Research: Care Delivery

HbA$_{1c}$ determination from HemaSpot$^\text{TM}$ blood collection devices: comparison of home prepared dried blood spots with standard venous blood analysis

J. M. Hall$^1$, C. F. Fowler$^2$, F. Barrett$^3$, R. W. Humphry$^4$, M. Van Drimmelen$^2$ and S. M. MacRury$^5$

$^1$Division of Rural Health and Wellbeing, Institute of Health Research and Innovation, University of the Highlands and Islands, Centre for Health Science, Inverness, UK, $^2$Department of Biochemistry, Blood Sciences, Raigmore Hospital, Inverness, UK, $^3$Highland Clinical Research Facility, NHS Highland, Centre for Health Science, Old Edinburgh Road, Inverness, UK, $^4$Epidemiology Research Unit, Scotland’s Rural College, An Lochran, Inverness Campus, Inverness, UK and $^5$Institute of Health Research and Innovation, University of the Highlands and Islands, Centre for Health Science, Inverness, UK

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Abstract

Aim To assess the clinical performance and patient acceptance of HemaSpot$^\text{TM}$ blood collection devices as an alternative blood collection method.

Methods Adult men and women with any type of diabetes, routinely carrying out self-monitoring of blood glucose were recruited ($n = 128$). Participants provided a venous blood sample and prepared two HemaSpot dried blood spots, one at clinics and one at home. HbA$_{1c}$ analysis was by Tosoh G8 high-performance liquid chromatography. Participants also completed a questionnaire.

Results Strong linear relationships been HbA$_{1c}$ levels in dried blood spots and venous blood were observed and a linear model was fitted to the data. Time between dried blood spot preparation and testing did not impact the model. Participants were accepting of the approach: 69.2% would use this system if available and 60.7% would be more likely to use this system than going to their general practitioner.

Conclusions The combination of a robust desiccating dried blood spot device, home sample preparation and return by post produces HbA$_{1c}$ data that support the use of a time-independent linear calibration of dried blood spot to venous blood HbA$_{1c}$. A robust remote sample collection service would be valuable to people living with diabetes in urban areas who are working or house-bound as well as those living in remote or rural locations.

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Introduction

The benefits of good blood glucose control in preventing long-term complications of diabetes are well documented [1]. Complications, arising from poor blood glucose control over extended periods, place an economic burden on health services and significantly reduce health-related quality of life in people with diabetes [2,3].

Ongoing blood glucose control is assessed by regular measurement of HbA$_{1c}$, with several laboratory methods available for use, with fresh blood obtained using either venepuncture or fingerprick with collection in capillary tubes. Point-of-care instruments are now available for measuring HbA$_{1c}$ levels in fresh capillary blood [4].

In the Scottish Highlands (NHS Highland Health Board area), HbA$_{1c}$ determinations are performed centrally in Inverness using ion-exchange high-performance liquid chromatography (HPLC) analysis (Tosoh G8 HPLC analyser, Tosoh Bioscience, Tokyo, Japan) on venous blood samples collected locally at general practitioner practices. If there is no recent HbA$_{1c}$ result, DCA Vantage point-of-care instruments (Siemens Healthcare GmbH, Erlangen, Germany) are used at hospital appointments.

Current sampling methods are acceptable in terms of HbA$_{1c}$ determination; however, the use of venepuncture with centralized testing is not providing users in the NHS...
Highland area with an acceptable approach, as evidenced by the frequency with which HbA1c results are not available at clinical appointments.

Individualized HbA1c targets should be agreed and regularly reviewed at diabetes appointments with clinicians and lifestyle and/or medication changes discussed with the aim of optimizing HbA1c levels. The value of diabetes appointments where HbA1c levels are not available is greatly diminished. For hospital-based appointments, point-of-care instruments are available for the immediate determination of HbA1c levels. However, the vast majority of people with diabetes (those with uncomplicated Type 2 diabetes) are managed in the community by general practitioners, where point-of-care instruments are not generally available. In the NHS Highland Health Board area, the cost of HbA1c analysis is borne by secondary rather than primary care, so the costs and maintenance implications of general practitioner-based point-of-care instruments are not straightforward.

Method and convenience of place of collection and timeliness of results are potential factors that impact the availability of HbA1c results at appointments and consequently impact the opportunity for discussion of HbA1c levels and targets.

In line with recognition by the UK and Scottish governments that ‘patients need to be empowered to manage their care’ [5,6], the long-term aim of our approach is for people with diabetes to be able to take responsibility for sending off their own blood samples and for results to be sent directly to them so that they can attend review appointments having had the opportunity to reflect upon their latest HbA1c result and what it might mean for them in terms of their individual HbA1c target. To address this aim we have identified a robust blood sampling device (HemaSpot, Spot on Sciences, Austin, TX, USA) for preparing dried blood spots (DBS), which has the potential to fulfil the requirements of our overall approach.

HemaSpot blood collection devices comprise a robust plastic wallet enclosing an eight-bladed filter paper surrounded by desiccant (Fig. 1). A protective cover allows blood application through a central hole. The device is designed to absorb two hanging drops of blood, equivalent to about 65–105 μl of blood.

The use of filter papers for collection of DBS is accepted as an alternative method of blood collection for a variety of applications [7] as they are simple to prepare, have low collection and transportation costs, and are safer and more acceptable to study participants [8].

A systematic review identified 17 studies using DBS for HbA1c [9], and two other related studies have recently been published [10,11]. Variation and bias increase with increasing time between sample preparation and testing have been observed, meaning that even when HbA1c can be calibrated against standard venous HbA1c, calibration needs to consider the time between sample preparation and testing.

A laboratory-based study previously carried out in our laboratory compared HbA1c analysis of laboratory-prepared HemaSpot DBS (n = 40) with HbA1c values obtained from fresh capillary blood. A strong correlation between HbA1c from DBS and fresh capillary blood was observed, suggesting that HemaSpot devices have the potential to be used as an alternative to current blood collection methods if they are well calibrated using a linear model and DBS are tested within 3 days of preparation (see Table S1).
The purpose of the current study was to assess the clinical performance and user acceptability of DBS prepared using HemaSpot devices by people with diabetes at home, as an alternative blood sample collection method for HbA1c determination.

Methods

Recruitment

Participants (n = 128) were recruited when they attended their routine diabetes clinic appointments in Inverness. It was anticipated that this number of participants would provide as a minimum the recommended 100 returned home-prepared DBS samples for the purposes of comparison [12].

Adult men and women, aged 18–75 years, with any form of diabetes and regularly carrying out self-monitoring of blood glucose, were included in the study. Pregnant women and patients receiving renal replacement therapy were excluded.

All participants gave written informed consent. NHS research ethics approval was obtained (16/NW/0214).

While attending diabetes clinics, venous blood samples were taken for routine HbA1c analysis. Under the guidance of a research nurse, participants prepared DBS from fingerprick blood using HemaSpot blood collection devices by applying blood from a hanging drop of blood until the filter paper in the device was visibly filled. HemaSpot devices were closed immediately after blood application and stored at 4°C until analysis.

Participants were given a home pack that included a DBS preparation kit, questionnaire and information about HbA1c. Freepost envelopes were provided for the return of home-prepared DBS and questionnaires. Participants were asked to post their DBS on the day of its preparation.

Questionnaire

A five-point Likert scale 17-item questionnaire assessed each participant’s experience of preparing DBS, their thoughts on a remote HbA1c service and their views regarding the information provided about HbA1c.

HbA1c analysis

HbA1c analyses were performed using HPLC (Tosoh HPLC 723-G8 analyser, Tosoh Bioscience) using a cation exchange TSKgel Variant HSi column. The column was calibrated to the International Federation of Clinical Chemistry recommendation using Tosoh calibrators. Lyphocheck Diabetes bi-level controls (Bio-Rad Laboratories, CA, USA) were used daily, with coefficient of variation of 2% for the low control [mean of 33 mmol/mol (5.2%)] and 0.9% for the high control [mean of 78 mmol/mol (9.3%)].

Blood from DBS samples was eluted by placing one HemaSpot filter blade in 1 ml hemolysis/wash solution for 2 hours at ambient temperature. For analysis, 4 μl of eluate were aspirated by the analyser before injection onto the column. DBS were stored at 4°C in the laboratory. Processing and analysis was performed within 4 days of preparation.

Chromatograms were assessed visually using the G8 operator’s manual specifications for results acceptability, with guidance from the software flags.

Data analysis

Data analysis was carried out using IBM SPSS versions 19/20 for Windows (IBM Corporation, NY, USA), R and Excel software (Microsoft Corporation, WA, USA). Correlation between sample collection methods was investigated using Pearson coefficient and regression analysis. Agreement and bias between sample collection methods was investigated using Bland-Altman plots. Statistical significance was determined at the 5% level.

Covariates that were considered to be potential confounders were tested separately to one another within the general linear model and as a full interaction with the main predictor variable (home result) to assess whether a confounder was affecting the relationship (i.e. the calibration) between the home result and the venous reading. Nested models (with and without the additional covariate) were tested for statistical significance using an F-test (using the function ‘anova ()’ in R).

Results

Participant characteristics

Participant characteristics are presented by type and duration of diabetes (Table 1). More women (61.3%) than men with Type 1 diabetes and more men (69.0%) than women with Type 2 diabetes participated; however, the overall numbers of men (n = 53) and women (n = 51) participants were similar.

Blood samples available

HbA1c results were available for 127 venous blood samples, 125 clinic and 104 home-prepared DBS. Minimum and maximum times between home DBS preparation and testing were 1 and 4 days, with 38.5, 43.3, 16.3 and 1.9% of samples tested on day 1, 2, 3 and 4, respectively.

HbA1c analysis

HbA1c from both home- and clinic-prepared DBS exhibited strong correlations with venous HbA1c (R^2 values close to 0.98) (Fig. 2). There was a significant difference between the clinic and home DBS relationships with venous blood. We have excluded the time between sample preparation and HbA1c analysis as a potential source of the difference. Early transfer of clinic-prepared DBS to storage at 4°C differs from...
home DBS treatment immediately after preparation; however, we have not been able to confirm or exclude this as a reason for the difference observed.

The mean bias of home DBS compared with venous blood across the measurement range was +4.27 mmol/mol (+0.39%). A plot of the absolute difference against the mean of venous and home DBS HbA1c indicates that the absolute difference increases with the mean of the pair (Fig. 3), suggesting that while home DBS HbA1c results may not be used directly as equivalent to venous results, they may be successfully calibrated against one another. A general linear model was used to establish a calibrating relationship between home DBS results and venous results. Diagnostic plots supported the assumption of normality among residuals and did not suggest heterogeneity of variance, supporting the use of this model.

The model fitted is:

\[
[HbA1c_{\text{Venous}} = 1.18[HbA1c_{\text{HomeDBS}} - 7.5(\text{mmol/mol})]
\]

\[
[HbA1c_{\text{Venous}} = 1.18[HbA1c_{\text{HomeDBS}} - 0.69(\%)].
\]

The model allows prediction of venous blood HbA1c levels from DBS HbA1c results. Concordance values were 100, 92.5 and 96.6% between venous and predicted values from home DBS for HbA1c values of <48 mmol/mol (<6.5%), 48–64 mmol/mol (6.5–8%) and >64 mmol/mol (>8%), respectively.

The model holds only for the range of HbA1c values in the study sample [35–115 mmol/mol (5.4–12.7%)] and when HbA1c analysis from HemaSpot is performed using a Tosoh G8 Analyser.

A number of covariates were individually tested to assess how they affected the calibration using a set of nested linear models with each of the variables added separately to the main model (Table 2). Of the covariates tested, only a laboratory factor covariate (with laboratory staff carrying out the test as a proxy) statistically significantly affected the results.

**Questionnaire**

One hundred and ten (86%) questionnaires were returned. Of these, 101 had a corresponding home DBS sample. The majority (99.1%) of respondents found the instructions easy to use and 83.5% found it easy to get their DBS sample in the

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**Table 1** Description of study population for whom both venous and home dried blood spots HbA1c levels were available

| Type of diabetes | n    | Age (years) | Duration of diabetes (years) |
|------------------|------|-------------|-----------------------------|
|                  |      | Mean  | Minimum | Maximum | Mean  | Minimum | Maximum |
| Type 1           |      |       |         |         |       |         |         |
| Women            | 38   | 48.8  | 19      | 71      | 26.8  | 3       | 60      |
| Men              | 24   | 44.8  | 19      | 71      | 19.3  | 0.1     | 44      |
| Total            | 62   | 47.3  | 19      | 71      | 23.9  | 0.1     | 60      |
| Type 2           |      |       |         |         |       |         |         |
| Women            | 13   | 55.6  | 31      | 69      | 12.0  | 2       | 20      |
| Men              | 29   | 64.0  | 39      | 84      | 14.0  | 0.3     | 44      |
| Total            | 42   | 61.4  | 31      | 84      | 13.4  | 0.3     | 44      |
| Total population | 104  | 53.0  | 19      | 84      | 19.6  | 0.1     | 60      |

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**FIGURE 2** Home and clinic prepared dried blood spots (DBS) HbA1c plotted against venous HbA1c. Home DBS: solid symbols, dotted line. Clinic DBS: open symbols, dashed line.
post on time. Obtaining enough blood, blood application to the device, and deciding when there was enough blood on the device were less easy (Table 3).

When asked if they would use the system if it was available, 69.2% of respondents reported they would, while 61.7% agreed that they would be more likely to use a DBS system than making an appointment with their practice nurse. A similar percentage (60.7%) responded that they would have a preference for using this system at home compared to having blood taken at their general practitioner’s surgery.

Sixty per cent of respondents agreed that they would be more likely to have their HbA1c test performed if the system was available, while 50.0% of respondents felt that using a system like this would help them to feel more in control of their diabetes management. The majority (88.0%) of respondents found the information provided about HbA1c interesting and 81.5% found the information useful.

**Discussion**

The principal finding from the study is that HemaSpot DBS prepared by study participants at home and analysed using the Tosoh G8 system produce clinically acceptable HbA1c results when the DBS method is calibrated to Tosoh G8-determined venous HbA1c results using a general linear model. Time between sample preparation and testing did not significantly affect the calibration up to 4 days. For this analysis, the unbalanced nature of the number of observations in each ‘bin’ (i.e. the number of days between sampling time and testing) is not ideal, but it does not violate any of the assumptions in a general linear model such as this, it merely reduces the statistical power of the test.

A statistically significant effect on calibration was observed for the laboratory factor covariate tested (Table 2), where laboratory personnel were used as a proxy. For example, as a consequence of logistics, there may have been a relationship between personnel and the day, or time of day, on which a sample was tested. It is also possible that a type I error has occurred (given that five statistical hypotheses were tested, there is an estimated 23% chance of a type I error). In favour of the hypothesis that a type I error may have occurred is the observation that for each of the particular proxies the additive and interaction terms affecting the calibration relationship all had confidence intervals encompassing zero, i.e. no individual proxy appears to be statistically or

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**Table 2** The effect of the addition of potential covariates on top of the base model of the venous reading (dependent variable) regressed against the home result (the independent variable). Each additional covariate was added separately and as a full interaction with the home result. Each nested pair of models (without covariate and with) were compared using an analysis of variance. For each nested pairwise comparison of models the dataset used was the full dataset, less any observations that had missing data for either the home result or the added covariate. For further details see Table S2

| Additional covariate                              | P-value for full interaction cf. base model |
|--------------------------------------------------|--------------------------------------------|
| Own lancet (Yes = 27, No = 74)                   | 0.40                                       |
| Type of diabetes (Type 1 = 64, Type 2 = 42)      | 0.47                                       |
| Sex (F = 52, M = 53)                             | 0.11                                       |
| Time between sampling and testing (N = 105) [days (n): 1 (39), 2 (47), 3 (17) and 4(2)] | 0.30                                       |
| Laboratory factor covariate (A = 15, B = 38, C = 1, D = 2, E = 17, F = 13, G = 3, H = 16) | 0.016                                      |
Several HbA1c DBS studies have been published [10,11,13–15] with analysis by turbidimetric inhibition immunoassay [13,16–18], HPLC analysis [10,11,15,19,20] and affinity chromatography [21,22]. A systematic review and meta-analysis by Affan et al. [9] reported that, although results from venous and DBS were different, there was close agreement (meta-analysis regression equation: \[\text{HbA1c}_{\text{DBS}} = 0.9553 \times \text{HbA1c}_{\text{venous}} + 0.2566 \; (\%)\]) between venous and DBS samples, except when analysis was by affinity chromatography [9]. Slope and intercept ranges in the meta-analysis were 0.88–1.25 and 0.002–1.8%, respectively. Our model slope and intercept fit within these ranges; however, the model is only valid when used with the measurement method used in our study.

In vitro glycation of haemoglobin and degradation of HbA1c during storage have been suggested as possible reasons for differences observed between DBS and fresh blood samples [13,23]. Our results show increasing bias as HbA1c increases, which supports the in vitro glycation theory due to increased blood glucose levels (and hence in vitro glycation) associated with higher HbA1c levels.

Precision of the DBS sample elution and analysis method was assessed by repeat analysis of high and low quality control samples that had been applied to filter papers and eluted using the DBS sample elution and analysis protocol described. Coefficient of variation were comparable to coefficient of variation reported for fresh blood analysis, suggesting that minimal error is introduced due to DBS sample elution and analysis protocols.

Both venous blood collected in EDTA tubes [11,14,16,18,19,24] and fingerprick capillary blood [10,13,15,17,20–22] have been used to prepare DBS on filter paper, with drying times ranging from 20 minutes to overnight reported [22], before placing the DBS in a storage bag or envelope. The HemaSpot device has no requirement for a pre-drying step.

With the exception of two previous studies [10,13], DBS have been prepared by healthcare professionals or researchers. For routine, remote monitoring of HbA1c, a DBS approach needs to be evaluated in the hands of the end user. Our findings show acceptable clinical results when DBS were prepared by users.

The stability of HbA1c on DBS has been a concern, with an indication that a time-dependent calibration for estimating venous HbA1c levels from DBS is required [15,16]. Our findings suggest that with the HemaSpot device a single calibration could be used for samples tested up to 4 days after preparation.

In agreement with our findings, high patient satisfaction with a potential DBS HbA1c monitoring system was reported in The Netherlands [13]. Although participants in our study reported that the instructions were easy to follow, several participants experienced difficulties with blood application and in deciding when there was sufficient blood on the device; their comments included ‘I don’t think I got enough blood into

| I found… | Easy or very easy to use (%) | Neither easy nor difficult (%) | Difficult or very difficult (%) |
|----------|-----------------------------|-------------------------------|------------------------------|
| …following the instructions (n = 108) | 99.1 | 0 | 0.9 |
| …using the lancet provided (n = 94) | 89.4 | 8.5 | 2.1 |
| …getting my sample in the post on time (n = 109) | 83.5 | 7.3 | 9.2 |
| …getting enough blood (n = 109) | 50.5 | 21.1 | 28.4 |
| …applying the blood to the device (n = 108) | 44.5 | 22.2 | 33.3 |
| …deciding when I had applied enough blood (n = 109) | 56.9 | 20.2 | 22.9 |

| Would use if available (n = 107) | 69.2 | 11.2 | 19.6 |
| More likely to use than making an appointment with practice nurse (n = 107) | 61.7 | 15.0 | 23.3 |
| Prefer to use this system at home compared with having blood taken at general practitioner’s (n = 107) | 60.7 | 17.8 | 21.5 |
| More likely to have HbA1c test done (n = 107) | 35.8 | 15.0 | 49.2 |
| Help feel more in control of my diabetes (n = 106) | 50.0 | 22.6 | 27.4 |
| Prefer to have pack sent to them by post (n = 105) | 66.7 | 15.2 | 18.1 |
| Happy to collect pack from general practitioner (n = 104) | 51.0 | 19.2 | 39.8 |
| Found information sheet about HbA1c interesting (n = 108) | 88.0 | 10.2 | 1.8 |
| Found information sheet about HbA1c useful (n = 108) | 81.5 | 16.7 | 1.8 |
| HbA1c information sheet detail about right (n = 109) | 83.5 | 14.7 | 1.8 |
| Would like HbA1c information sheet to be more detailed (n = 107) | 28.0 | 32.7 | 39.3 |

Table 3 Analysis of questionnaire responses to questions relating to the experience of using and potential use of the HemaSpot, and the information provided about HbA1c. The total number of responses to each question (n) is shown in the left hand column.
the device’ and ‘[it] does take a bit of work to “fill” the
device to the edges’. However, concern about sufficient filling
was not reflected in the results, where a strong correlation
between venous and DBS HbA1c results was observed. The
difficulties reported could be overcome by the inclusion of
photographs of sufficiently and insufficiently filled devices
with the instructions to give patients confidence that they are
providing an adequate amount of blood for analysis. Additional tips on blood application could also be incorpo-
rated.

A number of participants felt that they would still prefer to
have an appointment at their general practitioner’s practice,
because they had other tests carried out at the same time and
valued the time spent with their healthcare professional. One
participant wrote: ‘When visiting the nurse for an HbA1c I
also get my blood pressure, weight, and feet checked and the
opportunity for questions and instructions/guidance from the
nurse. I would miss this testing at home.’ The introduction of
a remote monitoring service for HbA1c needs to consider not
only what might be gained by this approach, but also what
patients might lose through a lack of contact with healthcare
professionals.

The provision of information about HbA1c was welcomed
by participants. The opportunity to provide simple clear
information about HbA1c and its importance in the manage-
ment of diabetes should be considered in any remote HbA1c
monitoring approach.

The combination of a robust desiccating DBS device, home
sample preparation and return by post, to our knowledge has
not been reported for HbA1c, and provides the opportunity
to introduce a remote sample collection service that would be
equally valuable for people living with diabetes in urban
areas who are working or house-bound, as well as for those
living in remote or rural locations.

The observation that the time between sampling and
testing did not significantly affect the linear model indicates
that use of the HemaSpot device might enable a single model
to be adopted which is independent of the time between
preparation of the DBS and the day of testing.

Further studies are planned to assess the performance,
acceptability and service delivery options for HemaSpot DBS
prepared by people with uncomplicated Type 2 diabetes
whose diabetes management is supported solely by general
practitioner practices.

The health economics of introducing a remote HbA1c
monitoring service using HemaSpot devices needs to be
assessed, taking into consideration both the immediate
impacts on costs and the longer term costs associated with
complications.

Study limitations

Some limitations of this study should be noted. First,
participants were all regularly carrying out self-monitoring
of blood glucose and so were familiar with obtaining drops
of capillary blood. The wider community with diabetes will
have a similar familiarity, so this is a population in which the
model derived in the study would need to be validated prior
to practical application. Second, only one batch of Hema-
Spot devices was available to evaluate over the period of the
study, so it was not possible to assess the impact of batch to
batch variation. Third, the study focussed only on analysis of
HbA1c using the Tosoh HbA1c analyser, the method used in
the laboratory where routine HbA1c analyses for the Scottish
Highlands region are performed. Fourth, the difference
observed between clinic-prepared and home-prepared DBS
remains unexplained and warrants further investigation.
Finally, further exploration of the observed laboratory factor
effect is needed.

Clinical implications

HbA1c monitoring plays a pivotal role in preventing compli-
cations of diabetes and therefore in achieving as good a
quality of life as possible. The HemaSpot blood collection
device provides an opportunity for improvements in rates of
HbA1c monitoring and more effective consultations.
Increased participation by the community with diabetes in
self-management would be anticipated.

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Competing interests

None declared.

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**Supporting Information**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** The deviation of HbA1c results collected on filter paper from routine dilute blood samples (mmol/mol) and the relationship (with confidence intervals) between filter paper and dilute sample HbA1c results.

**Table S2.** The effect of the addition of potential covariates on the top of the base model of the venous reading (dependent variable) regressed against the home result (the independent variable). Each additional covariate was added separately and as a full interaction with the home result. Each nested pair of models (without covariate and with) were compared using an analysis of variance. For each nested pairwise comparison of models the dataset used was the full dataset, less any observations that had missing data for either the home result or the added covariate.