Novel use of menstrual blood for monitoring glycaemic control in patients with diabetes: a proof-ofconcept study

Sara Naseri ^(D), ¹ Ryan Charles Leung Brewster, ² Paul D Blumenthal¹

ABSTRACT

Background Glycated haemoglobin (HbA1c) is the diagnostic and prognostic standard for clinical management of diabetes mellitus (DM). Unfortunately, patient adherence to guidelines for routine testing can be poor and there are significant gender-based disparities in DM management and outcomes. Recent evidence suggests that menstrual blood may be comparable to systemic blood for monitoring of common biomarkers. The objective of the present study was to assess the concordance of HbA1c levels between menstrual and systemic blood in healthy women and women with diabetes of reproductive age.

Methods In this prospective, observational cohort study, we enrolled healthy and diabetic (type 1 and type 2 DM) reproductive-age women (aged \geq 18 and \leq 45 years). Menstrual blood and venous systemic blood specimens were simultaneously obtained at time of menstruation, and analysed for HbA1c levels. Participants selfcollected menstrual blood using a QPad, a novel, modified menstrual pad with an embedded dried blood spot strip.

Results Among 172 participants, 57.6% were healthy and 42.4% had a diagnosis of either type 1 or type 2 DM. There were no significant differences in mean HbA1c values in menstrual and systemic blood across the overall cohort or within the diabetic subgroup. Furthermore, HbA1c levels between blood sources were robustly correlated and demonstrated a significant linear relationship.

Conclusions There is a strong concordance in HbA1c levels between menstrual and systemic blood. Empowered by self-collection technologies, these findings suggest that menstrual blood may serve as a reliable, noninvasive and potentially cost-effective alternative to serum for HbA1c monitoring among reproductive-age women with DM.

Key messages

- In a cohort of healthy women and women with diabetes of reproductive age, levels of glycated haemoglobin (HbA1c) across menstrual and systemic blood were significantly correlated.
- Menstrual blood was self-collected by study participants using a novel menstrual pad modified with dried blood spot technology.
- Menstrual blood has potential utility as a minimally invasive, convenient and cost-effective alternative to systemic blood for routine monitoring of HbA1c in women with diabetes.

INTRODUCTION

glycated For decades. haemoglobin (HbA1c) has been the diagnostic and prognostic standard for primary management of diabetes mellitus (DM).¹ It serves as an index of long-term glycaemic control and a predictive indicator of preventable microvascular and macrovascular complications, making routine monitoring an essential clinical practice.²³ To ensure timely therapeutic adjustments, guidelines advise biannual to quarterly HbA1c assessments, depending on the severity of the disease. Unfortunately, adherence to testing recommendations has been shown to be suboptimal.^{4 5} The current paradigm typically involves multiple clinical visits (eg, for laboratory collection and follow-up consultation). This introduces considerable logistical and financial challenges for patients and potential delays in communicating results.^{6–8} Barriers to compliance may be even higher for lowresource, rural and other vulnerable populations facing decreased healthcare access, competing priorities (eg, childcare) and

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underinsurance.^{9–11} Lack of consistent HbA1c surveillance contributes to poor glycaemic control and, by extension, an increased risk of poor outcomes and disease progression.¹²

Menstrual blood is a complex fluid comprising whole blood, vaginal secretions and cells of the endometrial lining. To date, little is known about its characteristics at a molecular level. Proteomics analyses have revealed a profile similar to systemic blood, along with the presence of clinically relevant indicators of uterine abnormalities.¹³ A recent pilot study demonstrated concordance between menstrual and systemic blood for common biomarkers.¹⁴ HbA1c, among seven other biomarkers, was found to significantly correlate between the two sources. While still preliminary, these results suggest that menstrual blood may be a safe, non-invasive and cost-effective option for screening, diagnostics and monitoring in women and a mechanism to reduce known gender-based disparities in effective diabetes management.¹⁵

To more definitively assess this relationship, we performed a prospective, observational study to characterise the association between HbA1c levels measured in menstrual and systemic blood among healthy women and women with diabetes of reproductive age who regularly menstruate. Menstrual blood specimens were selfcollected with the QPad (Qurasense, Palo Alto, USA), a modified menstrual pad containing a paper-based, dried blood spot (DBS) strip (online supplemental figure 1). The device enabled convenient, non-invasive acquisition and stabilisation of menstrual blood specimens, and subsequent comparison of HbA1c levels with whole blood samples.

METHODS

This was a prospective, observational study of reproductive-aged healthy women and women with diabetes. All research protocols were approved by the Stanford University Institutional Review Board and the Integreview Institutional Review Board (https://integreview.com/aahrpp_accreditation).

Participant recruitment and eligibility criteria

Prospective participants were recruited through physical flyers and social media advertising and underwent a screening telephone appointment to assess eligibility. Major inclusion criteria included women aged between 18 and 45 years old who regularly menstruate. Postmenopausal state and pregnancy were exclusion criteria. Those who were eligible via telephone screening completed in-person screening to provide study materials and signed consent. We recorded basic demographic information and diabetes status (healthy, or clinical diagnosis of type 1 DM or type 2 DM).

Study procedure

All participants were issued with a study kit containing two QPads for menstrual blood self-collection. Participants were instructed to self-collect menstrual blood with the QPad on the second day of their menstrual cycle, which generally corresponded with the highest volume of flow, and schedule a peripheral blood draw within 36 hours. Once saturated, the participant placed the DBS strip in a sample return box provided with the kit, which was returned to the study team on the same day of the venous blood draw.

Venous blood samples were drawn by a mobile phlebotomist (Coast Phlebotomy Services LLC) on the same day that menstrual blood DBS samples were returned. Each participant provided a single menstrual blood and systematic blood specimen for analysis. The systemic blood was then stored at 5°C while the QPad samples were stored at room temperature, in a provided humidity-controlled container, until further processing. Both blood samples were transported to a Clinical Laboratory Improvement Amendments (CLIA)/College of American Pathologists (CAP) Certified Laboratory and DBS analysis specialist, US Specialty (San Diego, CA, USA), for percentage HbA1c levels using a Beckman Coulter Au680 analyser. Participants were compensated with a gift card for completion of the study protocol.

Statistical analysis

Participants with type 1DM and type 2DM were pooled for the purposes of statistical analysis. Mean levels of HbA1c in menstrual and systemic blood were compared with a paired t-test. We used the Pearson correlation test to evaluate the association between systemic and menstrual blood values and fit a least squares regression model to determine the parameters to estimate systemic blood values from those of menstrual blood. The threshold for statistical significance was defined as a p value <0.05. All statistical analyses and data visualisations were performed with R (v4.0.0) with packages ggplot2 (v3.3.0) and dplyr (v0.8.5).^{16–18}

RESULTS

A total of 235 volunteers were consented for the study between April 2018 and May 2019. Menstrual blood and systemic blood specimens were collected from 172 participants (figure 1). Among the cohort, a total of 57.6% were healthy, 13.4% had a diagnosis of type 1 DM and 29.1% had a diagnosis of type 2 DM (table 1). The mean age at enrollment was 32.2 years.

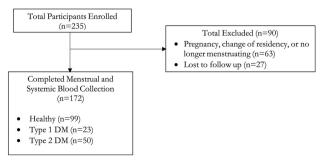


Figure 1 Enrollment of study participants. DM, diabetes mellitus.

Table 1 Participant ch	aracteristics	
Characteristic	Overall (n=172)	Women with diabetes (n=73)
Age (years) (SD)	32.2 (9.17)	36.2 (8.31)
BMI (kg/m ²) (SD)	27.6 (7.69)	32.9 (9.08)
Period length (days) (SD)	5.77 (2.10)	5.98 (3.13)
DM status (n (%))		
Healthy	99 (57.6)	-
Type 1 DM	23 (13.4)	23 (31.5)
Type 2 DM	50 (29.1)	50 (68.5)

BMI, body mass index; DM, diabetes mellitus; SD, standard deviation

There was a statistically significant correlation between menstrual and systemic blood HbA1c levels overall (p<0.001) and in patients with diabetes (p<0.001) (table 2). A sensitivity analysis of individual groups stratified by history of diabetes (healthy, type 1DM, type 2DM) revealed that HbA1c levels were significantly correlated between menstrual and systemic blood in both type 1 (p < 0.001) and type 2 (p < 0.001) DM patients (online supplemental table 2).

Mean HbA1c levels were 6.53% for menstrual blood and 6.50% for systemic blood (online supplemental table 1). There were no statistically significant differences in mean HbA1c between menstrual and systemic blood among the overall cohort (p=0.471)or among the patients with diabetes (p=0.272). Stratifying the diabetic cohort by type, mean HbA1c levels in menstrual and systemic blood were not significantly different for patients with either type 1 (p=0.561) or type 2 (p=0.356) DM. Menstrual blood HbA1c exhibited a significant linear relationship with systemic blood HbA1c (figure 2) (table 2).

DISCUSSION

In this prospective, observational study of healthy women and women with diabetes of reproductive age, we compared the performance of menstrual and systemic blood in measuring HbA1c. Menstrual blood was obtained using a novel, non-invasive collection pad transforming the specimen into a stable, transportable DBS specimen. Among the 172 participants, there were no statistical or clinical differences in mean HbA1c between menstrual and systemic blood, and values across blood sources were significantly

Table 2Mean menhaemoglobin (HbA1c)		ood levels of glycated
Parameter	Overall	Women with diabetes
Systemic blood (%)	6.50 (1.89)	8.02 (2.06)
Menstrual blood (%)	6.53 (2.05)	8.14 (2.29)
Mean difference (%)	0.036	0.121
95% CI of difference	-0.133 to 0.061	-0.336 to 0.096
P value	0.471	0.272
CI, confidence interval.		

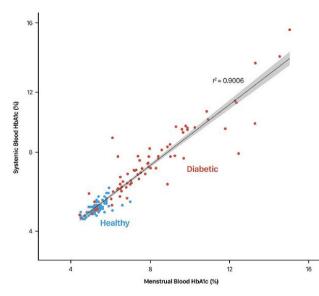
 Table 3
 Correlation and regression analysis for glycated
 haemoglobin (HbA1c) levels in menstrual and systemic blood

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Parameter	Overall	Women with diabetes
Pearson correlation		
Pearson correlation coefficient	0.949	0.914
95% CI	0.932 to 0.962	0.866 to 0.945
P value	<0.001	<0.001
Linear regression		
Coefficient	0.874	0.823
SE	0.022	0.043
P value	<0.001	<0.001
Bold type denotes statiistical signification	ance.	

CI, confidence interval; SE, standard error.

correlated. The strong relationship between blood sources was maintained for the spectrum of normaland diabetic-range HbA1c levels. Our results expand on and corroborate previous pilot analyses, which demonstrate a concordance between menstrual blood and serum for numerous common biomarkers.¹⁴

Self-sampling has emerged as a viable screening and diagnostic approach across numerous clinical domains. Well-validated applications include saliva for ovulation or DNA testing,^{19 20} cervical specimens for human papillomavirus (HPV) testing^{21–23} and, most recently, nasal swabs for COVID-19 testing.^{24 25} These methods address many of the logistical and structural barriers associated with conventional testing such as time limitations and transportation challenges. Moreover, given the convenience and ease of use, they afford patients more autonomy and privacy. HPV self-sampling, for example, has shown to be widely accepted and has significantly expanded the reach of testing programmes to medically underserved populations.²¹⁻²³ We posit that menstrual blood-based testing can carry analogous





practical, clinical and economic value in the context of routine HbA1c monitoring. Indeed, the current testing model - wherein multiple visits are often required for sample collection and follow-up - is inconvenient and costly for patients. It is also prone to delays in communicating results and treatment intensification. Although a different methodology, the early successes of point-of-care technologies highlight the opportunities to advance care delivery and improved outcomes within this system.²⁶⁻²⁸ Perhaps the greatest potential for self-collection lies with low socioeconomic status and minority populations, who bear a disproportionate burden of diabetes-related morbidity and mortality,^{9 29 30} and low- and middle-income countries, where non-communicable diseases are becoming increasingly prevalent.^{31 32}

Importantly, we found that the QPad performed well with respect to sample acquisition, efficiency and processing. Alternative methods for menstrual blood self-collection, including menstrual cups, may be unfamiliar to users and are not typically equipped with mechanisms to efficiently transfer the specimen to a laboratory-ready conveyance or prevent specimen degradation. By contrast, the DBS technology is a widely used approach for blood collection, transport and storage for numerous clinical assays, and the DBS strip embedded in the QPad was reliable for these purposes. While the stability of HbA1c from menstrual blood has not been previously evaluated, studies of DBS approaches using whole blood indicate minimal variation in HbA1c measurement for up to 44 days and at different temperatures.³³ With further validation, the QPad has potential utility to facilitate further investigations and downstream clinical applications involving menstrual blood. The possible indications within sexual and reproductive health issues are broad and span fertility and preconception counselling (eg, follicle-stimulating hormone levels), cancer screening (eg, HPV, ovarian and endometrial cancer biomarkers) and sexually transmitted infection testing (eg, chlamydia, gonorrhoea), among many others.

Novel uses of menstrual blood should be taken in the context of well-described gender disparities in diabetes management and outcomes.¹⁵ Previous research indicates that women with diabetes experience disproportionately higher rates of cardiovascular complications and have poorer adherence to treatment regimens.^{34–36} The causes underlying these differences are poorly understood, but biological, metabolic and psychosocial factors have been implicated.^{37 38} Additional risks are incurred for patients of childbearing age, where poor glycaemic control before or during gestation can result in adverse maternal and neonatal outcomes.³⁹ Altogether, targeted solutions to address the unique barriers to effective diabetes care in women should be prioritised.

There are limitations to the present study. Menstrual and systemic blood specimens were subject to differential storage and transport conditions. An unbroken cold chain was maintained for serum samples from collection to processing, while the QPads were left at ambient temperatures throughout. Until more rigorous testing of HbA1c stability over time is conducted, we will be unable to determine the effect of sample quality loss on the specimens. Another limitation was that participants' demographic information regarding race or ethnicity was not collected, which have been shown to be important factors in HbA1c variability.⁴⁰ That said, there is little reason to suspect that menstrual or serum specimens themselves would behave differently by race or ethnicity.

In summary, leveraging a novel menstrual pad for self-collection, we found a high degree of concordance between HbA1c levels in menstrual blood and systemic blood in healthy women and women with diabetes of reproductive age. Future research is needed to establish menstrual blood-specific reference ranges for HbA1C and other biomarkers and more comprehensively assess both the user experience and the cost-effectiveness associated with QPad usage. This will inform adjustments in the technology to optimise convenience, costs and accuracy. Ultimately, menstrual blood-based testing could become a safe, non-invasive and potentially cost-effective alternative to conventional serum-based approaches to improve primary diabetes screening and management in women. More broadly, our findings open the possibility of transforming the significance of menstrual blood from a reproductive waste product to a valuable clinical tool with the potential to address sex-specific differences in healthcare access and outcomes and reduce menstrual stigma globally.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Institutional review board approvals were obtained and all subjects consented to their participation.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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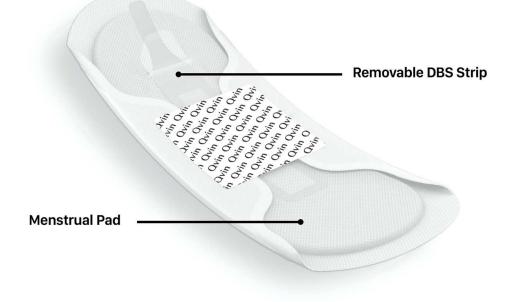
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SUPPLEMENTAL ONLINE CONTENT

Supplementary Figure 1. Composition of the QPad. The QPad is a modified menstrual pad made from 100% organic cotton with an embedded, removable dried blood spot (DBS) strip.
Supplementary Table 1. Mean menstrual and systemic blood levels of HbA1c
Supplementary Table 2. Correlation and regression analysis for HbA1c levels in menstrual and systemic blood, by diabetes status



Supplementary Figure 1. Self-collection of menstrual blood specimens was achieved with the QPad[®] (Qurasense, Palo Alto CA), a modified conventional organic-cotton menstrual pad containing a removable, dried blood spot (DBS) strip. The device enables non-invasive acquisition and stabilization of menstrual blood specimens and was developed with medical grade materials that are commonly used for *in vitro* medical devices and that are FDA, CE or WHO-prequalified.

Supplementary Table 1. Mean menstrual and systemic blood levels of H	lbA1c
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	OVERALL	DIABETIC
Systemic Blood, %	6.50 (1.89)	8.02 (2.06)
Menstrual Blood, %	6.53 (2.05)	8.14 (2.29)
Mean Difference, %	0.036	0.121
95% Confidence Interval of Difference	-0.133 - 0.061	-0.336-0.096
P-value	0.471	0.272

	HEALTHY	TYPE 1 DM	TYPE II DM
Pearson Correlation			
Correlation Coefficient	0.65	0.94	0.91
95% Confidence Interval	0.52-0.75	0.86-0.97	0.84-0.95
P-value	<0.001	<0.001	<0.001
Linear Regression			
Coefficient	0.54	0.72	0.86
Standard Error	0.06	0.06	0.06
P-value	<0.001	<0.001	<0.001

Supplementary Table 2. Correlation and regression analysis for HbA1c levels in menstrual and
systemic blood, by diabetes status