Evaluation of two HbA1c point-of-care analyzers

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Abstract

Background: Measurement of HbA1c is the most important parameter to assess glycemic control in diabetic patients. Different point-of-care devices for HbA1c are available. The aim of this study was to evaluate two point-of-care testing (POCT) analyzers (DCA Vantage from Siemens and Afinion from Axis-Shield). We studied the bias and precision as well as interference from carbamylated hemoglobin.
Methods: Bias of the POCT analyzers was obtained by measuring 53 blood samples from diabetic patients with a wide range of HbA1c, 4%–14% (20–130 mmol/mol), and comparing the results with those obtained by the laboratory method: HPLC HA 8160® Menarini. Precision was performed by 20 successive determinations of two samples with low 4.2% (22 mmol/mol) and high 9.5% (80 mmol/mol) HbA1c values. The possible interference from carbamylated hemoglobin was studied using 25 samples from patients with chronic renal failure.
Results: The means of the differences between measurements performed by each POCT analyzer and the laboratory method (95% confidence interval) were: 0.28% (p < 0.005) (0.10–0.44) for DCA and 0.27% (p < 0.001) (0.19–0.35) for Afinion. Correlation coefficients were: r = 0.973 for DCA, and r = 0.991 for Afinion. The mean bias observed by using samples from chronic renal failure patients were 0.2 (range –0.4, 0.4) for DCA and 0.2 (–0.2, 0.5) for Afinion. Imprecision results were: CV = 3.1% (high HbA1c) and 2.97% (low HbA1c) for DCA, CV = 1.95% (high HbA1c) and 2.66% (low HbA1c) for Afinion.
Conclusions: Both POCT analyzers for HbA1c show good correlation with the laboratory method and acceptable precision.

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Introduction

Diabetes mellitus, especially type 2 diabetes (DM2) represents a major public health issue, not only due to its high prevalence and incidence, but also because it is associated with high morbidity and mortality (1).

HbA1c has been considered to be a useful tool for metabolic control in patients with diabetes mellitus since 1977 (2). The importance of HbA1c for diabetes control was indicated in 1986, when the American Diabetes Association (ADA) recommended HbA1c measurements to be performed twice a year when glycemic control was adequate, and every 3 months when treatment was modified or glycemic control was inadequate. Currently, HbA1c is used widely as a routine method for monitoring long-term glycemic status in patients with type 1 or 2 diabetes mellitus. More recently, the International Expert Committee for the role of HbA1c in the diagnosis of diabetes has concluded that HbA1c values higher than 6.5% (48 mmol/mol) should be included in the diagnostic criteria for diabetes (3).

In addition, HbA1c also helps estimate the risk of developing diabetes associated micro- and macro-complications. This was reflected by the results obtained in the DCCT (Diabetes Control and Complication Trial Research) (4) and UKPDS (UK Prospective Diabetes study) (5) trials. According to these results, the ADA recommends several aims when treating hyperglycemia; starting from the premise that HbA1c concentrations lower than 7% (53 mmol/mol) minimize the risk of suffering micro-vascular complications. For higher HbA1c concentrations, the risk of complications is increased acutely, and therefore it is assumed that glycemia is controlled poorly. Thus, therapeutic changes are recommended when HbA1c concentrations are > 8% (64 mmol/mol).

In 1999, Cagliero et al. published the first randomized trial showing that point-of-care testing (POCT) HbA1c determinations improve glycemic control (6). In 2003, the results of the first multicentric study of POCT HbA1c implementation and evaluation in Australia were published (7). Miller et al. concluded in a prospective study that immediate HbA1c results led to changes in treatment, achieving a significant decrease in HbA1c (8). Moreover, in certain groups, such as newborns or patients with chronic disease, sample volume is an important consideration. New devices have been developed in the last years which allow rapid HbA1c determinations from capillary blood instead of conventional venipuncture (9). The main advantages of HbA1c determinations using POCT are: simplification of the pre-analytical phase,

including administrative procedures and hospital circuits, prompt availability of results, and finally, these devices may be handled by nursing professionals for immediate results in ambulatory patients (10). Prompt availability of HbA1c measurements in follow-up of diabetic patients improves glycemic control in both type 1 and type 2 diabetes. Therapy changes and measurement of HbA1c concentrations by POCT improves glycemic control by means of rapid, precise and reliable results (7–9, 11, 12). The use of POCT for HbA1c in the physician's office leads to faster patient treatment and improved outcomes, including enhanced physician and patient satisfaction. These are the reasons that the National Academy of Clinical Biochemistry laboratory practice guidelines recommended the use of POCT HbA1c (12).

The aim of this study was to evaluate two POCT methods for HbA1c measurements. We evaluated the Afinion and DCA Vantage by studing bias and imprecision, as well as possible interference from carbamylated hemoglobin. We compared the POCT results with our laboratory reference method, the HA 8160, a widely used and previously validated cationic-exchange high-performance liquid chromatography (HPLC) method.

Materials and methods

Laboratory method

The central laboratory determined HbA1c using cationic exchange HPLC with the HA 8160 (Menarini®, ARKRAY Factory, Inc. 1480 Koji, Konan-Cho, Koka-Shi, Shiga, Japan). The Clinical Biochemistry laboratory of the Virgen Macarena University Hospital obtained Level I certification, specific to this method, reagents, controls and calibrators following the NGSP (National Glycohemoglobin Standardization Program) guidelines.

POCT analyzer methods

The DCA Vantage system (Siemens Medical Solutions Diagnostics, Tarrytown, New York 10591-5097, USA) is based on a heterogeneous immunoassay using latex agglutination. The method uses a monoclonal antibody raised against a specific glycated amino acid sequence of HbA1c. The Afinion system (Axis-Shield PoC AS, P.O. Box 6863 RodelØkka, NO-0504 Olso, Norway) is based on a boronate affinity binding method. Both devices can accept capillary or venous blood collected by venipuncture into EDTA tubes.

The POCT systems were designed to operate with ready-to-use cartridges and were certified by the NGSP (Missouri, USA). Results are adjusted to the DCCT/UKPDS trials.

Study design

The study was approved by the institutional Ethical Board. HbA1c values were quantified in 53 samples. Samples were collected by venipuncture into EDTA tubes and analyzed in duplicate using all instruments. We obtained a total of 106 measurements in each instrument and used the mean values.

Samples were stored refrigerated at 4°C until analysis, which was always within 48 h of blood collection. Results obtained with the two POCT instruments were compared to our current method using

the HA 8160. Results obtained by the three systems are traceable to IFCC values (13–15).

Four HbA1c ranges were selected: 4% (20 mmol/mol) to 6% (42 mmol/mol), 6% (42 mmol/mol) to 8% (64 mmol/mol), 8% (64 mmol/mol) to 10% (86 mmol/mol) and >10% (86 mmol/mol). We included approximately 10 samples per range and analyzed each in duplicate, simultaneously with each instrument.

For intra-assay variability, the same sample was repeated 20 consecutive times. The samples used for intra-assay variability had HbA1c values of 9.5% (80 mmol/mol) and 4.5% (26 mmol/mol), as determined by the laboratory method.

To investigate the possible interference of carbamylated hemoglobin on HbA1c determinations by both POCT analyzers, we compared the results obtained from 25 samples from patients with chronic renal failure (urea levels between 70 and 350 mg/dL) with those obtained by the method used in the central laboratory. We evaluated the bias and performed regression analysis.

Statistical analysis

Statistical analysis was performed using SPSS software v13.0 (SPSS Inc. 233 S. Chicago, IL, USA). We used Student's t-test for paired samples after assessment of normality of the data using the Kolmogorov-Smirnov test, Pearson linear correlation coefficient for method correlation, the HbA1c ranges mentioned previously for categorization of samples and Cohen Kappa coefficient to study concordance between groups. For imprecision studies, standard deviation (SD) and coefficient of variation (CV) were calculated.

Results

Data obtained from the study on bias was found to have a normal distribution using the Kolmogorov-Smirnov test. The
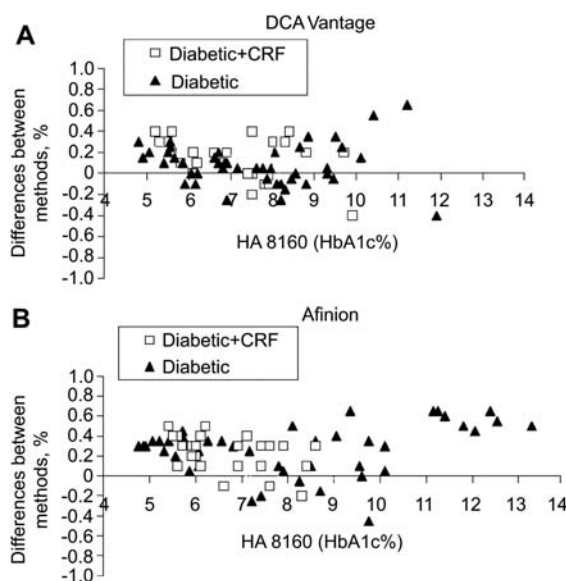
Figure 1   Bias plot of the differences between methods (y-axis) for the DCA Vantage (A) and Afinion analyzer (B) compared with the target HbA1c concentrations for the HA 8160 (x-axis).
Triangles indicate diabetic patients and squares refer to diabetic patients with chronic renal failure.
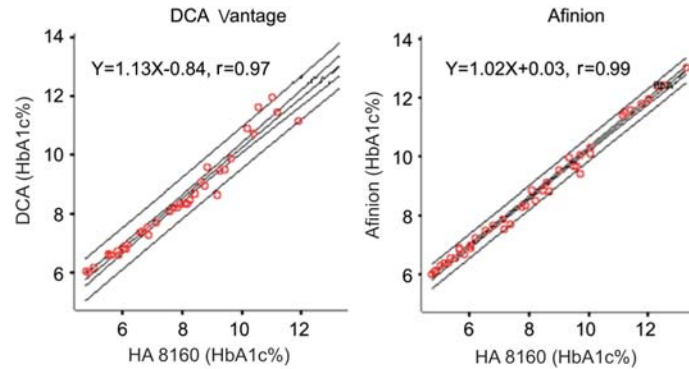
Figure 2 Method correlation of the DCA Vantage (left panel) and Afinion (right panel) analyzer compared with the HA 8160. Samples for HbA1c were from diabetic patients without uremia. The 95% confidence interval are also shown.

bias of HbA1c measurements for each POCT analyzer are shown in Figure 1. The mean difference between the POCT and the HPLC reference methods, with a confidence interval of a 95%, were 0.28% (p < 0.005) (0.10–0.44) for the DCA (Figure 1A), and 0.27% (p < 0.001) (0.19–0.35) for the Afinion (Figure 1B).

Pearson's correlation coefficient between each POCT and the laboratory method was used to assess the performance of the POCT devices. As shown in Figure 2, the correlation coefficient for DCA vs. HPLC was r = 0.973 (Figure 2, left panel) and 0.991 for the Afinion vs. HPLC (Figure 2, right panel).

The coefficients of variation (CV) were calculated to assess imprecision. For the DCA vs. HPLC method, the CV was 3.1% for high HbA1c concentrations and 2.97% for low HbA1c concentrations. For the Afinion vs. HPLC, the CV was 1.95% for high HbA1c and 2.66% for low HbA1c concentrations.

Cohen's kappa coefficient was calculated to assess the concordance between each POCT and the laboratory method, as well as the percentage of agreement with HPLC when classifying patients according to HbA1c concentrations. For the DCA vs. HPLC, the kappa was 0.94 with 96.2% agreement, and for the Afinion vs. HPLC, the kappa was 0.873 with 90.4% agreement. The concordance obtained for each interval of HbA1c values was 100% (4%–6%, 20–42 mmol/mol),

100% (6%–8%, 42–64 mmol/mol), 88% (8%–10%, 64–86 mmol/mol) and 100% (>10%, >86 mmol/mol) for the DCA Vantage. For the Afinion, the concordance was 82% (4%–6%, 20–42 mmol/mol), 100% (6%–8%, 42–64 mmol/mol), 82% (8%–10%, 64–86 mmol/mol) and 100% (>10%, >86 mmol/mol).

Possible interference from carbamylated hemoglobin was investigated by studying the bias of HbA1c using samples from patients with chronic renal failure. The HPLC method that we used is not affected by carbamylated hemoglobin (16). Figure 3 shows the correlation of both methods with the HPLC method when using samples from patients with uremia. Neither the correlation nor the bias seemed to be affected by carbamylation of hemoglobin. Thus, the bias was 0.2% (range –0.4, 0.4) for the DCA (Figure 1A), and 0.2% (–0.2, 0.5) for the Afinion (Figure 1B). The Pearson correlation coefficient was 0.98 for the DCA (Figure 3, left panel) and 0.98 for the Afinion (Figure 3, right panel). Finally, the turn-around-time (TAT) was assessed for each instrument. The TAT was 3 min for the Afinion, and 6 min for the DCA.

Discussion

Several recommendations specify the required analytic quality for HbA1c assays in the follow-up of diabetic patients.
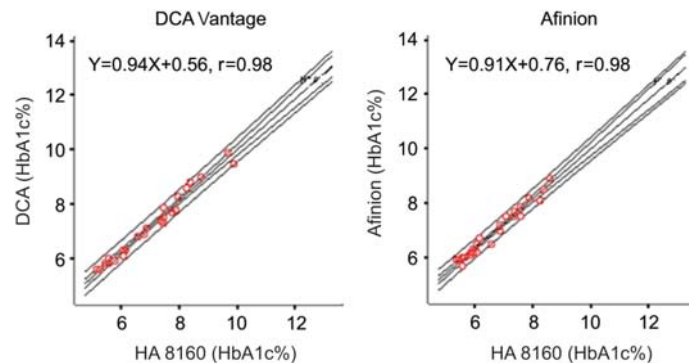
Figure 3 Method correlation of the DCA Vantage (left panel) and Afinion (right panel) analyzer compared with the HA 8160. Samples for HbA1c were from diabetic patients with chronic renal failure. The 95% confidence intervals are shown.

In this study, the POCT methods we evaluated have been certified by the National Glycohemoglobin Standardization Program (NGSP). Moreover, our reference Biochemistry Laboratory has previously obtained Level I certification in methods, reagents, controls and calibrators.

Considerable effort has been invested in research and technological development of new POCT methods. POCT devices for HbA1c measurement are currently used as routine near-patient analyzers with acceptable guarantee of quality in those situations where conventional analyses in the central biochemistry laboratory may take too long due to the type of patient (pediatric, poorly controlled glycemia, etc).

In this study, we performed a side-by-side evaluation of two POCT devices to measure HbA1c. The devices evaluated showed good linear correlation (r) and precision, with an intra-assay CV between 1.9% and 3.1%. In addition, the devices report results in a rapid manner. These results are in agreement wih those previously reported (17).

One of the most frequent interferences in HbA1c determination is modification of hemoglobin by carbamylation, which occurs in patients with chronic renal failure (18–22). However, this type of interference depends on the method used to measure HbA1c (23–25). Thus, the method employed in our central laboratory (HPLC by Menarini HA-8160) is not significantly affected by carbamylation (16). In this context, both techniques used by the evaluated POCT devices (immunoassay and boronate affinity) have been previously found to show less interference from this type of modification of hemoglobin (23, 26). Moreover, as we have seen in our evaluation, even though HbA1c determinations by both POCT devices are not significantly affected by carbamylation of hemoglobin, the small number of patients with chronic renal failure is a limitation of this study. However, it should be considered that rapid POCT methods still have certain limitations, such as training of personnel, quality control and the possibility of other interferences, especially from patients with hemoglobinopathies (27).

POCT methods permit rapid and decentralized HbA1c testing using capillary blood samples. This allows for effective preventive treatment and early detection of diabetes-related complications, such as retinopathies, nephropathies and neuropathies. Thus, health professionals are offered immediate solutions when using POCT analyzers (12, 28). In this way, HbA1c determination using these methodologies have a promising future, as new devices should be more precise. However, clinical trials evaluating the effectiveness, safety and cost of HbA1c determination through rapid methods have not been published.

The assessment of the performance of the two POCT analyzers showed bias and imprecision values compatible with the clinical use of HbA1c in the control of the diabetic patients according to recommendations of the NGSP. However, bias and imprecision are not low enough to recommend the use of POCT HbA1c for diagnostic purposes, as suggested in a previous study by Lenters-Westa et al. (14, 17).

In summary, POCT HbA1c offers the potential for fast and reliable test results and more rapid treatment, and therefore is suitable for the control, but not for the diagnosis, of diabetes.

Conflict of interest statement

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