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Volumetric absorptive microsampling at home as an alternative tool for the monitoring of HbA_{1c} in diabetes patients

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Abstract

Background: Microsampling techniques have several advantages over traditional blood collection. Dried blood spot (DBS) sampling and blood collection with heparinized capillaries are the standard techniques. Volumetric absorptive microsampling (VAMS) is a novel technique that collects a fixed volume of blood by applying an absorbent tip to a blood drop. In the present study we explored the feasibility of HbA_{1c} monitoring with VAMS sampling at home and analysis in the laboratory.

Methods: Diabetic patients were enrolled in this study during consultation with the endocrinologist. A venous (adults) or capillary (children) sample was taken for immediate HbA_{1c} analysis. DBS (n = 1) and dried VAMS (n = 2) were collected at home and sent to the laboratory. For 25 pediatric patients one VAMS was collected during consultation for immediate analysis (without drying), referred to as "wet VAMS". HbA_{1c} analyses were performed on a Tosoh HLC-723 G8 high-performance liquid chromatography (HPLC) analyzer.

Results: The median time between sampling at home and analysis was 3 days. Results of HbA_{1c} in dried VAMS showed a poor agreement with venous/capillary blood collected in hospital (concordance correlation coefficient CCC = 0.72). Similar observations were found with standard DBS. An excellent agreement was obtained between HbA_{1c} results on wet VAMS (CCC = 0.996) and standard blood samples. Patients experienced VAMS and DBS as easy and convenient to use.

Conclusions: Utilizing equipment standard available in the clinical laboratory, the use of home-sampled dried VAMS and DBS is not a reliable tool for the monitoring of HbA_{1c}. However, perfect agreement between HbA_{1c} measured on wet VAMS and capillary microsamples was obtained.

Keywords: diabetes; dried blood spots; hemoglobin A_{1c}; home-sampling; volumetric absorptive microsampling.

Introduction

Measurement of hemoglobin A_{1c} (HbA_{1c}) is essential for the diagnosis and monitoring of glycemic control both in type 1 and in type 2 diabetes mellitus [1]. The HbA_{1c} result reflects the average glycemia of the last 100–120 days and is a predictive value for the development of micro- and macrovascular diabetes complications [2].

Diabetes mellitus has become a major public health problem causing significant morbidity and mortality. Especially type 2 has become a worldwide epidemic, both in adults and in children. The prevalence of diabetes mellitus is further increasing. In 2000 the global prevalence of diabetes was approximately 2.8% and for 2030 this is estimated to be 4.4%, an increase of total patients from 171 million to 366 million [3]. This implies a growing need for HbA_{1c} analyses, as it is the biomarker for diagnosis and follow-up of diabetes mellitus.

Microsampling refers to the collection of a small amount of blood (typically < 50 µL), most often via a fingerprick. It is considered more patient-friendly, given its

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minimal invasiveness. Also for HbA_{1c} analysis, capillary microsampling (using precision capillaries) is increasingly being applied as an alternative to traditional venous blood collection, especially in pediatric patients. Several studies have demonstrated a good agreement between venous and capillary HbA_{1c} results in diabetic out-patients [4, 5], indicating that capillary and venous HbA_{1c} results can be used interchangeably, although slight differences might be present in some populations [6].

Apart from liquid blood microsamples, also dried blood spots (DBSs) have been used for HbA_{1c} analysis, with overall a good agreement between HbA_{1c} results in liquid and dried blood samples [7]. It should be noted, however, that in the majority of these studies the DBS samples are artificial laboratory samples, generated by spotting ethylenediaminetetraacetic acid (EDTA)-whole blood onto filter paper [8–15]. Only in a few studies a comparison was made between HbA_{1c} in traditional venous samples and capillary DBS that were collected from patients at home [16–19]. While in DBS-based methods, the hematocrit, the volume of blood spotted on the DBS card, the spot homogeneity and capillary-venous differences can influence the derived results [20], these effects are unlikely to affect the HbA_{1c} result, since the latter is a ratio (mmol/mol) [21]. DBS microsampling offers the advantage that it can be performed by non-phlebotomists, implying that a patient does not have to go to the hospital for a venepuncture but can perform the sampling at home [22]. Following drying, the DBS can be sent via standard postal services under ambient conditions to the analyzing laboratory prior to consultation. This allows the actual HbA_{1c} value of the patient to be available at the time of consultation, allowing insight into the most recent data. As a result, better adaptation of the treatment and glycemic control is to be expected. Volumetric absorptive microsampling (VAMS) is a novel microsampling technique advocated as an alternative to classical DBS sampling to eliminate the volumetric bias associated with the latter. An absorbent polymeric tip, attached to a handle, collects a fixed volume of blood (approximately 10 µL) by capillary action. Compared to DBS, the VAMS procedure is similar and even ensures further simplification of sampling and processing in the laboratory [23–25]. To the best of our knowledge, no study has already evaluated the use of VAMS for HbA_{1c} analysis.

We explored the possibility of using VAMS as an alternative sampling procedure for HbA_{1c} monitoring in a home sampling context, utilizing standard equipment for HbA_{1c} analysis of routine liquid blood samples. To this end, we compared the HbA_{1c} data from VAMS and DBS samples to those obtained following traditional liquid venous or capillary blood sampling. We also investigated the possibility of using wet VAMS, which were collected in the hospital and immediately sent to and analyzed in the laboratory after collection, as an alternative sampling method in pediatric practice. Lastly, we also investigated the user friendliness of the different sampling techniques and which one would be preferred by patients to be used in future.

Materials and methods

Participants

This study was approved by the Ethics Committee of Ghent University Hospital. Diabetes patients (n = 100; 50 adults and 50 children) were recruited during consultation at the endocrinology department of Ghent University Hospital. The participants gave written informed consent prior to participation. Samples from 86 patients were obtained. Only one exclusion criterion was applied: samples received 6 days after home sampling were excluded (one adult at 10 days and one child at 12 days). All patients were diagnosed with type 1 or type 2 diabetes. Characteristics of the participants are summarized in Table 1. There was one pediatric patient who only sent the VAMS samples back, without a DBS sample.

Specimen collection

This study took place from May to September 2015. For adults, a venous K_2-EDTA-blood (Venosafe 4 mL VF-054SDK, Terumo, Leuven, Belgium) sample, and for children a capillary blood sample in a heparinized capillary (Minicaps, Hirschmann, Neckartenzlingen, Germany) was collected in the hospital for routine HbA_{1c} measurement. Samples were sent at ambient temperature to the laboratory via a

Table 1: Characteristics of the patient cohort.

	All	Adults	Children
Patients, n	84	40	44
Age (years) median (IQR)[a]	16.5 (12.0–51.8)	54.0 (43.0–64.0)	12.0 (10.0–16.0)
Gender (males/females)	57 M/27 F	28 M/12 F	29 M/15 F
Hospital sampled HbA_{1c}[b] (mmol/mol) median (IQR)	56 (49–66)	59 (49–67)	56 (50–63)

[a]IQR, interquartile range; [b]hospital sampled: for adults a venous K_2-EDTA-blood sample and for the children a capillary blood sample in a heparinized capillary tube.

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pneumatic tube system and were analyzed upon arrival. These samples were considered as reference when comparing with the dried blood matrices, and are referred to as "hospital sampled blood".

Following some explanation about the sampling, a home sampling kit including a sampling brochure (see Supplemental data, Figure 1) and a small survey was handed over to the participants. They were asked to spot a filter paper and fill two VAMS samples with capillary blood obtained by a finger prick. Pediatric patients were asked to use their own lancet (used for glycemia measurements). Adult participants received a disposable lancet (BD Microtainer Contact-Activated Lancet: large flow, Becton, Dickinson and Company, Franklin Lakes, NJ, USA), although they were also allowed to use their own lancet. The second VAMS was collected to check the reproducibility of this novel sampling technique, allowing calculation of the imprecision of the VAMS sampling and the HbA_{1c} analysis on these sampling systems. DBS were collected as described by Wilhelm et al. [26]. Blood drops were directly collected from the fingertip onto Whatman 903 Specimen Collection Paper (Whatman-GE Healthcare Life Sciences, Buckinghamshire, UK). The VAMS devices (Mitra, Phenomenex, Torrance, CA, USA) were filled according to the company instructions. In brief, capillary blood was obtained by piercing a finger using a lancet. After wiping off the first blood drop, the tip of the VAMS sample was applied to the surface of the drop of blood. Upon turning completely red, the tip was held in place for an additional 2 s to ensure that it was completely filled. All samples were then dried at room temperature for at least 2 h, and one DBS and two VAMS were sent to the laboratory at ambient (non-controlled) temperature in a padded (bubble-wrap) envelope in the presence of a desiccant (Minipax absorbent packets, Sigma-Aldrich, St. Louis, MO, USA). We did not specifically inquire if the sampling at home was performed independently by the child. The HbA_{1c} results from these dried blood matrices were compared with the reference.

The pediatric population was further split into two subgroups. Twenty-five patients were instructed to collect at home one DBS and two dried VAMS (the same procedure as for the adults). For the second half of the pediatric patients, one VAMS was collected during consultation together with the heparinized capillary tube sample. This VAMS sample was capped with a shell (we used a pipet tip) to delay the drying process, and was immediately (within 1 h) analyzed in the laboratory. These samples are referred as "wet VAMS". These patients were asked to fill one dried VAMS and one DBS at home.

HbA_{1c} analysis

Both liquid blood and dried blood analyses were performed on a Tosoh HLC-723 G8 automated ion-exchange high-performance liquid chromatography (HPLC) analyzer (Tosoh Bioscience, Tokyo, Japan). All results were expressed in the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) units. HbA_{1c} is separated from other hemoglobin components by the differences in ionic interactions with the cation exchange group on the column. Within-run and between-run imprecision of the analyzer was ≤ 0.5%, measured with a low (30 mmol/mol) and high (84 mmol/mol) control. Imprecision is expressed as the obtained coefficient of variation (CV).

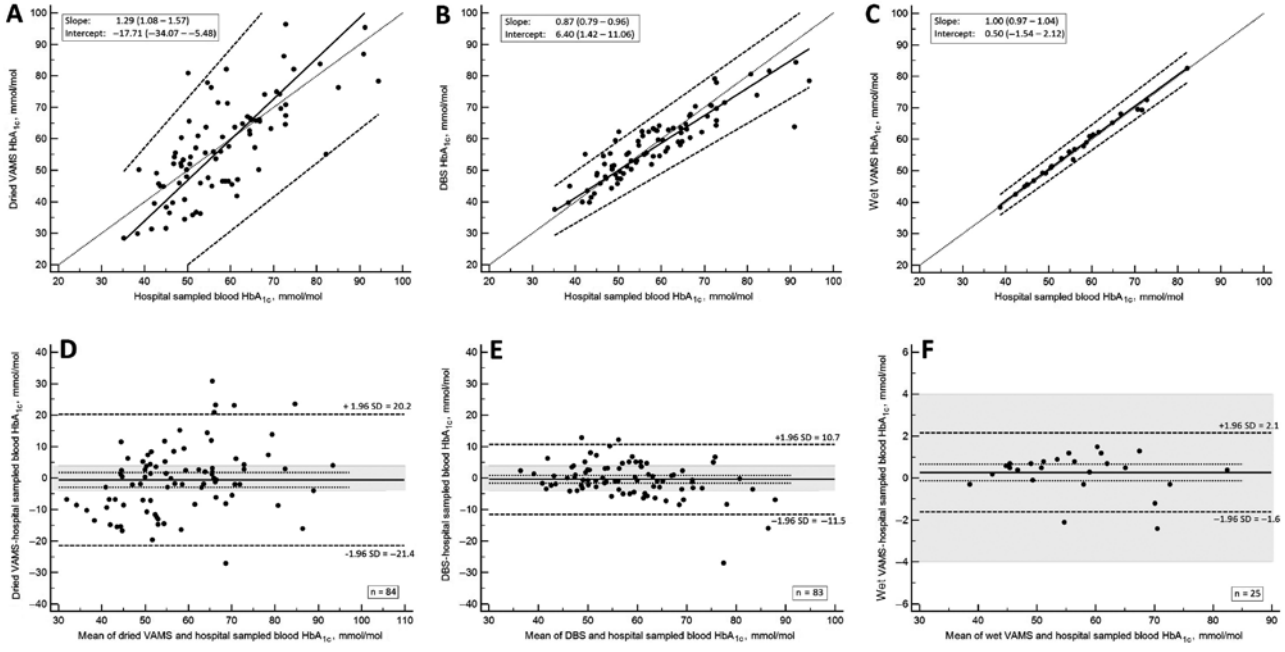

Figure 1: Passing-Bablok regression analyses of HbA_{1c} measurements in dried VAMS (A), DBS (B) and wet VAMS (C) relative to the capillary/venous hospital blood samples.
The solid line represents the regression line with its 95% CIs indicated as dashed lines. Also the line of equality is shown as a dotted line. The slope and intercept are shown on the graphs with their 95% CIs in parentheses. Bland-Altman plots of HbA_{1c} measurements in dried VAMS (D), DBS (E) and wet VAMS (F) relative to the capillary/venous hospital blood samples. The solid line represents the average difference with its 95% CI indicated as dotted lines. The dashed lines are the lower and upper limit of agreement (±1.96 SD). The gray area indicates the allowable error according to RCPA quality requirements (±4 mmol/mol). Note the differences in scale between D–E and F.

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The acceptance criteria for the HbA_{1c} analyses on VAMS and DBS were based on the Royal College of Pathologists of Australasia (RCPA) quality requirements [27] and on unit-specific acceptance criteria defined by Weykamp et al. which are based on biological variation [28]. Throughout this article, the RCPA requirements were used as acceptance criteria (unless otherwise specified). These RCPA requirements state that if the target HbA_{1c} result is ≤ 86 mmol/mol, an allowable error should be within ± 4 mmol/mol. If the target HbA_{1c} result is > 86 mmol/mol, the measured value on VAMS and DBS should be within ± 5% limits of the target value [27].

Singlicate disks of 3 mm diameter were punched out of the DBS with a Harris Uni-Core Micropunch (Agilent Technologies, Santa Clara, CA, USA) and placed in 1 mL cups. Two hundred and fifty micro liter de-ionized water was added to the cup for extraction. The tips from the VAMS samples were separated from the body and placed in 1 mL cups. Four hundred micro liter de-ionized water was added to the cup for extraction. The punches and the tips were both vortexed (Vortex V-1 Plus, Biosan, Riga, Latvia) for twice 30 s. The choice for twice 30 s was based upon preliminary experiments, where we compared twice 30 s with 10 min vortexing (data not shown). The extracts were transferred to cups and analyzed on the Tosoh G8.

Data analysis

Data were analyzed using Excel software (Microsoft Corporation, Redmond, WA, USA) and MedCalc Statistical Software (MedCalc Software bvba, Ostend, Belgium). Medians, interquartile ranges (IQRs) and CVs were calculated. The IQR is defined as the range between the 25th and 75th percentile. The Spearman's rank correlation coefficient ρ and the concordance correlation coefficient (CCC) were calculated. CCC quantifies the agreement between two measures of the same continuous variable. Following McBride GB, the CCC results were interpreted as: > 0.99, excellent agreement; 0.95–0.99 substantial agreement; 0.90–0.94, moderate agreement and < 0.90, poor agreement [29]. Wilcoxon and Mann-Whitney statistical tests were used. $p < 0.05$ was used for statistical significance. Passing-Bablok regression analyses were performed and Bland-Altman plots were constructed to compare HbA_{1c} results from both sampling techniques. Box and whisker plots were drawn to indicate the influence of the time between sampling and analysis on the HbA_{1c} results.

Results

Prospective cohort study

For the evaluation of the HbA_{1c} results, adults and children were treated as a single cohort. The median time between sampling and analysis in the laboratory was 3 days, ranging from 1 to 6 days (two samples of 10 and 12 days were excluded).

A CV of 5.80% was obtained for the duplicate measurements of dried VAMS samples. The 95% confidence interval (CI) of the slope of the Passing-Bablok regression of the duplicate measurements contains 1 and the 95% CI of the intercept contains 0 (see Supplemental data, Figure 2).

Median HbA_{1c} measured in dried VAMS was 56 mmol/mol (n = 84; IQR 46–67 mmol/mol), in DBS 58 mmol/mol (n = 83; IQR 50–63 mmol/mol), and in hospital sampled blood (for adults a venous blood sample and for children a capillary blood sample collected in a heparinized capillary) 56 mmol/mol (n = 84; IQR 49–66 mmol/mol). Results

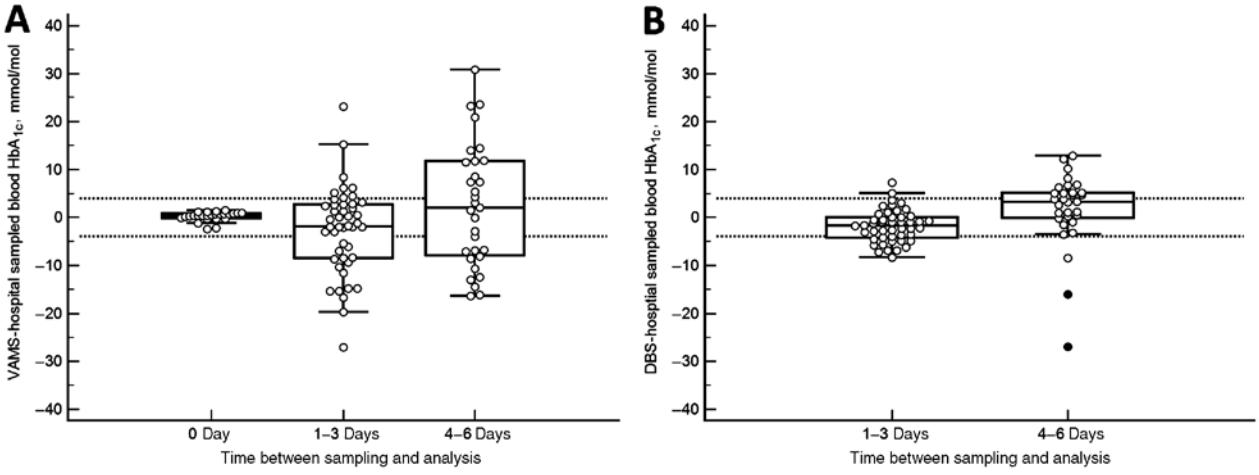

Figure 2: Box and whisker plots indicating the distribution and influence of time between sampling and analysis on HbA_{1c} results in VAMS (A) or DBS (B).
The samples analyzed 0 days after sampling in figure A are the wet VAMS. The boxes represent medians and interquartile ranges, the minimum and maximum are indicated by the flags. The dotted lines represent the allowable errors according to RCPA quality requirements (± 4 mmol/mol). Outside and far outside values are shown as separate points. An outside value (indicated with an open circle) is defined as a value that is smaller/larger than the lower/upper quartile minus/plus 1.5 times the IQR. A far outside value (indicated with a closed circle) is defined as a value that is smaller/larger than the lower/upper quartile minus/plus 3 times the IQR.

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of HbA_{1c} in dried VAMS and DBS were not significantly different from results of HbA_{1c} obtained in the hospital acquired blood samples (Wilcoxon test $p > 0.05$). However, an unacceptably high number of samples did not meet the quality requirements, either using RCPA, IFCC or national glycohemoglobin standardization program (NGSP) acceptance criteria (Table 2). Agreement between HbA_{1c} results in dried VAMS and in venous/capillary hospital samples was poor ($\rho = 0.73$, $p < 0.0001$; CCC = 0.72). Passing-Bablok regression curves and Bland-Altman difference plots for these analyses are shown in Figure 1A and D. A poor agreement between DBS and capillary/venous hospital samples was obtained ($\rho = 0.90$, $p < 0.0001$; CCC = 0.88). Passing-Bablok regression curves and Bland-Altman plots for the difference between HbA_{1c} measured in DBS and venous/capillary blood samples are shown in Figure 1B and E. The same conclusions could be drawn when adults and children were treated as two single cohorts (data not shown).

Next, the influence of the time between sampling and analysis was investigated. The data were split in analyses performed 1–3 days or 4–6 days after sample collection. For the samples analyzed after 1–3 days (n = 46) a higher agreement with the capillary/venous hospital samples was obtained (VAMS CCC = 0.74; DBS CCC = 0.94) than for those that were analyzed after 4–6 days (n = 31) (VAMS CCC = 0.65; DBS CCC = 0.76). The absolute differences between dried VAMS and capillary/venous HbA_{1c} results analyzed after 1–3 days were not significantly different from those analyzed after 4–6 days (Mann-Whitney test $p > 0.05$). For the DBS, the absolute differences of the samples analyzed after 1–3 days were significantly different from the differences with the DBS analyzed after 4–6 days (Mann-Whitney test $p = 0.0001$). This is graphically represented in Figure 2. Although samples analyzed within 3 days resulted in a high agreement, the results did not meet the RCPA criterion, as is evident from Figure 2.

Wet versus dried VAMS

The median HbA_{1c} value measured in wet VAMS of the second pediatric cohort was 56 mmol/mol (n = 25; IQR 49–62 mmol/mol). The median of the corresponding capillary blood samples (collected in heparinized capillaries in the hospital) was 56 mmol/mol (IQR 49–62 mmol/mol). All the 25 wet VAMS fulfilled the RCPA quality requirements. An excellent agreement between the wet VAMS and capillary blood samples was obtained ($\rho = 0.995$, $p < 0.0001$; CCC = 0.996). Figure 1C and F shows the Passing-Bablok regression curve for the comparison of wet VAMS to capillary blood samples and the Bland-Altman difference plots.

User friendliness

Responses to questionnaires (see for detailed results Supplemental data, Table 1) indicated that most participants experienced the VAMS and DBS sampling technique as very convenient to use. When asked for the preferred sampling technique, VAMS clearly stood out, in both adults and children.

Discussion

Here, we present the results of a home sampling study for HbA_{1c} monitoring. Starting point for this study was to evaluate whether, utilizing the equipment available in a standard clinical laboratory, dried blood samples collected from VAMS and DBS can be applied for routine HbA_{1c} monitoring. Although median HbA_{1c} from VAMS and DBS did not differ significantly from venous/capillary HbA_{1c}, it is clear that in many instances the obtained HbA_{1c} value deviated substantially from that obtained by whole blood sample analysis. This can at least partially be explained by the employed technique, in which limitations are imposed regarding separation and integration of the different hemoglobin peaks on the chromatogram. Indeed, from our experiments it became evident that by aging of the dried samples the hemoglobin components are converted to oxidized and degraded hemoglobin [30]. The effect of this process on the HbA_{1c} results appeared unpredictable, which had a negative impact on the analytical reliability of the measurements in these dried samples.

Table 2: Numbers of dried VAMS and DBS samples meeting the acceptance criterion.

Applied acceptance criterion	RCPA [27]	Unit-specific [28]	
		NGSP units	IFCC units
Total error criterion	±4 mmol/mol	±0.50%	±5 mmol/mol
Number of dried VAMS meeting the criterion	33/84 (39%)	38/84 (45%)	35/84 (42%)
Number of DBS meeting the criterion	51/83 (61%)	64/83 (77%)	59/83 (71%)

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These variable effects on the HbA_{1c} results become more pronounced as the time between collection and analysis of the dried sample is increasing. This was demonstrated by the higher agreement with the whole blood results in dried blood samples analyzed after 1–3 days than those analyzed after 4–6 days. This time effect on DBS analyses was also observed by Mastronardi et al. [18]. If the dried samples would be analyzed with the IFCC reference method [31], a better agreement and less deviating results are expected due to less interference of the formed hemoglobin derivates. However, this would be at the expense of simplicity in the routine clinical laboratory. Therefore, we made a compromise and chose the routine HPLC method for the home sampling study because of the high throughput capability and the existing integration in the routine laboratory. Indeed, to our opinion, amongst the requirements for a successful, straightforward implementation of an alternative sampling strategy as an extra clinical tool is the compatibility with current standard procedures and equipment.

A poor correlation and agreement between HbA_{1c} results from dried VAMS and traditional sampling was observed. Also the Passing-Bablok regression showed a significant proportional difference. HbA_{1c} results on dried VAMS deviated from the liquid blood results, with only 39% of the samples having an error lower than the 4 mmol/mol limit. The differences shown on the Bland-Altman plot for VAMS were highly variable and the limits of agreement were wider than those for DBS. DBS performed in general better than VAMS, although the agreement between HbA_{1c} results in DBS and whole blood samples was also only moderate to poor ($\rho = 0.90$ and CCC = 0.88), with too many DBS that had a bias and did not meet the RCPA acceptance criterion. Passing-Bablok regression revealed a slope of 0.87. In contrast to Mastronardi et al. [18], it was in our case not possible to use a bias correction equation as the results demonstrate a large distribution in both directions. Interestingly, Fokkema et al. applying longer DBS elution times and utilizing immunoturbidimetry instead of automated ion-exchange HPLC, found a better concordance (Pearson correlation $r = 0.987$) between HbA_{1c} measured in home sampled DBS and venous blood samples [19]. This might be owing to a higher robustness of immunoturbidimetry towards the hemoglobin conversions that take place upon drying. However, in Belgian laboratories, HbA_{1c} analysis via immunoturbidimetry is greatly outnumbered by automated ion-exchange HPLC, as the latter method has the advantage that it can be included in automated hematology systems. Moreover, ion-exchange HPLC is able to flag and visualize hemoglobin variants in the chromatograms.

In conclusion, when envisaging HbA_{1c} measurements by standard automated ion-exchange HPLC and when taking into account the RCPA criterion, both DBS and VAMS failed. Notably, the results from dried VAMS were even considerably worse than those obtained from DBS, rendering the application of dried VAMS for routine home sampling for HbA_{1c} measurements by standard clinical equipment, as applied here, clinically unacceptable. We hypothesize that the different constitution of VAMS (a hydrophilic polymer with wide pores) and filter paper (a multi-layered network of cotton fibers) may result in a better oxygenation – and hence more hemoglobin conversion- in the former.

To our knowledge, this is the first study that evaluated the feasibility of HbA_{1c} measurements in VAMS in a real-life home sampling scenario. A large number of samples were obtained from both adult and pediatric diabetic patients, as both are the target population for measurement of HbA_{1c} in these dried blood matrices. Previous studies were limited to adult participants. All but one (Fokkema et al.) of the few published studies that made a comparison between HbA_{1c} in traditional venous samples and capillary DBS collected from patients did not evaluate true patient-based sampling in a non-controlled environment (i.e. non-supervised sampling at home). As outlined above, the results from the Fokkema study cannot be fully compared with ours, as they used immunoturbidimetry, which is less commonly applied (at least in Belgium) [19]. In other studies, DBS were either collected by phlebotomists in a controlled examination center [16], by study examiners at the patient's home [17] or by patients themselves in a controlled research setting [18]. In our study, the participants collected, after clear instructions, VAMS and DBS on their own at home. The samples were shipped to the laboratory via standard postal services. Hence, given our study design, a higher pre-analytical variation was expected. These aspects may explain why we obtained a somewhat lower correlation coefficient ($\rho = 0.90$) for the comparison between DBS and whole blood samples than another study ($r = 0.96$) that also used an ion-exchange HPLC technique to compare HbA_{1c} in venous blood and capillary DBS [16]. Incompletely filled VAMS and small DBS were also analyzed and included in the study. We suspect that this has no influence on the results since HbA_{1c} is a ratio measure.

For the dried VAMS technique, an imprecision of 5.80% was obtained on duplicate measurements. This is higher than the desirable specification for imprecision (0.9%) based on biological variation [32]. However, when bearing in mind the deviating results of the dried VAMS and the unpredictability of aging on the HbA_{1c} results

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when analyzed via automated ion-exchange HPLC, VAMS can be considered as a reproducible sampling technique. Hence we hypothesize that the deviations are caused by the pre-analytical variability in the dried samples. In comparison, for the venous samples an imprecision of 0.40% and Bland-Altman ± 1.96 standard deviation (SD) limits of agreement of −0.59 and 0.53 were obtained on duplicate measurements (n = 30).

In this study we also evaluated the usability of the VAMS and DBS sampling and the donor's preference for the various collection techniques. In general, VAMS and DBS sampling were found easy and convenient to use. Most of the participants preferred the VAMS sampling technique instead of the traditional blood sampling. This was even more striking in the pediatric population. We also showed that children are able to follow printed sample collection instructions.

Further research is necessary to evaluate how dried VAMS (and DBS) may be rendered more suitable to HbA_{1c} measurement with the commonly applied ion-exchange HPLC routine clinical analyzers. A possibility is to pre-immerse the tips of the VAMS in an anticoagulant (EDTA) or antioxidant, such as ascorbic acid, which can theoretically prevent the oxidation of hemoglobin. Although it is not known whether or not the blood truly coagulates on VAMS or DBS samples, in our preliminary study we used EDTA-anticoagulated venous blood for generating dried samples and those results deviated less than those from the patient cohort (data not shown). Interesting to note in this respect is that also a better correlation was observed in the studies that used the artificial laboratory samples (anticoagulated venous blood spotted on filter papers).

To evaluate the intrinsic potential of VAMS for HbA_{1c} measurement, we also analyzed VAMS samples immediately (i.e. within an hour) after collection. This yielded an excellent agreement with HbA_{1c} results in liquid capillary blood samples ($\rho = 0.995$ and CCC = 0.996). Hence, this type of sampling can be used as an alternative for the rather inconvenient and cumbersome capillary microsampling technique used in pediatric practice. Moreover, the simplicity of VAMS might be combined with other approaches, allowing home sampling without the need for drying-thereby overcoming the issue of hemoglobin interconversions. Recently introduced systems for capillary blood sampling include a capillary tube that after blood collection is transferred into a sample preparation vial containing a hemolyzing solution, which has a stabilizing effect on HbA_{1c} [33]. Combining VAMS collection with the stabilizing effect of such a solution may render home sampling of HbA_{1c} and analysis with routine equipment a feasible option in the near future.

Conclusions

VAMS is a novel sampling technique allowing simple collection of capillary blood and processing in the laboratory. In this study, we evaluated the feasibility of VAMS as a home sampling tool for the monitoring of HbA_{1c} when utilizing standard equipment (automated ion-exchange HPLC) for the analysis of routine liquid blood samples. Results of HbA_{1c} measured in home sampled dried VAMS showed a poor agreement with the HbA_{1c} measured in these liquid samples. Results were more deviating as the time between collection and analysis of the dried sample was increasing. Yet, the excellent agreement between HbA_{1c} measured on wet VAMS and capillary microsamples shows the intrinsic potential of VAMS. Hence, while in pediatric practice these wet VAMS can be used as an alternative for the more cumbersome glass capillaries, the dried VAMS approach, as applied here, needs further adaptation before becoming clinically acceptable. While both VAMS and DBS were experienced by the patients as convenient microsampling techniques, VAMS was by far the patients' preferred technique.

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