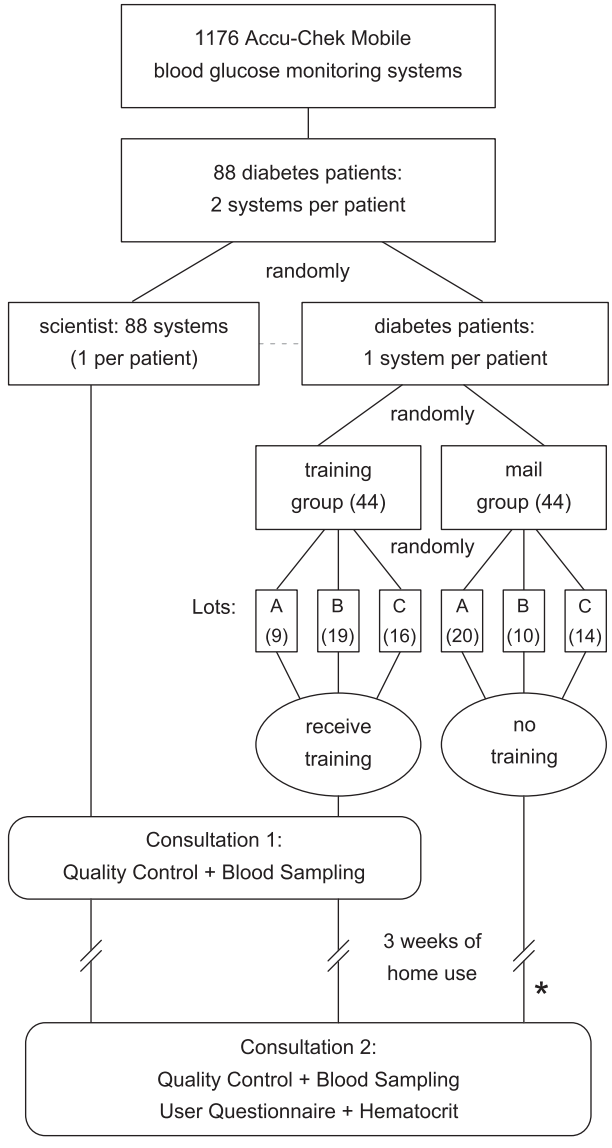

Figure 1. Study protocol. Patients received random glucometer with random test cassette. Scientist received one separate glucometer per patient with matched test cassette. (*) Measurements from two participants in the 'mail group' were discarded.

Table I. Characteristics of the diabetes patients.

Total		$N = 88$
Gender	Male	52
	Female	36
Diabetes	Type 1	31
	Type 2	57
Treatment	Insulin	37
	Insulin pump	4
	Insulin and tablets	6
	Tablets	31
	Diet	10
Frequency of SMBG	Less than weekly	4
	1–3 times per week	17
	4–6 times per week	6
	7–10 times per week	14
	>10 times per week	46
	No measuring	1
Age	interval 25–72 years, median 62.5	
Hematocrit	interval 27–40%, median 40%	
Glucose	interval 2.8–20.3 mmol/L, median 9.8	

assigned one out of three lots of test cassettes (designated A, B or C). The laboratory scientist used one separate glucometer system with a matched test cassette for each of the participants.

Both patient groups used the Accu-Chek systems at home, parallel to their own glucometers, for 3 weeks. They were asked to employ the meters according to their own habits for 2 weeks but to use it regularly for at least the last week.

At both consultations at the hospital an internal quality control of the respective glucometers of patient and scientist was performed using the Accu-Chek Mobile control solution supplied by the manufacturer. Blood glucose measurements were then carried out according to the following sampling procedure:

- Scientist took first capillary sample for the comparative method.
- Scientist performed duplicate measurement on patient using Accu-Chek.
- Patient performed duplicate measurement on himself using Accu-Chek.
- Scientist took second capillary sample for comparative method.

The capillary samples for the comparative method were taken using 300 µl Microvette Li-heparin tubes (Sarstedt AG, Nümbrecht, Germany) and immediately centrifuged at 10,000 *g* for 3 min. Plasma was stored at −80°C until analysis. These samples were used to evaluate the stability of the patient's glucose level. Variations of less than 10% during a sampling period of at most 10 min were defined acceptable. The glucose measurements of two patients in the mail group were excluded due to lack of glucose concentration stability during the sampling time. The second capillary sample was analyzed in duplicate to evaluate the precision of the comparative method, see above. Additionally, for one patient the first of the two samples for the comparative method was missing; an estimate was made from the duplicate measurement of the second sample. Note that the latter does not compromise the validity of the evaluation since the inclusion of unstable samples would at worst lead to an underestimated analytical performance of the glucometer.

At the second consultation, a venous blood sample was drawn from each participant to determine their hematocrit content. The participants also answered a questionnaire regarding their experience with the glucometer, consisting of a grading system for the overall use of the meter and certain aspects of the operation, plus a set of yes/no questions about the quality of the user guide and whether the patients encountered technical problems.

Statistical analysis

The precision, i.e. the agreement between replicate measurements of the Accu-Chek Mobile was determined by two types of measures. Firstly, the coefficient of variation (CV) of the internal quality control as performed by the laboratory scientist during the consultations was determined to estimate reproducibility. Secondly, the imprecision at three different glucose levels was calculated based on duplicate measurements of patient samples carried out by the scientist and the patients themselves, respectively. In the absence of systematic bias between the duplicates, the CV can be calculated using the formula:

$$SD = \sqrt{\frac{\sum_n d^2}{2n}}$$

where d is the difference between two paired measurements and n equals the number of such paired measurements [12,13]. Outliers were detected by the criterion promoted by Burnett [14] at a significance level of 5% and excluded from the statistical analysis. As the results are divided into groups according to glucose levels, the outlier testing was done for each group.

The trueness of Accu-Chek Mobile, i.e. the absence of bias, was assessed by paired t-tests on the mean values of duplicate results of both the comparative and the evaluated method, acquired by the laboratory scientist at the second consultation and grouped in three different glucose ranges. Additionally, the agreement between the three lots of test cassettes was assessed by plotting their respective deviation from the comparative method.

The accuracy, i.e. the total error of individual measurements versus the values obtained by the comparative method, was illustrated using Bland-Altman-like scatter plots [15] with the abscissa representing the mean value of duplicate samples analyzed with the comparative method and the

ordinate representing the difference between the first measurement on the Accu-Chek Mobile and the mean value of the comparative method. The influence of blood hematocrit on the accuracy of individual measurements was estimated by linear regression.

Quality goals

The American Diabetes Association (ADA) requires new glucose devices to operate with an imprecision (CV) <5%, while the inaccuracy of individual measurements is not to exceed 10% in the glucose concentration interval from 1.67–22.2 mmol/L [16].

ISO 15197 requires 95% of the individual glucose results obtained to fall within ± 0.83 mmol/L of the results of the comparative method at glucose concentrations <4.2 mmol/L and within ± 20% at glucose concentrations >4.2 mmol/L [17].

Previous investigations [10,18] have shown that few of the self-monitoring glucose meters tested met the ISO requirements in the hands of patients. Therefore, NOKLUS has suggested a modified goal ('Adjusted ISO') for SMBG requiring that 95% of the individual glucose results shall fall within ± 1.0 mmol/L of the results of the comparative method at glucose concentrations <4.2 mmol/L and within ± 25% at glucose concentrations > 4.2 mmol/L.

Results

Comparative method

A small but systematic deviation from the SRM 965a reference values was found and corrected for all subsequent analyses on the comparative method using the formula:

$$\text{Glucose}_{\text{real}} = 0.948 \times \text{Glucose}_{\text{Architect}} + 0.18 \text{ [mmol/L]}$$

Post factorization, the obtained glucose concentrations of the human serum controls were highly compatible with their specified values ($R^2 > 0.99$).

The precision of the comparative method was good as indicated by a CV between 0.9 and 1.7% (95% CI) calculated from paired measurements of patient samples.

Analytical performance of the test method

The measurements of Accu-Chek Mobile's internal quality control resulted in an imprecision CV (95% CI) of the scientist's meters of 3.3% (3.0–3.8), whereas the CV (95% CI) obtained from the patients' meters at first and second consultation was 2.8% (2.3–3.6) and 3.7% (3.2–4.4), respectively. These results indicate that there was no significant difference between the meters used by the patients and those in use by the scientist.

The relative difference between repeated measurements of patient samples, grouped in three glucose ranges and carried out by the laboratory scientist or the patients themselves, respectively, are shown in Figure 2A. Note that the imprecision CVs obtained by the scientist were below 3%. Among the patient-performed measurements, there were no significant differences between the training and the mail group.

The trueness of the test method is shown as mean deviation from the comparative method in Figure 3A. There was a significant positive bias for glucose concentrations below 10 mmol/L. There was also a difference in the mean deviation from the comparative method among the three lots of test cassettes, as shown in Figure 2B. Note that the mean deviation of one of these lots differed significantly from that of the others.

The accuracy of the Accu-Chek Mobile was evaluated by the number of individual results within the ADA, ISO and adjusted ISO limits. Of the measurements carried out by the scientist at the first consultation ($n = 44$), 68% were within the ADA limit and 93% within the ISO limit, whereas at the second consultation ($n = 86$) the ratios were 87% and 100%, respectively. Considering measurements performed by the patients, the proportion within ADA, ISO and adjusted ISO at the first consultation ($n = 44$) were

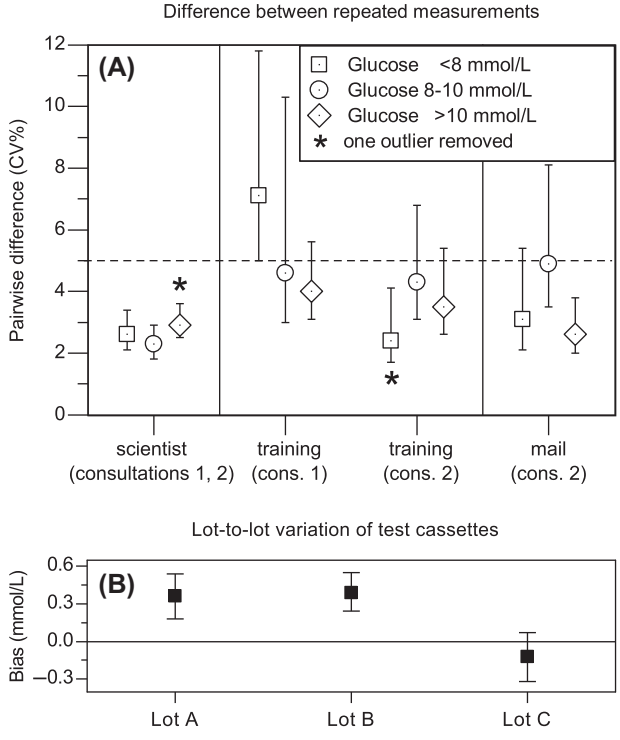

Figure 2. (A) Precision. Relative difference between duplicate measurements performed by the scientist (both consultations), the training group (both consultations, shown separately) and the mail group (second consultation only). (B) Mean deviation from comparative method showing lot-to-lot variation between test cassettes.

73%, 93% and 98%, respectively and 84%, 99% and 100% at the second consultation ($n = 86$). Figures 3B and 3C show the accuracy of Accu-Chek Mobile during the second consultation achieved by the scientist and the patients.

At the second consultation the hematocrit of the participants varied between 27 and 49% (median: 40%). Although there was a tendency towards a small negative correlation between hematocrit and the deviation of Accu-Chek Mobile from the comparative method, this was not significant.

Ease of use of the test method

In the questionnaire, the patients gave a mean score of 4.8 out of 6 for the overall use of the meter, and even higher grades for certain crucial aspects of the operation such as applying blood to the test spot and reading the result on the display. None of the mean scores for the details of the operation were below 4.8. While eight patients reported that the tip cover was difficult to open, 77 patients (82%) did not experience any technical problems. Finally, of the 73 who read the user guide, 66 patients (90%) were satisfied.

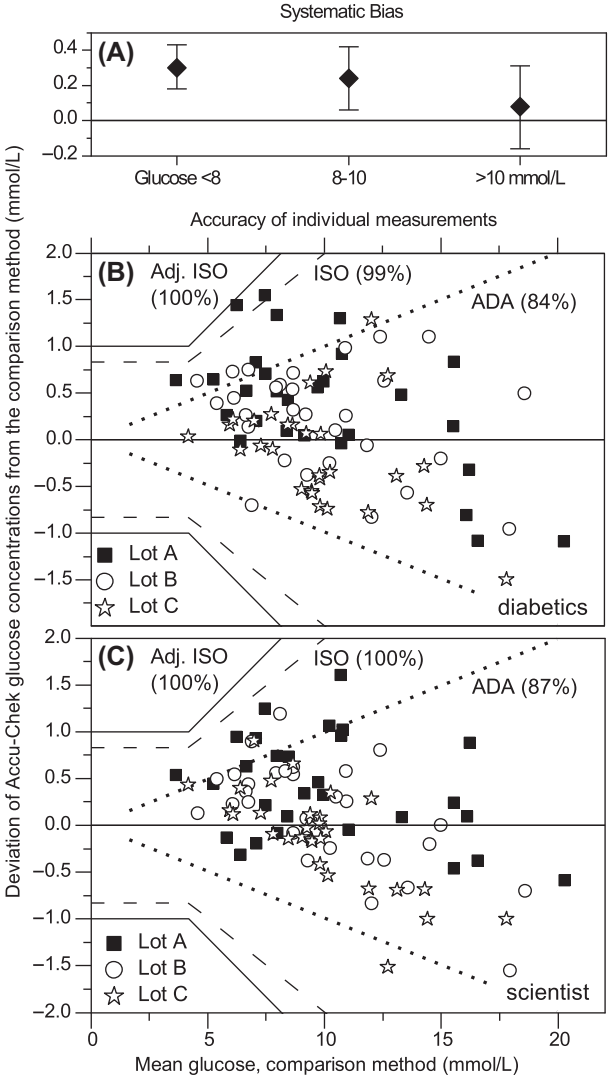

Figure 3. (A) Bias. Mean deviation from comparative method at different glucose levels. (B), (C) Accuracy. Individual difference of the first measurement of the second consultation performed on Accu-Chek Mobile by the laboratory scientist and the patients, respectively. Lines represent accuracy goals set forth by ADA, ISO and NOKLUS ('Adjusted ISO').

Discussion

The Accu-Chek Mobile is a monitoring system intended for home use. Thus, the two most critical questions must be whether the device produces reliable readings and whether the patients can confidently and comfortably use it on their own.

Accu-Chek Mobile seems to be reasonably easy to use. Most patients in this study did not experience technical problems and were satisfied with the instructions given in the user guide. Note that the personal training did not have a significant effect on the precision of the self-monitoring, see Figure 2A. It should, however, be emphasized that all patients in this study had previous experience with self-monitoring of blood glucose, and personal training could very well be important in a patient group without the same background. After 3 weeks of practice, both patient groups performed equally well in terms of precision, with only a few measurements above the ADA goal of a CV $< 5\%$ [16], although not as good as the laboratory scientist who consistently fulfilled the requirement. Both the scientist and the patients performed better at the second consultation, indicating that experience using the glucometer over time improves performance and that this may be more important than how the user received instructions.

What matters to the patient in terms of analytical performance is the accuracy, i.e. the total error of an individual measurement. This study shows that, after 3 weeks, experienced patients are able to meet ISO 15197 requirements in a hospital setting, with 99% instead of ISO's 95% of the glucose measurements within 20% of the true value, or within $\pm$ 0.83 mmol/L when the glucose concentration was below 4.2 mmol/L [17]. The laboratory scientist achieved a 100% success rate in meeting the ISO requirement. The much stricter ADA goal of $\pm$ 10% in the glucose concentration interval from 1.67–22.2 mmol/L was fulfilled 84% and 87% of the time by the patients and the scientist, respectively, which is promising, but also an incentive for further development and improvement.

Since good accuracy implies both satisfactory trueness and precision, we hold the former to be most informative. The other performance measures, however, can serve as pointers to further improvements. A major contribution to the total error in samples with low to normal glucose concentration was the positive bias found for samples below 10 mmol/L. A close inspection of Figures 3B and C also showed that

the test cassettes from Lot C were in fact close to meeting the much stricter ADA standards for total error, indicating a significant potential for improved quality control of the test cassettes.

Hematocrit may affect the result when measuring glucose on whole blood [19]. However, since the accuracy was determined from patient samples with a wide hematocrit range and still fulfills ISO specifications, this does not seem to be a practical problem. This finding is in line with the information provided by the manufacturer, mentioned above.

Although the ISO and even the ADA accuracy goals may eventually be fulfilled, these will sooner or later be replaced by stricter rules. ADA itself already proposed a future limit of 5% total error [6] and there are indications that a limit of as little as 2% would be necessary to assure the right treatment in 95% of the cases [20].

Conclusion

Diabetes patients considered the Accu-Chek Mobile user-friendly. After some practice, they were able to reach acceptable analytical quality using the meter for self-testing under controlled conditions. While we cannot generalize these findings to actual home use or to hypoglycemic patients, we remark that the quality control of the test cassettes may offer a potential for further performance improvements.

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