ORIGINAL ARTICLE

Journal of the ASEAN Federation of Endocrine Societies

Discordance between Fasting Plasma Glucose (FPG) and HbA1c in Diagnosing Diabetes and Pre-diabetes in The Malaysian Cohort

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Abstract

Objective. In this present study, we aim to evaluate the accuracy of the HbA1c relative to fasting plasma glucose (FPG) in the diagnosis of diabetes and pre-diabetes among The Malaysian Cohort (TMC) participants.

Methodology. FPG and HbA1c were taken from 40,667 eligible TMC participants that have no previous history of diabetes, aged between 35-70 years and were recruited from 2006 – 2012. Participants were classified as normal, diabetes and pre-diabetes based on the 2006 World Health Organization (WHO) criteria. Statistical analyses were performed using ANOVA and Chi-square test, while Pearson correlation and Cohen's kappa were used to examine the concordance rate between FPG and HbA1c.

Results. The study samples consisted of 16,224 men and 24,443 women. The prevalence of diabetes among the participants was 5.7% and 7.5% according to the FPG and HbA1c level, respectively. Based on FPG, 10.6% of the participants had pre-diabetes but this increased to 14.2% based on HbA1c (r=0.86; P<0.001). HbA1c had a sensitivity of 58.20 (95% CI: 56.43, 59.96) and a specificity of 98.59 (95% CI: 98.46, 98.70).

Conclusion. A higher prevalence of pre-diabetes and diabetes was observed when using HbA1c as a diagnosis tool, suggesting that it could possibly be more useful for early detection. However, given that HbA1c may also have lower sensitivity and higher false positive rate, several diagnostic criteria should be used to diagnose diabetes accurately.

Key words: type 2 diabetes mellitus, fasting plasma glucose, HbA1c, The Malaysian Cohort, diagnosis, population differences

INTRODUCTION

The prevalence of Type 2 diabetes mellitus (T2DM) has been increasing worldwide. It is projected that approximately 300 million people will be diagnosed with T2DM by 2025.[1] Malaysia has also observed tremendous hikes in the number of T2DM. The National Health and Morbidity Survey (NHMS) in 2015 reported that the prevalence of T2DM was 17.5%[2] which was similar to findings from The Malaysian Cohort (TMC) study that showed a prevalence of 16.6%.[3] Based on the latest NHMS in 2019, one in five adults or equivalent to 3.9 million people aged 18 years and above in Malaysia have diabetes.[4] The prevalence of diabetes had increased from 13.4% in 2015 to 18.3% in 2019.[4] Early diagnosis is vital for diabetic patients, hence, intervention and treatment can be commenced immediately to prevent macrovascular or microvascular complications of diabetes.

Fasting plasma glucose (FPG) and oral glucose tolerance test (OGTT) have been used as the primary screening tools to diagnose diabetes.[5] FPG, however, is commonly used in both clinical and epidemiological studies due to the inconsistency of the OGTT results that rely on the 2-hour post glucose load (2HPG) which is also laborious to perform.[6,7] Glycalated hemoglobin (HbA1c) is a form of hemoglobin (Hb), produced by non-enzymatic reaction, chemically linked to a sugar and indicative of increased blood sugar in the body over the past 3-4 months.[8,9] The use of HbA1c in monitoring or controlling the glucose metabolism was proposed by Anthony Cerami and colleagues in 1976.[10] Unlike FBG and 2HPG, HbA1c detection is more convenient and patients do not need to fast overnight. In addition, is more accurate and convenient, with less pre-analytical and analytical variability.

The use of HbA1c to diagnose diabetes has been widely recommended and this is further expedited by the worldwide standardization of the HbA1c measurement.[11] In 2009, the diagnosis of diabetes using HbA1c was proposed by the International Expert Committee[12] and was

ISSN 0857-1074 (Print) | eISSN 2308-118x (Online)
Printed in the Philippines

Received: August 26, 2020. Accepted: June 14, 2021.
Published online first: July 19, 2021.
https://doi.org/10.15605/jafes.036.02.02

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endorsed by both ADA and WHO in 2011.[13] Nonetheless, there is evidence showing that HbA1c level varies between different ethnicities or populations.[14-17] For example, Asians have been reported to have higher HbA1c levels than Caucasians.[18] A recent study on the Vietnamese population by Ho-Pham et al., showed that the prevalence of pre-diabetes was about three times higher using the globally recommended HbA1c level of 6.5% or more as compared to using FPG.[19] The prevalence of diabetes and pre-diabetes based on the HbA1c from the Ho Chi Minh City, Vietnam was 9.7% and 34.6% respectively.[19] In Korea, Hee Kim and colleagues analyzed 35,624 non-diabetic Koreans and 1,491 participants were identified as newly diagnosed diabetes.[20] From these 1,491 participants, 31.6% met the FPG criteria only (≥7.0 mmol/l), 23.5% met HbA1c only (≥6.5%) and 44.9% met both FPG and HbA1c.[20] In Malaysia, Nazaimoon and colleagues studied 4,341 individuals from five zones and based on the World Health Organization (WHO), the prevalence of diabetes was 22.9%, with 10.8% was known diabetes and 12.1% was newly diagnosed diabetes.[16] Using HbA1c of 45 mmol/mol (6.3%) as diagnostic criteria, the prevalence of diabetes was only 5.5%

In this present study, we aim to evaluate the accuracy of the HbA1c relative to fasting plasma glucose (FPG) in the diagnosis of diabetes and pre-diabetes among The Malaysian Cohort (TMC) participants.

METHODOLOGY

Study design, study participants and sample size

This study was derived from the prospective cohort study that consists of 106,527 persons whose data infers that of the Malaysian population based on the Census Malaysia Report of 2000. Furthermore, our previous finding indicated that 16.6% of TMC participants were diabetic.[21] Based on this prevalence, with 95% confidence interval and 80% power of study, the sample size needed for this study is only 214. However, since 40,667 participants were eligible, all participants were included into this study. The study was approved by the Research and Ethics Committee, Universiti Kebangsaan Malaysia (UKM) (FF-205-2007), in accordance with the declaration of Helsinki. Written informed consent was taken from all subjects.

Data collection

Anthropometric measurements recorded for each participant included body mass index (BMI), waist circumference (WC) and waist-to-hip ratio (WHR). Weight and height were obtained using a Seca weight scale (SECA, Jerman) and Harpenden stadiometer (Holtain Limited, UK) respectively. Blood pressure was measured using Omron HEM-907 (Omron Corporation, Japan). All measurements were performed three times and the average measurements were recorded. Each participant was interviewed face-to-face by a trained interviewer. Data obtained included age, gender, ethnicity and history of diabetes and other diseases.

Blood collection and bioanalytical analysis

Peripheral blood samples were collected by venipuncture from each participant after an overnight fasting. Biochemical analysis was performed within 24 hours post-blood collection. The blood sample for HbA1c was collected in the EDTA tube whereas the sample for FPG was collected in the sodium fluoride tube. For full lipid profile (total cholesterol, high density lipoprotein (HDL-c) and low-density lipoprotein (LDL-c), samples were collected using the SST II Advance vacutainer. FPG and full lipid profile were analyzed using the COBAS Integra® 800 (Roche Diagnostics Gmbh, Germany). Quality control was performed using Lyphochek Assayed Chemistry Control from Bio-Rad Laboratories. HbA1c was analyzed using the high-performance liquid chromatography (HPLC) in the Variant™ II Turbo machine (Bio-Rad Laboratories Inc, USA). Quality control was performed using Liquichek™ Diabetes Control form Bio-Rad Laboratories. All analyses were performed according to the protocols recommended by the manufacturer.

Subjects with a FPG concentration greater than or equal to 7.0 mmol/l were classified as having T2DM, those with levels between 6.1–6.9 mmol/L as pre-diabetes and level less than 6.1 mmol/l as normal. For HbA1c, those with values at 6.5% and above were classified as T2DM, values between 6.0-6.4% were deemed to have pre-diabetes and values less than 6.0% defined as normal. As for full lipid profile, total cholesterol levels of more than 5.2 mmol/L were classified as elevated and less than 5.2 mmol/L as normal, HDL more than 1.6 were classified as normal and less than 1.6 as deficient, while LDL less than 1.7 were classified as normal and more than 1.7 were classified as elevated. The tests were performed in an accredited bioanalytical laboratory.

Statistical analysis

The prevalence of diabetes and pre-diabetes was determined by percentage. The differences between groups were assessed using the Chi-square test for categorical data and ANOVA for continuous data. The association and agreement between HbA1c and FBG were assessed by Pearson correlation and Cohen's kappa. The diagnostic test including sensitivity, specificity and accuracy of HbA1c in relative to FBG were determined using MedCalc Software. A *p*-value threshold of 0.05 was used for declaring significance. All analyses were performed using IBM SPSS Statistics 21.

RESULTS

Population characteristics

A total of 40,667 subjects were enrolled in this study with the mean age of 51.8 ± 8.2 years. Table 1 shows the status of pre-diabetes and diabetes according to the FPG and HbA1c levels in three Malaysian major ethnic groups including Malay, Chinese and Indian. Based on the FPG measurement, 10.6% and 5.7% of TMC participants were classified as having pre-diabetes and diabetes, respectively. When the HbA1c level measurement was used, we observed significant increases in the prevalence of pre-diabetes (14.2%) and diabetes (7.5%). There were significant differences ($p<0.001$) between diabetes, pre-diabetes and normoglycaemia using the FPG and HbA1c diagnostic criteria for all characteristics (Table 1).

We also examined the relation between the prevalence of diabetes and ethnicity using both criterions. Using the FPG, we noticed that diabetes was more prevalent among Indians (8.3%), followed by Malay (7.0%) and Chinese (3.2%). The pattern was similar when we employed the HbA1c level measurement as the diagnostic tool. However, we observed that the diabetes prevalence in each ethnic group was higher

Table 1. Subjects characteristics and prevalence of pre-diabetes and diabetes using FPG and HbA1c

Characteristics / Guidelines	Fasting Plasma Glucose			*P*-value	HbA1c (WHO)			*P*-value
	Normal (<6.1 mmol/L)	Pre-diabetes (6.1-6.9 mmol/L)	DM (≥7.0 mmol/L)		Normal (<6.0%)	Pre-diabetes (6.0-6.4%)	DM (>6.5%)	
N (%)	34,063 (83.8)	4,292 (10.6)	2,312 (5.7)		31,829 (78.3)	5,778 (14.2)	3,060 (7.5)	
Age (years), Mean (SD)	51.36 (8.25)	54.45 (7.57)	53.51 (7.75)	<0.001	51.24 (8.27)	53.99 (7.71)	53.62 (7.63)	<0.001
Gender (%)								
Male	12,943 (79.8)	2,128 (13.1)	1,153 (7.1)	<0.001	12,064 (74.36)	2,671 (16.46)	1,489 (9.18)	<0.001
Female	21,120 (86.4)	2,164 (8.9)	1,159 (4.7)		19,765 (80.86)	3,107 (12.71)	1,571 (6.43)	
Ethnicity (%)								
Malays	15,150 (81.5)	2,140 (11.5)	1,309 (7.0)	<0.001	14,200 (76.35)	2,734 (14.70)	1,665 (8.95)	<0.001
Chinese	14,537 (88.5)	1,365 (8.3)	533 (3.2)		13,726 (83.52)	2,014 (12.25)	695 (4.23)	
Indians	4,376 (77.7)	787 (14.0)	470 (8.3)		3,903 (69.29)	1,030 (18.29)	700 (12.43)	
Locality (%)								
Urban	27,377 (84.4)	3,382 (10.4)	1,696 (5.2)	<0.001	25,818 (79.55)	4,432 (13.66)	2,205 (6.79)	<0.001
Rural	6,686 (81.4)	910 (11.1)	616 (7.5)		6,011 (73.20)	1,346 (16.39)	855 (10.41)	
Body mass index								
BMI Mean (SD)	25.58 (4.53)	27.64 (4.64)	28.47 (4.67)	<0.001	25.9 (4.66)	25.98 (4.63)	25.96 (4.67)	0.487
Waist circumference (cm)								
Male								
Mean (SD)	88.29 (10.51)	92.31 (10.38)	95.47 (11.10)	<0.001	0.3 (0.61)	0.3 (0.61)	0.31 (0.61)	0.891
Female								
Mean (SD)	81.76 (11.06)	88.29 (11.15)	90.23 (10.75)	<0.001	1.08 (0.85)	1.1 (0.85)	1.07 (0.85)	0.316
Waist -to-hip ratio								
Male								
Mean (SD)	0.90 (0.06)	0.92 (0.06)	0.94 (0.05)	<0.001	0.13 (0.42)	0.16 (0.45)	0.14 (0.41)	0.050
Female								
Mean (SD)	0.83 (0.07)	0.86 (0.07)	0.88 (0.07)	<0.001	1.37 (0.85)	1.38 (0.85)	1.35 (0.86)	0.700
Blood pressure, FBS and HbA1c								
Systolic blood pressure (mmHg), Mean (SD)	127.30 (18.88)	134.60 (18.91)	136.49 (19.84)	<0.001	129.58 (19.27)	129.77 (19.84)	129.2 (18.8)	0.499
Diastolic blood pressure (mmHg), Mean (SD)	81.58 (11.64)	85.17 (11.47)	86.99 (12.05)	<0.001	76.88 (11.35)	77.03 (11.61)	76.8 (11.27)	0.662
FBS, Mean (SD)	5.30 (0.40)	6.43 (0.25)	9.55 (3.08)	<0.001	5.35 (0.53)	5.84 (0.7)	8.47 (3.17)	<0.001
HbA1c, Mean (SD)	5.51 (0.43)	6.00 (0.57)	8.00 (2.04)	<0.001	5.42 (0.35)	6.14 (0.13)	7.86 (1.74)	<0.001
Fasting blood lipid profile								
Total Cholesterol (mmol/L) Mean (SD)	5.67 (1.06)	5.80 (1.09)	5.99 (1.18)	<0.001	5.65 (1.04)	5.83 (1.12)	5.97 (1.18)	<0.001
HDL, Mean (SD)	1.47 (0.42)	1.31 (0.37)	1.24 (0.33)	<0.001	1.48 (0.43)	1.35 (0.38)	1.25 (0.32)	<0.001
LDL, Mean (SD)	3.57 (0.97)	3.73 (1.03)	3.84 (1.08)	<0.001	3.54 (0.99)	3.73 (1.05)	3.83 (1.07)	<0.001

compared to FPG where 12.43% of Indians were classified as diabetes, followed by Malay (8.95%) and Chinese (4.23%). In addition, the prevalence of diabetes was higher among those in the rural areas compared to the urban population using both FPG and HbA1c criteria (p<0.001).

For the mean systolic blood pressure, the patients with diabetes using FBG, had higher readings compared to normal and pre-diabetes subjects. The mean total cholesterol (TC) and LDL cholesterol levels showed increasing trends as the plasma glucose increases across the glucose tolerance groups using either FPG or HbA1c. Obesity, indicated by the increase in body mass index (BMI), waist circumference and waist hip ratio, is associated with high-risk of developing diabetes. In line with this, we observed that those who have diabetes, diagnosed using either FPG or HbA1c criteria, have larger waist circumference, higher BMI and WHR compared to normal and pre-diabetes subjects (Table 1).

Correlation and concordance between HbA1c and FPG

Of the 3,060 individuals with diabetes according to the HbA1c criteria, only 1,781 (58.2%) were concordantly classified as diabetes based on FPG criteria. Table 2 shows the concordance in the classification of diabetes and pre-diabetes between HbA1c and FPG. Out of 5,778 subjects diagnosed with pre-diabetes based on HbA1c diagnostic criterion, 1,462 (25.3%) had similar diagnosis based on FPG. Using HbA1c alone, pre-diabetes was diagnosed about 30% greater than the FPG, and almost 2-fold for diabetes (Table 1). There was a moderate agreement between the diagnosis of diabetes by HbAIc and FPG (Kappa=0.64, p<0.001), whilst the agreement for pre-diabetes was poor (Kappa=0.19, p<0.001). There was a highly significant correlation between HbA1c and FPG, as shown in Figure 1 (r^2=0.86; P<0.001). The use of the HbA1c level of ≥6.5% to diagnose diabetes led to a sensitivity of 58.2% and a specificity of 98.59%, with a positive predictive value of 77.03% and a negative predictive value of 96.67% compared to FPG (Table 3).

Table 2. Concordance in diagnostic classification between HbA1c and FPG

Diagnosis Based on FBG	Diagnosis Based on HbA1c			Total
	Normal	Pre-diabetes	Diabetes	
Normal	29,534 (92.79)	3,995 (69.14)	534 (17.45)	34,063
Pre-diabetes	2,085 (6.55)	1,462 (25.30)	745 (24.35)	4,292
Diabetes	210 (0.66)	321 (5.56)	1,781 (58.20)	2,312
Total	31,829	5,778	3,060	40,667

Table 3. Sensitivity, specificity, positive predictive values (PPV) and negative predictive values of HbA1c over FPG as a gold standard

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)
Diabetes	58.20 (56.43, 59.96)	98.59 (98.46, 98.70)	77.03 (75.41, 78.58)	96.67 (96.53, 96.80)	95.55 (95.34, 95.75)
Pre-diabetes	16.62 (16.02, 17.23)	92.91 (92.59, 93.22)	57.27 (55.87, 58.66)	66.10 (65.92, 66.28)	65.17 (64.70, 65.63)

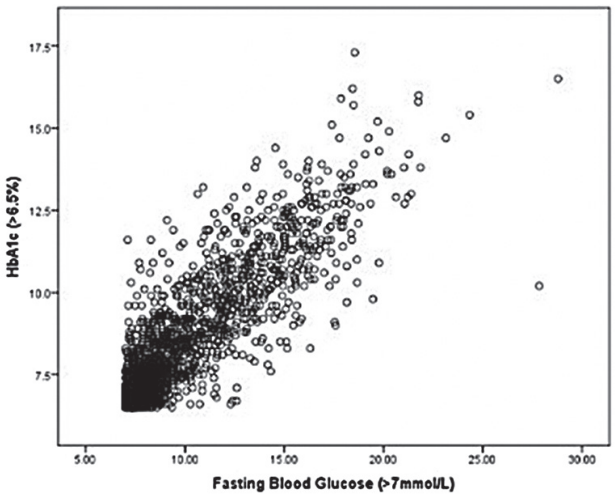

Figure 1. Scatterplot between FPG>7mmol/L and HbA1c >6.5%.

DISCUSSION

The screening methods used to diagnose T2DM have evolved over time, from the measurement of FPG, OGTT and to the use of HbA1c. Our study showed that using the HbA1c threshold level of ≥6.5%, resulted in about 14.2% and 7.5% of the studied population was identified as pre-diabetes and diabetes. This finding is of concern because if the FPG criterion is used for screening, these subjects will not be diagnosed as having diabetes and will live with persistent hyperglycemia without treatment for a significant period of time. This will eventually lead to diabetic complications, including cardiovascular disease (CVD), diabetic nephropathy and diabetic retinopathy. In addition, the increase in pre-diabetes prevalence by about four-fold using the HbA1c level criteria needs immediate attention and action. Untreated pre-diabetes is 37% likely to developed diabetes in 4 years' time.[22] However, with proper lifestyle intervention, the risk of developing diabetes can be reduced to 20%.[22] Based on our results, HbA1c is more sensitive to identify diabetes. However, there were also patients with diabetes by FBG but normal based on HbA1c (n=210, 0.66%). About 321 (5.56%) participants with diabetes by FBG were found to be pre-diabetes by HbA1c. A total of 2,085 (6.55%) normal individuals based on HbA1c were identified as pre-diabetes by FBG. These results suggested that HbA1c may also have a lowered specificity in diagnosing diabetes with high false positive rate.

Although this study showed a high correlation (r^2=0.86) and moderate agreement between fasting plasma glucose and HbA1c in the diagnosis of diabetes, the two tests showed a poor agreement in detecting pre-diabetes. Discordance in the diagnosis of diabetes between HbA1c and FPG screening methods have been reported mainly among Asian populations.[19] A smaller scale population-based study in Malaysia about a decade ago involving 4,341 subjects showed consistent results with the studies from other Asian populations.[16] The discordance might be explained by the different information given by both HbA1c and FPG on the glycaemic exposure. FPG is the measurement of blood glucose at the particular time point, whereas HbA1c reflects the blood glucose level for the past 3 months.[14,21] It is suggested that the use of HbA1c can avoid the problem of within-subject fluctuation in glucose measurements. Thus, it is not surprising that individuals were classified differently by both methods based on the exposure of the blood glucose. It is also important to be aware about the different processes involved in measuring HbA1c and FPG, and the variation in the glycation process between individuals which might also contribute to the variations.[22]

The findings of this present study are likely to be representative of the actual diabetes prevalence in the general population who come from different ethnic groups. A study by Booth and colleagues in Canada showed similar findings where different ethnic groups will have different HbA1c levels in order to detect dysglycemia or diabetes.

Measuring HbA1c is a convenient approach for diabetes diagnosis due to its pre-analytical stability, less intra-individual variability and more importantly, unlike the oral glucose tolerance test, HbA1c level measurement does not require an overnight fast. However, there are several limitations using HbA1c for the diagnosis of diabetes. First, HbA1c cannot be used in individuals with haemoglobinopathies, anemia and disorders where the patients had abnormal red cell turnover.[23] Other processes such as erythropoiesis, glycation, erythrocyte destruction as well as different HbA1c assays used may also lead to differences in the HbA1c levels.[24]

For example, in erythrocyte destruction, increased erythrocyte life span and splenectomy could lead to increase HbA1c levels, whereas decreased erythrocyte life span, haemoglobinopathies, splenomegaly, rheumatoid arthritis or drugs such as anti-retrovirals, ribavirin and dapsone may decreased HbA1c levels.[24]

Appendix 1 shows several factors that could influence the HbA1c measurement and Appendix 2 shows the advantages and disadvantages of glucose and HbA1c assays (adapted from Gallagher et al., and WHO, 2011). Based on the WHO report in 2011, HbA1c can be used when rigorous quality assurance tests are applied, the assays are standardize based on the international reference value and the diabetic patients have no conditions as mentioned above that could result in imprecise measurement.[8] In addition, The American Association of Clinical Endocrinologists recommended that the HbA1c test should be considered as an additional, not as a primary diagnostic criterion.[25]

CONCLUSION

In summary, our results showed a higher prevalence of pre-diabetes and diabetes upon using the HbA1c compared to FPG. We also showed the differences in prevalence of diabetes across the different ethnic groups. We believe there is a basis to use the HbA1c for diagnosis of pre-diabetes and diabetes among the Malaysian population for early intervention and prevention. However, given that HbA1c may also led to lower specificity and high false positive rate, several criteria should be used in diagnosing and controlling diabetes.

Acknowledgments
The authors would like to thank all the members of The Malaysian Cohort (TMC) Study Group, UMBI staff and the participants involved in this project, as well as the community leaders and officers from the local authorities who have assisted in the recruitment processes.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
The authors declared no conflicts of interest.

Funding Source
This research was funded by a top-down grant from the Ministry of Higher Education (MOHE) Malaysia, grant number PDE48. This study was approved by the Research Ethics Committee UKM (Ethic No: FF-205-2007) and have followed the principles outlined in the Declaration of Helsinki for all human investigations. Additional funding, including infrastructure and utilities, was provided by Universiti Kebangsaan Malaysia (UKM).

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APPENDICES

Appendix 1. Several factors that could influence HbA1c levels[24] (adapted)

Description	Increased HbA1c	Decreased HbA1c
Erythropolesis	iron, vitamin B12 deficiency, decreased erythropoiesis	administration of erythropoietin, iron, vitamin B12, reticulocytosis, chronic liver disease
Altered Haemoglobin	genetic or chemical alterations in haemoglobin: haemoglobinopathies, HbF, methaemoglobin, may increase or decrease HbA1c.	
Glycation	alcoholism, chronic renal failure, decreased intra-erythrocyte pH	aspirin, vitamin C and E, certain haemoglobinopathies, increased intra-erythrocyte pH. variable HbA1c: genetic determinants.
Erythrocyte destruction	increased erythrocyte life span: Splenectomy.	decreased erythrocyte life span: haemoglobinopathies splenomegaly, rheumatoid arthritis or drugs such as antiretrovirals, ribavirin and dapsone
Assays	hyperbilirubinaemia, carbamylated haemoglobin, alcoholism, large doses of aspirin, chronic opiate use. variable HbA1c: haemoglobinopathies.	hypertriglyceridaemia

Appendix 2. Advantages and disadvantages of glucose and HbA1c assays in the diagnosis of diabetes[13]

Description	Glucose	HbA1c
Patient preparation prior to collection of blood	Stringent requirements if measured for diagnostic purposes	None
Processing of blood	Stringent requirements for rapid processing, separation and storage of plasma or serum at 4°C	Avoid conditions for more than 12 hr at temperatures >23°C. Otherwise keep at 4°C (stability minimally 1 week).
Measurement	Widely available	Not readily available world-wide
Standardization	Standardization for procedures is needed	Standardization for procedures is needed
Routine calibration	Adequate	Adequate
Interferences: illness	Severe illness may increase glucose concentration	Severe illness may shorten red-cell life and could reduce HbA1c levels
Haemoglobinopathies	Less problematic unless the patient is ill	May interfere with measurement in some assays
Haemoglobinopathy traits	No problems	Not affected by most assays
Affordability	Affordable in most low and middle income country settings (Cheap)	Unaffordable in most low and middle-income country settings (Expensive)