Published in final edited form as:
Diabet Med. 2011 December ; 28(12): 1525–1529. doi:10.1111/j.1464-5491.2011.03404.x.

Comparison of longitudinal point-of-care and high-performance liquid chromatography HbA_{1c} measurements in a multi-centre trial

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Abstract

Aims—Point-of-care HbA_{1c} is routine in clinical practice. Comparison of point-of-care HbA_{1c} against laboratory measurements across sites and over time is warranted.

Methods—One hundred and twenty-one young persons with Type 1 diabetes from four centres provided 450 paired samples collected over 10 months for point-of-care HbA_{1c} and central laboratory-based high-performance liquid chromatography (HPLC) HbA_{1c} determinations. Change in HbA_{1c} over time was assessed by difference from initial to final HbA_{1c} and by growth modelling with annualized slope calculation. Change in HbA_{1c} was categorized as improved (decrease of ≥ 0.5% or negative slope), no change (± 0.4% of initial HbA_{1c} or slope = 0) or worsened (increase of ≥ 0.5% or positive slope).

Results—The 450 paired samples (median of four pairs/patient) were highly correlated ($r = 0.97$, $P < 0.0001$), as were time-specific and site-specific pairs ($r = 0.94$ to 0.98, $P < 0.0001$). Initial-to-final point-of-care HbA_{1c} and HPLC HbA_{1c} changes were 0.3 ± 1.1% (range −2.7 to 4.1) and 0.4 ± 1.2% (–3.9 to 4.5), respectively, with 21% of patients ($n = 26$) discordant for change categories. ΔHbA_{1c} by point-of-care HbA_{1c} vs. HPLC HbA_{1c} differed across the HbA_{1c} range and by ≥ 0.5% absolute difference in ΔHbA_{1c} in 14 (54%) of the 26 patients discordant for HbA_{1c} change categories. Mean annual HbA_{1c} slope was 0.4 ± 1.5% (−5.4 to 4.8) for point-of-care HbA_{1c} and 0.4 ± 1.6% (−6.9 to 5.2) for HPLC HbA_{1c}, with 18% ($n = 22$ pairs) discordant for change categories.

Conclusions—Assessment of absolute HbA_{1c} change may not be different for point-of-care HbA_{1c} compared with HPLC HbA_{1c}; however, misclassification of patients by discrete cut-off values may occur with point-of-care HbA_{1c} compared with HPLC HbA_{1c} determinations.

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Competing interests
Nothing to declare.

Portions of this manuscript were presented at the 70th Scientific Sessions of the American Diabetes Association (2010).

Keywords

children; HbA_{1c}; point-of-care; Type 1 diabetes

Introduction

HbA_{1c} is the standard measure of glycaemic control. Provider and patient knowledge of HbA_{1c} is associated with improved outcomes [1–4]. High-performance liquid chromatography (HPLC), the assay used in the Diabetes Control and Complications Trial (DCCT) [5,6] has been the standard for measuring HbA_{1c}. In clinical settings, point-of-care instruments have become routine because of their ease of use, finger-stick sampling and rapid turnaround. Immediate HbA_{1c} results help guide diabetes management, especially when the patient provides no blood glucose data [2,4]. Cross-sectional validation studies indicate that point-of-care HbA_{1c} values are equivalent to laboratory measurements [7–9]. Point-of-care devices are waived under Clinical Laboratory Improvement Amendments (CLIA) and certified by the National Glycohemoglobin Standardization Program (NGSP).

Clinical research, particularly longitudinal multi-centre trials, generally employs central laboratory HPLC HbA_{1c} determinations. In clinical trials, HbA_{1c} outcomes often include mean change in HbA_{1c} from baseline, as well as the proportion of subjects achieving either target HbA_{1c} levels, an absolute HbA_{1c} decrease of ≥ 0.5% or a relative decrement in HbA_{1c} of ≥ 10% [10–13]. As point-of-care HbA_{1c} measurements are correlated with laboratory assays, some research studies have utilized point-of-care HbA_{1c} assays as the primary HbA_{1c} outcome [14,15]. Thus, there is a need to determine the utility of point-of-care HbA_{1c} c assays for longitudinal assessments and multi-centre clinical investigations. Our aim was to compare changes in point-of-care HbA_{1c} with HPLC HbA_{1c} over time and across sites in a longitudinal study.

Patients and methods

Young people at four geographically distinct paediatric diabetes centres participated in a family-based pilot study [16]. Eligibility criteria included age 9.0–14.5 years, Type 1 diabetes duration ≥ 1 year, insulin dose > 0.5 units kg^{-1} day^{-1} and HbA_{1c} ≤ 119 mmol/mol (13.0%). Blood samples for point-of-care HbA_{1c} and HPLC HbA_{1c} measurements were simultaneously drawn by finger stick every 3 months for four sequential visits over 9.7 ± 2.2 (mean ± SD) months. Only visits with both point-of-care HbA_{1c} and HPLC HbA_{1c} for a subject were included. Written informed consent/assent was obtained from parents/young person. The study was approved by the Institutional Review Boards at participating institutions.

HPLC HbA_{1c} samples, obtained by research assistants who received standardized training in sample processing, were shipped to a central laboratory (Joslin Diabetes Center) for HbA_{1c} assay (Tosoh A1c 2.2 Plus Glycohemoglobin Analyzer™; Tosoh Medics, South San Francisco, CA, USA). Quality control procedures were performed daily and met the requirements of the College of American Pathologists. The National Glycohemoglobin Standardization Program reference range for HbA_{1c} is 20–42 mmol/mol (4.0–6.0%) [assay range 22–204 mmol/mol (4.2–20.8%)]. The interassay coefficient of variation was < 5% for both low and high controls. The coefficient of variation was 4.8% at an HbA_{1c} value of 5.55% per Diabetes Control and Complications Trial [low control limit 36–39 mmol/mol (5.4–5.7%)] and 2.6% at an HbA_{1c} value of 10.9% per Diabetes Control and Complications Trial [high control limit 85–107 mmol/mol (9.9–11.9%)].

Point-of-care HbA_{1c} samples were analysed by immunoassay using the DCA 2000®+ Analyzer (previously Bayer Healthcare, Elkhart, IN, USA, now Siemens Healthcare Diagnostics, Deerfield, IL, USA). All sites used identical protocols for calibration, control and testing procedures. In addition, all sites obtained almost exclusively the same lots for low and high control solutions and assay cartridges. Reference range for point-of-care HbA_{1c} was 23–39 mmol/mol (4.3–5.7%) [assay range 4–130 mmol/mol (2.5–14.0%)]. The coefficient of variation was 5.6% for the low control [control limit 25–49 mmol/mol (4.4–6.6%)] and 6.0% for the high control [control limit 70–116 mmol/mol (8.6–12.8%)].

For both HPLC and point-of-care determinations, change in HbA_{1c} over time was calculated by two methods: (1) change from initial to final HbA_{1c} (ΔHbA_{1c}) and (2) growth modelling with annualized slope calculation (ΔHbA_{1c} /year). Change in HbA_{1c} was categorized as improved (decrease of ≥ 0.5% or negative slope), no change (± 0.4% of initial HbA_{1c} or slope = 0) or worsened (increase of ≥ 0.5% or positive slope). We also determined the proportion of participants achieving age-specific HbA_{1c} targets recommended by the American Diabetes Association (for ≤12 years old, HbA_{1c} < 8%; for ≥ 13 years old, HbA_{1c} < 7.5%) by each assay.

Analyses included Pearson correlations, linear mixed models, *t*-tests and χ^2-tests using SAS 9.2 software (SAS Institute, Cary, NC, USA). Growth modelling, assuming linearity with a short follow-up period, provided annualized slope calculations. Data are presented as means ± SD (range) or percentages. *P*-values < 0.05 were considered statistically significant.

Results

A total of 121 young persons (29–31 young persons/site) with Type 1 diabetes comprised the sample. Patients had a mean age of 12.2 ± 1.6 years and a mean duration of diabetes of 5.5 ± 3.2 years. Fifty per cent of the young persons were male and 27% represented ethnic/racial minorities.

There were 450 paired point-of-care HbA_{1c} and HPLC HbA_{1c} samples with a median of four pairs/patient (mean 3.7 ± 0.6 pairs). Initial mean point-of-care HbA_{1c} and HPLC HbA_{1c} values were 65 mmol/mol (8.1 ± 1.2%) and 68 mmol/mol (8.4 ± 1.4%) ($P < 0.0001$), respectively, and final mean values were 68 mmol/mol (8.4 ± 1.4%) and 73 mmol/mol (8.8 ± 1.6%) ($P < 0.0001$), respectively (see Table 1). Point-of-care HbA_{1c} values ranged from 33 to 130 mmol/mol (5.2–14.0%) and HPLC HbA_{1c} values ranged from 33 to 147 mmol/mol (5.2–15.6%). Only one point-of-care HbA_{1c} and six HPLC HbA_{1c} results were ≥ 14%. In cross-sectional analyses, the 450 paired samples were highly correlated ($r = 0.97$, $P < 0.0001$). Correlation by visit across sites (n = 109–118) and within site across visits (n = 102–120) were equally high (r = 0.94–0.98, $P < 0.0001$).

In longitudinal analyses, mean ΔHbA_{1c} from initial to final visit was 0.3 ± 1.1% (range −2.7 to 4.1%) for point-of-care HbA_{1c} and 0.4 ± 1.2% (−3.9 to 4.5%) for HPLC HbA_{1c}. Point-of-care HbA_{1c} and HPLC HbA_{1c} change categories were discordant for ΔHbA_{1c} in 21% of patients (n = 26) ($P < 0.0001$) (Fig. 1). In seven patients, point-of-care HbA_{1c} improved while HPLC HbA_{1c} showed no change. In four patients, point-of-care HbA_{1c} worsened while HPLC HbA_{1c} showed no change. In 10 patients, point-of-care HbA_{1c} showed no change while HPLC HbA_{1c} worsened. In five patients, point-of-care HbA_{1c} showed no change while HPLC HbA_{1c} improved. Discordant ΔHbA_{1c} classification occurred across sites and the entire HbA_{1c} range.

Mean ΔHbA_{1c}/year was 0.4 ± 1.5% (−5.4 to 4.8) for point-of-care HbA_{1c} and 0.4 ± 1.6% (−6.9 to 5.2) for HPLC HbA_{1c}. Point-of-care HbA_{1c} and HPLC HbA_{1c} were discordant for ΔHbA_{1c}/year in 18% of patients (n = 22) ($P < 0.0001$). In 11 patients, point-of-care HbA_{1c}

improved while HPLC HbA_{1c} worsened. In 10 patients, point-of-care HbA_{1c} worsened while HPLC HbA_{1c} improved. In one patient, point-of-care HbA_{1c} worsened while HPLC HbA_{1c} showed no change.

Because of the negative bias of the point-of-care HbA_{1c} assay compared with the HPLC HbA_{1c} assay, at initial visit, 41% (n = 40) and 31% (n = 38) of patients achieved age-specific HbA_{1c} targets by point-of-care HbA_{1c} and HPLC HbA_{1c}, respectively. At final visit, 37% (n = 43) and 28% (n = 34) achieved targets by point-of-care HbA_{1c} and HPLC HbA_{1c}, respectively. At initial visit, one patient attained the goal by HPLC HbA_{1c} but not by point-of-care HbA_{1c} and, at final visit, three patients attained the goal by HPLC HbA_{1c} but not by point-of-care HbA_{1c}. There was similar misclassification in 20% (n = 24) of patients, demonstrating a 10% change from initial to final HbA_{1c} by the two assay methods.

Discussion

Consistent with previous studies, point-of-care HbA_{1c} and HPLC HbA_{1c} values were highly correlated in cross-sectional analyses. The strong cross-sectional correlations between point-of-care HbA_{1c} and HPLC HbA_{1c} assays have been demonstrated by others and support the utility of point-of-care HbA_{1c} in clinical care [4,7–9]. DirecNet investigators showed high cross-sectional correlations (r = 0.94, $P < 0.001$) between point-of-care HbA_{1c} values (using DCA 2000®+) and HPLC HbA_{1c} values (performed by a central laboratory), although their point-of-care HbA_{1c} values were biased significantly higher than the HPLC HbA_{1c} values [7]. Interestingly, our HPLC HbA_{1c} values were biased consistently higher than point-of-care HbA_{1c} results. However, the bias does not alter our assessment of discordance in change in HbA_{1c} over time between assays, although the bias does account for much of the difference in proportions of patients achieving HbA_{1c} target values.

In longitudinal analyses, change in HbA_{1c} from initial to final visit showed similar means and standard deviations by point-of-care HbA_{1c} or HPLC HbA_{1c}. When classifying by change ≥0.5%, 21% of patients were discordant between point-of-care HbA_{1c} and HPLC HbA_{1c}. We selected to define change in HbA_{1c} from initial to final by a difference of ≥ 0.5%, as any result within 0.4% of the previous value might be considered within the assay's error range [17]. Using slope calculations, we found discordance between point-of-care HbA_{1c} and HPLC HbA_{1c} in 18% of patients.

Our population was diverse (27% minority) and offered a wide range of HbA_{1c} values, supporting the potential for generalizability. In addition, our study aimed to reduce variability in point-of-care HbA_{1c} measurements by standardizing the lots used across sites. If such care had not been taken, it is possible we might have encountered greater discordance in point-of-care HbA_{1c} results compared with the HPLC HbA_{1c} results [18].

Clinical trials often declare a priori outcomes that include absolute or relative change in HbA_{1c} from baseline to endpoint [10]. For example, a multi-centre trial might compare the proportion of patients who demonstrate a change in HbA_{1c} of ≥ 0.5% or relative change in HbA_{1c} of ≥ 10% in order to assess alteration in risk for microvascular complications as reported by the Diabetes Control and Complications Trial [5].

Our findings suggest that assessment of absolute HbA_{1c} change may not be different for point-of-care HbA_{1c} compared with HPLC HbA_{1c}. However, classification of patients by discrete cut-off values differs between point-of-care HbA_{1c} and HPLC HbA_{1c} determinations in one out of five patients followed longitudinally, resulting in potential misclassification of individual patient outcomes. These data support a need for a central reference laboratory for longitudinal observations in multi-site clinical research studies that include categories of HbA_{1c} change in addition to mean HbA_{1c} outcomes.

Acknowledgments

This work was supported by the intramural research programme of the National Institute of Child Health and Human Development (NICHD), NIH grants P30DK036836 and T32DK007260, the Maria Griffin Drury Pediatric Fund, the Katherine Adler Astrove Youth Education Fund and the Charles H. Hood Foundation. The following investigators and institutions made up the steering committee of the Family Management of Childhood Diabetes multi-site trial: Jill Weissberg-Benchell PhD, Grayson Holmbeck PhD (Children's Memorial Hospital, Chicago, Contract N01-HD-4-3363); Barbara Anderson PhD (Texas Children's Hospital, Houston, Contract N01-HD-4-3362); Tim Wysocki PhD, Amanda Lochrie PhD (Nemours Children's Clinic, Jacksonville, FL, Contract N01-HD-4-3361); Lori Laffel MD MPH, Deborah Butler MSW, Lisa Volkening MA (Joslin Diabetes Center, Boston, MA, Contract N01-HD-4-3364); Tonja Nansel PhD, Ronald Iannotti PhD (NICHD, Bethesda, MD); Cheryl McDonnell PhD, MaryAnn D'Elio (James Bell Associates, Arlington, VA, Contract N01-HD-3-3360).

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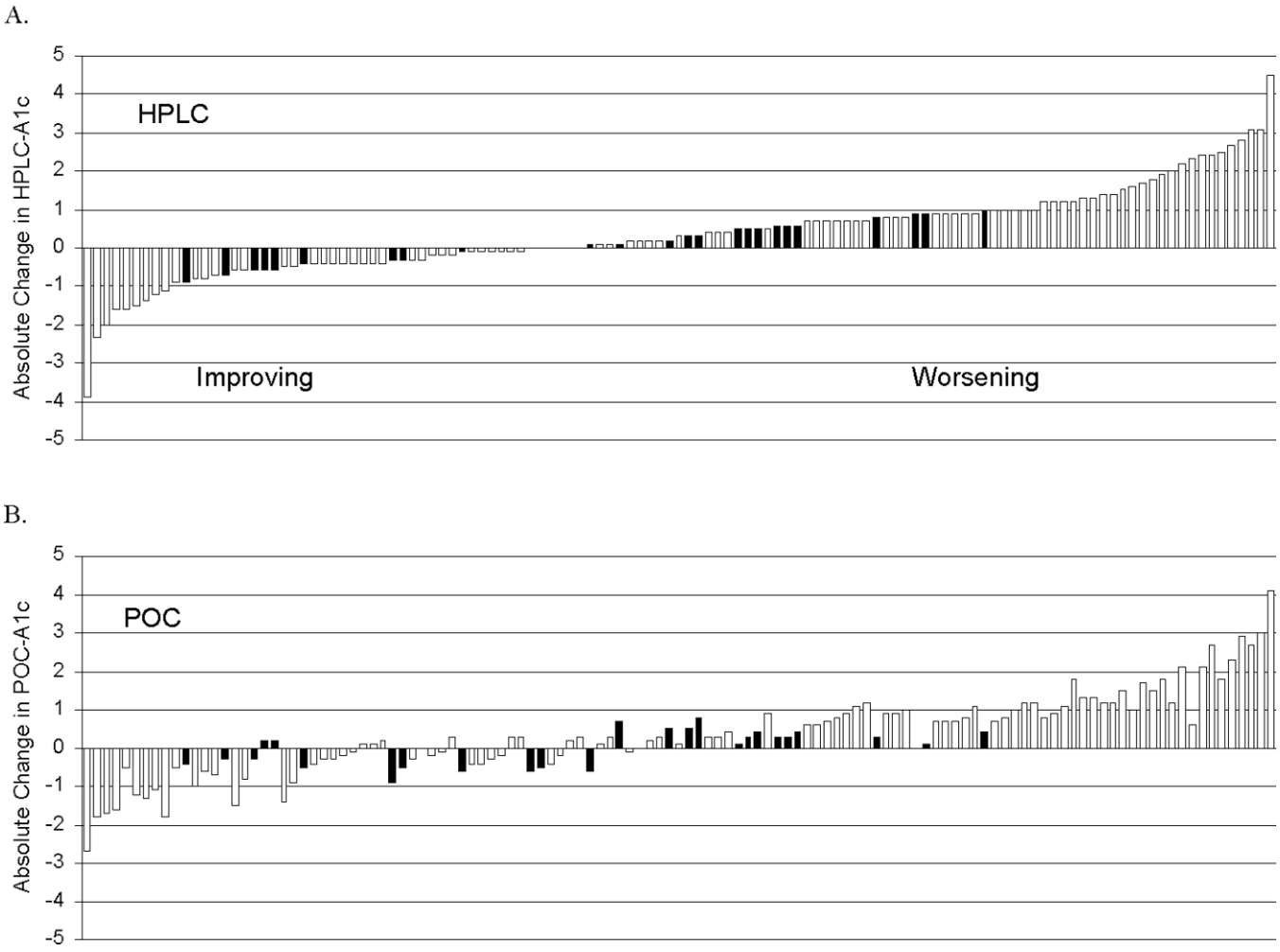

Figure 1.

Change from initial to final HbA_{1c} for HPLC HbA_{1c} (a) and point-of-care HbA_{1c} (b). In both figure parts, patients are rank ordered according to change in HPLC HbA_{1c}. Discordant patients are noted with darker bars.

Table 1

Comparison of HbA_{1c} values obtained by HPLC and point of care*

	Point-of-care HbA_{1c} (%)	**HPLC HbA_{1c} (%)**	**Correlation**	***P*-value**
Initial HbA_{1c} (*n* = 121)	8.1 ± 1.2 65 (40–104)	8.4 ± 1.4 68 (38–113)	0.97	< 0.0001
Final HbA_{1c} (*n* = 121)	8.4 ± 1.4 68 (38–130)	8.8 ± 1.6 73 (38–147)	0.97	< 0.0001
Absolute ΔHbA_{1c} (*n* = 121)	0.3 ± 1.1	0.4 ± 1.2	0.93	< 0.0001
Slope (ΔHbA_{1c}/year) (*n* = 121)	0.4 ± 1.5	0.4 ± 1.6	0.91	< 0.0001

*HbA_{1C} data presented as % with standard deviation and in mmol/mol with range.