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Comparison of Fasting Glucose, and HbA_{1c} for Use in Screening for Type 2 Diabetes

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Abstract

Background: Various cut-offs for fasting (FBP)and 2-hour plasma glucose (2-hr PG) post oral glucose test (oGTT) have been proposed. More recently, it has been recommended that glycated haemoglobin (HbA_{1c}) replace FBG and the oGTT.

Objective: To compare the usefulness of fasting glucose alone, and HbA_{1c} with the World Health Organisation (WHO) recommended fasting and 2-hr post oral glucose tolerance test glucose for use as screening tests for Type 2 diabetes mellitus.

Research Design and Methods: Data were from 3,465 participants aged 35-74 years who were from the Diabetes, Heart and Health Survey that was carried out between 2002 and 2003. Participants underwent a 75g oGTT and HbA_{1c} was determined by ion-exchange high-performance liquid chromatography.

Results: Using the American Diabetes Association (ADA) fasting glucose cut-off of 7.0 mmol/L (126 mg/dL) alone would miss 46.9% of participants with diabetes diagnosed by oGTT criteria, comprising 57.1% of Europeans, 54.5% of Māori, 32.8% of Pacific and 57.1% of Asian people. Using an HbA_{1c} only with cutoff of 48 mmol/mol (6.5%) would miss 59.2% of participants with WHO diagnosed diabetes, comprising 76.2% Europeans, 88.4% Māori, 50.0% Pacific, and 88.4% of Asian people. Compared to the oGTT and ADA fasting glucose criteria, an HbA_{1c} of $\geq$ 48 mmol/mol had a sensitivity of 55.1% and a specificity of 96.7% (WHO), and 31.3% sensitivity and 99.5% specificity (ADA), respectively.

Conclusions: Compared to the WHO oGTT criteria for diagnosing diabetes, fasting glucose alone and HbA_{1c} are less sensitive, but more specific.

Keywords: oGTT; HbA_{1c}; Diabetes; Diagnostic tests.

Abbreviations: HbA_{1c}: Glycated haemoglobin or haemoglobin A_{1c}; WHO: World Health Organisation; oGTT: Oral glucose tolerance test; ADA: American Diabetes Association; FPG: Fasting plasma glucose; 2-hr PG: 2 hour post 75g oral glucose load; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance.

Introduction

The World Health Organization (WHO) has made a number of recommendations for the diagnosis of diabetes mellitus between 1965 and 2006 [1-5]. The diagnosis of diabetes has been based on the fasting plasma glucose (FPG) and the oral glucose tolerance test (oGTT) with a FPG of ≥ 8.0 mmol/L in 1980, ≥ 7.8 mmol/L in 1985 and ≥ 7.0 mmol/L in 1999 and 2006, and a 2 hour post 75g oral glucose load (2-hr PG) of ≥ 11.1 mmol/l since 1985. The American Diabetes Association (ADA) introduced new diagnostic guidelines in 1997 [6]. A lower FPG level (≥ 7.0 mmol/l for venous plasma) was recommended for the diagnosis of diabetes in both clinical and epidemiological settings.

More recently in 2009, the ADA recommended that glycated haemoglobin (HbA_{1c}) be used in place of an oGTT with a threshold HbA_{1c} of ≥6.5% (≥ 48 mmol/mol) to diagnose diabetes [7]. However, because of the low sensitivity of the HbA_{1c} test in some populations [8-11], and ethnic disparities in the relationship between HbA_{1c} and glucose levels [12-14], the ADA now recommends that diagnosis can be based on either HbA_{1c} criteria or FPG criteria. Although seldom performed, the 2-h PG value after a 75g oGTT [15] could be used, with cut-offs' similar to the WHO cut-off levels [4].

The purpose of this study was to investigate the diagnostic utility of FPG and glycated hemoglobin (HbA_{1c}) in classifying the WHO oGTT diagnosed diabetes in a multiethnic sample of adults.

Research Design and Methods

The Auckland Diabetes, Heart and Health Survey was carried out between December 2001 and November 2003 in 4,049 participants. People with previously diagnosed diabetes mellitus (n=466), missing oral glucose tolerance test (oGTT) (n=19), missing HbA_{1c} (n=5) or missing 2-h PG (n=94) results were excluded, leaving 3,465. These participants comprised 48.0% males, 46.8% Europeans, 24.7% Māori, 21.5% Pacific and 6.9% Asian people. Ethical Committee approval was obtained from the Auckland Ethics Committees (Reference 2001/133).

Interviews were carried out in community venues or clinics close to participant's homes. Personnel were trained in the administration of the questionnaires and in taking blood pressure and other measurements. Ethnicity was defined according to the 2006 NZ census [16].

Biochemical Assessment

Participants fasted from 10pm the evening before the interview. A 75-g oGTT was carried out in participants who had not been previously diagnosed with diabetes, and morning FPG and 2-h PG post Glucaid drink samples were collected for glucose measurement. Plasma glucose was measured using an enzymatic method (Glucose oxidase; Roche Hitachi method).

Categorisation of glucose tolerance status was evaluated by 1998 WHO criteria (FPG ≥ 7.0 mmol/l and/or 2-h PG of ≥ 11.1 mmol/l for diabetes, 2-h PG < 7.0 mmol/l and 2-h PG 7.8-11.0 mmol/l for impaired glucose tolerance (IGT) [17], and by ADA criteria (using the FPG of ≥ 7.0 mmol/l for diabetes and 6.1 to 6.9 mmol/l for impaired fasting glycaemia (IFG)) [6]. The ADA criteria for diabetes is an HbA_{1c} ≥ 48 mmol/mol (6.5%) [7].

HbA_{1c} was measured by ion-exchange high-performance liquid chromatography on a Biorad Variant II instrument. The in-house inter-batch coefficients of variation for low control material were glucose 2.1%, and HbA_{1c} 1.7%, those of abnormal (high) control were glucose 1.3% and HbA_{1c} 2.1%. The laboratory maintained ongoing acceptable performance in the Royal Australasian College of Pathologists external proficiency QAP programme for all tests and continuous accreditation against ISO15189.

Statistical Analyses

The sensitivity, specificity, positive and negative predictive values were calculated. The sensitivity is the proportion of people with undiagnosed Type 2 diabetes who are correctly identified by the test (percentage true positives). The specificity is the proportion of people without undiagnosed Type 2 diabetes who are correctly identified as such by the test. The positive predictive value is the proportion of people with a positive result who have undiagnosed Type 2 diabetes. The negative predictive value is the proportion of people with a negative result who do not have undiagnosed Type 2 diabetes.

The weighted kappa (κ) statistic was used to assess the agreement between the two classification systems beyond agreement expected by chance for participants previously unknown to have diabetes [18]. A value close to 1 indicates perfect agreement and a value < 0.6 represents poor to moderate agreement [18].

The predictive characteristics of the tests were assessed by calculating Receiver Operator Curves (ROCs) (sensitivity versus 1 – specificity). The area under the ROC curve (AUC) shows the ability to discriminate people with and without diabetes. The AUC distinguish between non-predictive (AUC = 0.5), less predictive (0.5 < AUC < 0.7), moderately predictive (0.7 < AUC < 0.9), highly predictive (0.9 < AUC < 1) and perfect prediction (AUC = 1). An AUC of 1 is a perfect test, whereas an AUC of 0.5 is an uninformative test [19]. The two diagnostic tests were compared using the methods of Greenhouse and Mantel [20].

Results

The mean (SD) age of males was 53.3 (11.59) years and for females was 52.6 (11.56) years. All participants were categorised according to the 1997 ADA criteria and the 1998 WHO criteria (Table 1). Prevalence of diabetes by WHO criteria was 1.88 times higher than by FPG ADA criteria. However, the prevalence of IGT was over four times higher than IFG. The ADA criteria (using FBG only) would miss 46.9% of participants with WHO diagnosed diabetes (using both FPG and 2-h PG after the oGTT). Overall, the percentage agreement between the two diagnostic criteria (the sum of the diagonal numbers expressed as a percentage) was 86.5%, with 468 (13.5%) not concordant by the two criteria. In those participants who were classified as having diabetes by the WHO criteria, 17.7% would have been classified normal and 29.3 % as IFG using ADA criteria. Only 32% had both 2-hr PG ≥ 11.1 mmol/L and FPG ≥ 7.0 mmol/L (Figure 1). The overall weighted κ was 0.48 (95% CI: 0.43-0.52), indicating moderate agreement between the two tests. Prevalence of diabetes by WHO criteria was 1.8 times higher than by HbA_{1c} criteria (Table 1). The percentage agreement between the two diagnostic criteria was 59.0%, giving 41% discordance by the two criteria. In those participants who were classified as having diabetes by the WHO criteria, 8.8% would have been classified normal and 36.1% as high-normal using HbA_{1c} criteria. Only 55% had an HbA_{1c} ≥48 mmol/mol (Figure 1). The weighted kappa was only 0.24 (95% CI: 0.22-0.27) indicating poor agreement between the two tests.

Figure 1: Prevalence of diabetes by oGTT status of elevated FPG only, elevated 2-hr PG only, both fasting and 2-hr PG, and elevated HbA_{1c}, in all participants with WHO classified diabetes and by ethnic group.

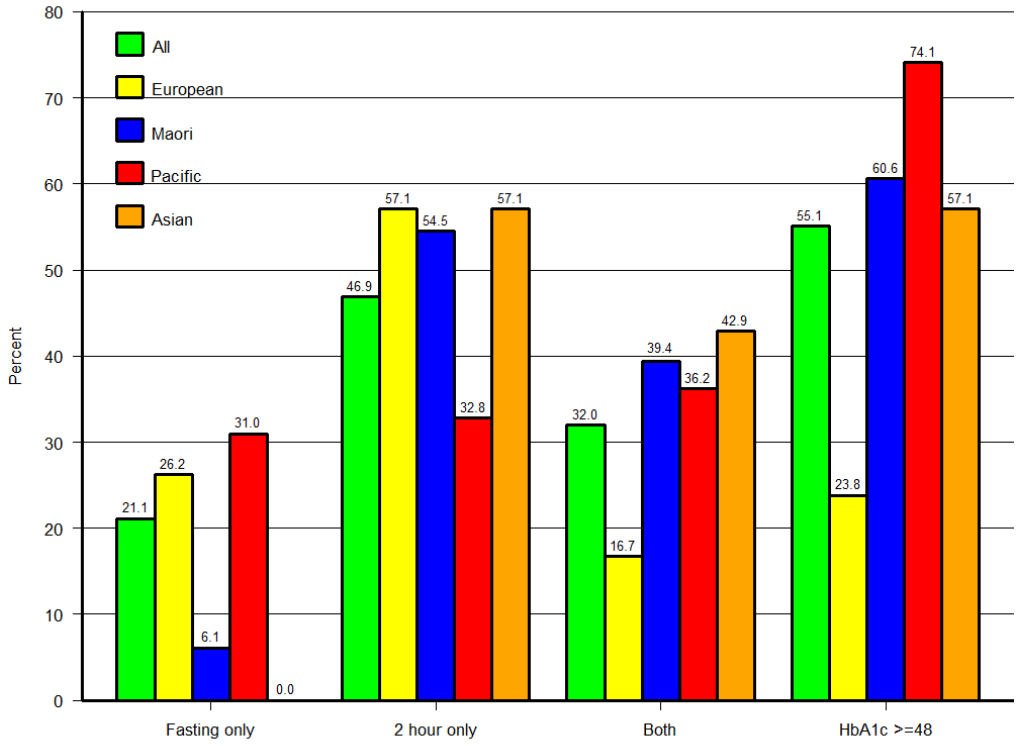


Table 1: Comparison of diagnostic criteria for glucose intolerance by the 1997 ADA and 1998 WHO criteria.Values are number (%).

	ADA FPG criteria				HbA_{1c} (mmol/mol)			
	Normal	IFG	Diabetes	Total	<39	39-<48	≥48	Total
WHO criteria[1]	Weighted kappa 0.48 (0.43-0.52)				Weighted kappa 0.24 (0.22-0.27)			
Normal	2,843 (82.1)	121 (3.5)	0	2,964 (85.5)	1,746 (50.3)	1,164 (33.6)	54 (1.6)	2964 (85.5)
IGT	278 (8.0)	76 (2.2)	0	354 (10.2)	85 (2.5)	212 (6.1)	57 (1.6)	354 (10.2)
Diabetes	26 (0.7)	43 (1.2)	78 (2.3)	147 (4.2)	13 (0.4)	53 (1.5)	81 (2.3)	147 (4.2)
Total	3,147 (90.8)	240 (6.9)	78 (2.3)	3,465 (100.0)	1,844 (53.2)	1,429 (41.2)	192 (5.5)	3,465 (100.0)
HbA_{1c} (mmol/mol)	Weighted kappa 0.19 (0.17-0.22)							
< 39	1,801 (52.0)	1,275 (36.8)	71 (2.0)	3,147 (90.8)				
39-<48	43 (1.2)	136 (3.9)	61 (1.8)	240 (6.9)				
≥48	0 (0.0)	18 (0.5)	60 (1.7)	78 (2.2)				
Total	1,844 (53.2)	1,429 (41.2)	192 (5.6)	3,465 (100.0)				

1. Based on both FPG and 2-hr PG values IGT = impaired glucose tolerance; IFG = impaired fasting glucose.

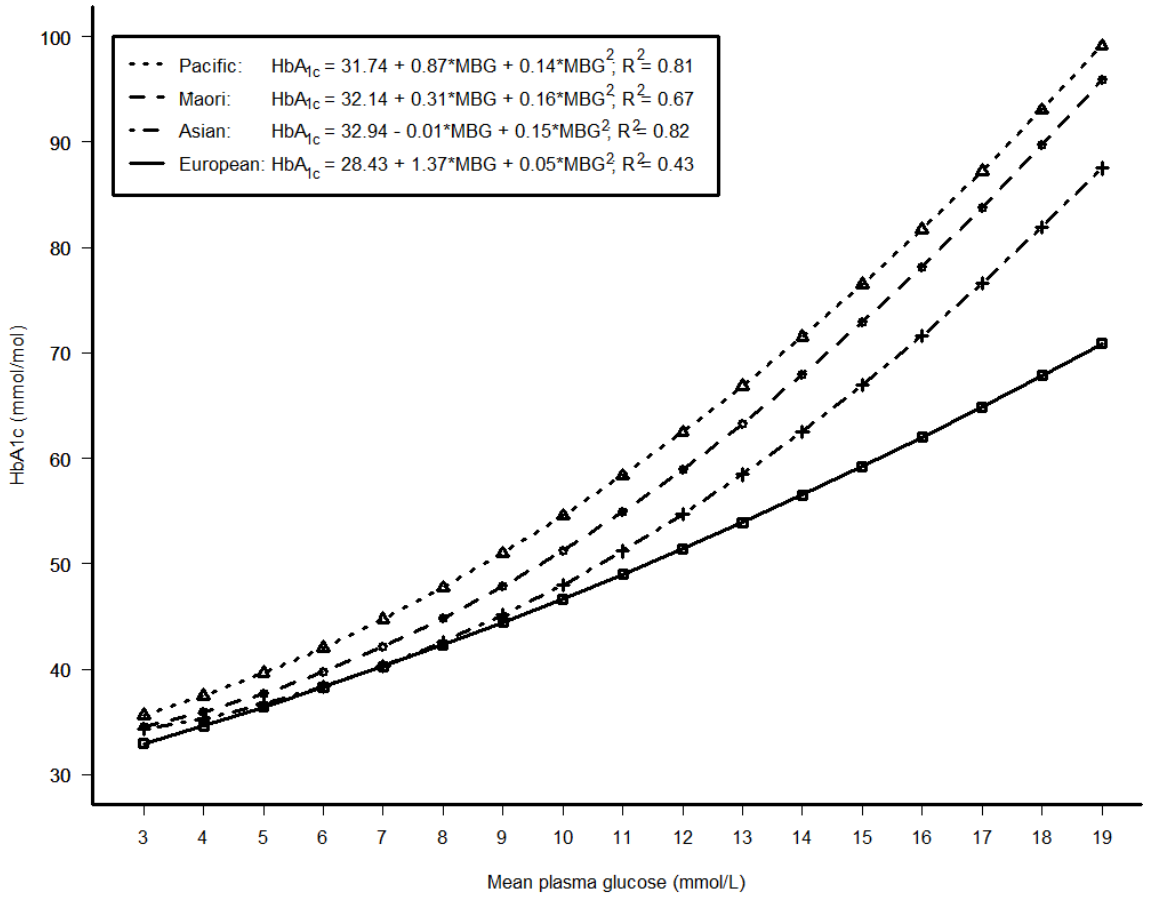
The ADA prevalence of diabetes was only 1.3 times higher than the HbA_{1c} criteria (Table 1). The percentage agreement of 58% was similar to the WHO versus HbA_{1c}. Only 32% of participants classified as having diabetes by the ADA criteria had a high-normal HbA_{1c}. However, the weighted kappa was only 0.19 (95% CI: 0.17-0.22) indicating poor agreement between the two tests.

Figure 1 shows the proportions with elevated FPG only, 2-hr PG only or both, and the proportion with an elevated HbA_{1c} overall and by ethnicity. No Asians who were diagnosed with WHO classified diabetes had a FPG ≥ 7.0mmol/L, i.e. all were on the basis of an elevated 2-hr PG oGTT result. In others diagnosed as diabetic using the WHO oGTT criteria, an elevated 2-hr PG was present in more than 50% of Europeans, Māori and Asians, but in only 33% of Pacific people. Less than 50% in each ethnic group had both elevated FPG and 2-hr PG levels. Only 17% of European, 39% Māori, 36% of Pacific and 43% of Asian participants with diabetes had both 2-hr PG ≥ 11.1 mmol/L and FPG ≥ 7.0 mmol/L. While more than 50% of Māori, Pacific and Asians diagnosed as diabetic using WHO oGTT criteria had an elevated HbA_{1c} (≥48 mmol/mol), a low proportion of Europeans (24%) satisfied this criteria (Figure 1). Ethnic differences in diagnostic rates for prediabetes (using IGT, IFG and HbA1c) are shown in Appendix 1.

The Pearson correlation coefficients between FPG and 2 hr-PG was 0.64, between FPG and HbA_{1c} was 0.71 and between 2-hr glucose and HbA_{1c} was 0.60. Quadratic regression analysis indicated a significant relationship between fasting and 2 hour measures of glucose homeostasis (model $R^2 = 0.52$). According to this model, the FPG that best predicted a 2 hour post-glucose level of 11.1 mmol/L was 6.3 mmol/L (95% CI: 5.1-7.5 mmol/L).

The relationship between mean plasma glucose and HbA_{1c} by ethnic group is shown in Figure 2. This graph shows that for a given mean plasma glucose level, Pacific, Māori and Asians have a higher HbA_{1c} compared to Europeans, particularly at higher mean plasma glucose levels. The quadratic regression coefficients are also reported, together with the model percentage of variation explained (R^2). The percentage of variation explained by the model was highest for Pacific and Asian people with $R^2 > 0.8$, followed by Māori ($R^2 = 0.67$), and was lowest in Europeans ($R^2 = 0.43$).

Figure 2: Ethnic comparison of relationship between mean of fasting and 2-hr glucose concentrations.



The areas under the ROC curves (AUC's) for diabetes mellitus overall, and by ethnic group are shown in Table 2. These were moderately predictive for HbA_{1c}, and highly predictive for FPG and 2-hr PG and the results were similar in all ethnic groups. On comparing the tests for the column labelled "All", FPG was significantly better than HbA_{1c} (P = 0.002). However, there was no significant difference between the FPG and 2-hr PG AUC's (P=0.1369). The AUC's for IGT and IFG are shown in Appendix 2.

Table 2: Areas under the curve (AUC and 95% CI) for diabetes mellitus and 95% confidence interval (95% CI) for Receiver Operator curves for each test overall and by ethnicity.

	All	Europeans	Māori	Pacific	Asians
HbA_{1c}	0.87 (0.84,0.97)	0.85 (0.79,0.91)	0.85 (0.75,0.94)	0.91 (0.86,0.95)	0.92 (0.84,1.00)
FPG	0.94 (0.91,0.96)	0.92 (0.86,0.97)	0.95 (0.92,0.99)	0.95 (0.91,0.99)	0.87 (0.75,0.99)
2-hr PG	0.96 (0.94,0.98)	0.97 (0.94,1.00)	1.00 (1.00,1.00)	0.93 (0.88,0.98)	1.00 (1.00,1.00)

Sensitivities, specificities, predictive values positive and predictive values negative overall and by ethnicity for HbA_{1c} compared to the WHO and ADA criteria are shown in Table 3. The sensitivity and negative predictive values were higher for the WHO criteria and specificity and positive predictive value were higher for the ADA criteria. Sensitivities were highest for Māori, Pacific and Asians, and higher for the ADA criteria compared to the WHO criteria. Both methods were highly specific. Predictive value positive were relatively low by both methods and in all ethnicities, whereas the positive predictive values negative was high in both methods and all ethnicities.

Table 3: Sensitivity, specificity, predictive value positive, predictive value negative and weighted kappa (κ) for HbA_{1c} compared to WHO and ADA criteria.

	WHO criteria	ADA criteria
All		
Weighted κ	0.24 (0.22-0.27)	0.19 (0.17-0.22)
Sensitivity	55.1%	31.3%
Specificity	96.7%	99.5%
PVP	42.2%	76.9%
PVN	98.0%	96.1%
Europeans		
Weighted κ	0.27 (0.22-0.33)	0.21 (0.16-0.26)
Sensitivity	23.8%	38.9%
Specificity	99.4%	99.3%
PVP	55.6%	38.9%
PVN	98.0%	99.3%
Māori		
Weighted κ	0.25 (0.19-0.31)	0.19 (0.14-0.25)
Sensitivity	51.5%	93.3%
Specificity	97.9%	98.6%
PVP	50.0%	53.8%
PVN	98.1%	99.9%
Pacific		
Weighted κ	0.27 (0.22-0.32)	0.25 (0.20-0.30)
Sensitivity	67.2%	82.1%
Specificity	93.9%	93.1%
PVP	48.1%	39.5%
PVN	97.1%	98.9%
Asians		
Weighted κ	0.37 (0.25-0.49)	0.31 (0.18-0.43)
Sensitivity	50.0%	83.3%
Specificity	98.2%	97.4%
PVP	63.6%	45.5%
PVN	96.9%	99.6%

PVP = predictive value positive; PVN = predictive value negative.

Table 4 shows the sensitivity, specificity, positive and negative predictive values for the standard diagnostic criteria, with the value giving equal weight to false positives and false negatives, and the value that maximised the sensitivity and specificity for FPG, and HbA_{1c}. When looking at the single tests and different cut-off levels, the highest sensitivity was found for HbA_{1c} levels ≥ 40 mmol/mol (5.8%).

Table 4: Selected threshold values of fasting plasma glucose (FPG), and HbA_{1c} with associated test sensitivity, specificity, positive (PV+) and negative (PV-) predictive value compared to the oGTT.

	FPG (mmol/L)			HbA_{1c} (%)		
Threshold	≥5.8[1]	≥6.4[2]	≥7.0[3]	≥40[1]	≥42[2]	≥48[3]
Sensitivity (%)	85.7	71.4	53.0	85.0	73.5	55.1
Specificity (%)	87.7	97.5	100.0	73.0	85.8	96.7
PV+ (%)	23.6	55.9	100.0	12.3	18.7	42.2
PV- (%)	99.3	98.7	98.0	99.1	98.6	98.0

1 = Maximizing the sensitivity and specificity.

2 = Giving equal weight to false negatives and false positives.

3 = Standard diagnostic criteria.

Discussion and Conclusions

In the present study HbA_{1c} identified 55.1% of diabetes diagnosed by oGTT (WHO criteria), and 2-hr PG alone identified a similar 46.9% (Figure 1). However, FPG alone only identified 21.1% with WHO diagnosed diabetes. In contrast, a study in Saudi Arabia reported that HbA_{1c}, FPG alone, and 2-hr PG alone identified 69.6%, 43.2% and 64.2, respectively [21]. A study in China reported lower numbers of diagnosed diabetes using HbA_{1c} (34.4%), FPG alone (23.5%), 2-hr PG alone (11.5%) and both (11.5%) [22]. Similarly, a study in Spain reported that HbA_{1c} alone, FPG alone, and 2-hr PG alone identified 15.4%, 32.3% and 98.5%, respectively [23]. The latter study reported that all participants with elevated FPG also had an elevated 2-hr PG. This was not the case in the current or other former studies.

The AUC for HbA_{1c} compared to the oGTT diagnosed diabetes in the current study was 0.87 (Table 2). This compares well with previous studies that have reported AUC's for HbA_{1c} between 0.64 in Iranian adults [24] to 0.96 in Bulgarian adults [25]. For FPG, the AUC was 0.95 in the current study. This was higher than previous studies that reported between 0.71 in Spanish adults [26] to 0.79 in Egyptian adults [27]. The AUC for 2-hr PG in the current study was 0.96 which was higher than the 0.71 [26] and 0.79 [28] reported in two studies from Spain.

The imperfect concordance of HbA_{1c} and glucose criteria reflects that fact that there are inter-individual, and inter-ethnic differences, in HbA_{1c} formation with variation in rate of glucose entry into red cells [29], variation in red cell turnover (even in subjects with normal haematology parameters [30], and other variations in red cell parameters and physiology such as intracellular iron levels [31] and oxidation status [32]. Indeed, genetic (GWAS) analysis indicates that glucose variation contributes only about 1/3 of total variation in HbA_{1c} [33].

Correlations

A higher correlation between FPG and HbA_{1c} (r=0.71) than between 2-hr PG and HbA_{1c} (r=0.60) has been observed previously. In general, correlations between FBG and HbA_{1c} have ranged from 0.47 to 0.82 [25, 38, 40, 43, 45, 56, 57] and between 2-hr PG and HbA_{1c} from 0.49 to 0.78 [25, 38, 40, 45, 57] with an outlier in an Italian population of 0.20 for this latter correlation [56]. Ko et al. also reported the correlations between FBG and 2hr glucose (r=0.74) [57]. These results and those reported here suggest that HbA_{1c} better reflects long-term mean FPG as well as post-load glucose.

We have previously reported a quadratic relationship between FPG and 2-hr PG levels in participants from a multi-ethnic workforce that explained 57.7% of the variation [58]. However, that model predicted a FPG of 7.3 mmol/L (95% CI: 6.0-8.5) for 2-hr PG of 11.1 mmol/L. That compares with 6.3 mmol/L (95% CI: 5.1-7.5) found in the current study explaining 52.6% of the variation (difference not significant).

WHO oGTT vs ADA FBG

Results from the current study (Figure 1) confirm the findings of previous studies showing that FPG alone diagnoses only about half as many patients with diabetes as does oGTT. A single FPG ≥ 7.0 mmol/L (126 mg/dL) identified only 21.1% of participants with Type 2 diabetes by oGTT (WHO) criteria. Other studies have reported that 50-70% of people with diabetes diagnosed by oGTT have FPG levels < 7.0 mmol/L [34, 35].

HbA_{1c} versus WHO oGTT

A number of studies have reported the sensitivities and specificities when comparing the WHO oGTT diagnosed diabetes with an HbA_{1c} ≥ 48 mmol/mol (6.5%). Sensitivities have ranged widely from 16.7% in Austria [36] and 20.9% in Brazil [10] to 98.1% in Malaysia [37], which covers the sensitivities reported in the current study (23.8%-67.2% Table 3). Similarly, specificity of the ADA criteria versus HbA_{1c} have varied widely from 36.7% in Malaysia [37] to 98.7% in Germany [38]. Positive predictive values have ranged from 33.3% in Poland [8] to 69% in China [39] similar to the current study (42.2%-63.6% Table 3) and negative predictive values have ranged from 74.2% in Korea [40] to 97.8% in China [41] which were lower than the current study.

A weighted kappa of 0.22 (similar to that found in Table 1 of 0.24) has been reported from Brazil [10].

HbA_{1c} versus ADA FPG

In the current study (Table 3), the sensitivity of HbA_{1c} compared to the ADA FPG criteria was low overall (31.3%), but was much higher in all non-European ethnic groups (83.3% to 93.3%). These differences may reflect a faster rate of HbA_{1c} formation in non-European populations. Previous studies have reported sensitivities of between 47% in the U.S. ARIC study [42] to 83.4% in the U.S NHANES study [43]. However, a study in Peru reported a tripling in prevalence of diabetes using the HbA_{1c} criteria compared to the FPG criteria [44]. Specificities (96.7%-99.4% Table 3) in the current study were generally comparable to other studies that have ranged from 89.1% in Korea [45] to 99% in Japan [46]. The positive predictive values varied widely in the current study, but the negative predictive values were generally high as has been observed previously [46, 47].

A study in Korea reported a weighted kappa of 0.60 [45], higher than 0.19 in the current study (Table 1).

Ethnicity

Similar to the varying levels of sensitivity observed in different ethnic groups in Table 3, the NHANES survey also reported varying sensitivities by ethnicity of 58.6% in non-Hispanic whites, 75.8% in non-Hispanic blacks, 83.6% in Mexican Americans and 68.1% in others using a cut off level of HbA_{1c} ≥6.1% (43 mmol/mol) [43]. A meta-analysis showed that optimal diagnostic cut points vary by age, gender and ethnicity [48].

Subtle but significant differences in the relationship between plasma glucose and HbA_{1c} between different ethnicities have been identified in other studies, e.g. NHANES reported that non-Hispanic blacks and Mexican Americans had higher levels of HbA1c compared to non-Hispanic whites [49] and the Durable trial also reported that people of Asian, Hispanic and African descent had higher HbA_{1c} levels compared to Caucasians [50]. These differences are similar in magnitude to those observed between the Pacific, Māori and Asians compared to Europeans in this study (Figure 2).

Individual differences in rates of HbA_{1c} formation tend to be consistent in individuals over time [51]. The rate of formation of HbA_{1c} can be compared with glycation of other markers such as fructosamine, which do not require entry of glucose into red cells. Patients who form HbA_{1c} more rapidly have a so-called high glycation index with a higher mean HbA_{1c} compared with their average ambient plasma glucose levels. Conversely those forming HbA_{1c} less rapidly have a narrow glycation index and mounting evidence suggests that these differences may be biologically significant. Patients with more rapid formation of HbA_{1c} are predisposed to certain complications such as nephropathy [52]. Such patients may also be predisposed to greater risk of hypoglycaemia for a given HbA_{1c}, as suggested by a recent post-hoc analysis of subjects the ACCORD trial [53].

These differences between ethnic groups highlight the problems in using different criteria for the diagnosis of diabetes, which have been primarily been based on prevalence thresholds for microvascular disease, especially retinopathy. Its value as a prognostic marker for macro vascular disease has also been shown, even after adjusting for fasting plasma glucose levels [54].

While HbA_{1c} is effectively a 'surrogate' for average glycaemia, mounting evidence shows that it is a more reliable and useful prognostic marker for micro- and macro vascular complications then its use would be empirically justified, despite the lower sensitivity. Use of HbA_{1c} for diagnosis would not only add convenience, but also possibly be preferable for non-Caucasian ethnic groups, who have a faster rate of HbA_{1c} formation (wider glycation index) and therefore may be more prone to complications. Indeed, it has been argued that the diagnostic threshold for HbA_{1c} should be lower for non-Caucasian populations such as American Blacks compared to whites [55].

Optimal Limits

A large number of studies have calculated the optimal HbA_{1c} cut point for the diagnosis of diabetes using the WHO oGTT and ADA criteria. Optimal cut points for HbA_{1c} have ranged from 41 (5.9%) [8] to 50 (6.7%) [27] mmol/mol, with the majority reporting lower cut off values than the currently recommended cut off level of 48 mmol/mol (6.5%). The lower limit is similar to that found in the current study (Table 4) where we observed the highest sensitivity for HbA_{1c} using a cut-off that maximized both sensitivity and specificity of $\geq$ 40 mmol/mol (5.8%).

Strengths and Limitations

Limitations include the fact that a single oGTT was carried out. A single FPG and 2-hr PG are not sufficient for a clinical diagnosis of dysglycaemia on an individual level, in the absence of symptoms (the full rule-set is 2 criteria, either 2 separate glucose measures or one glucose measure + symptoms), but it is adequate to demonstrate ethnic differences in HbA_{1c} and plasma glucose. Another limitation that Asians are a mixed category of high and low risk with different metabolic profiles as Indians have central body obesity at a relatively low BMI. Our strengths include the relatively large sample size and a multiracial sample, enabling ethnic differences in HbA_{1c} performance to be evaluated.

Conclusion

Compared to the WHO oGTT criteria for diagnosing diabetes, FPG alone and HbA_{1c} are significantly less sensitive, but more specific.

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Appendix 1: Comparison of diagnostic criteria for glucose intolerance by the 1997 ADA and 1998 WHO criteria by ethnicity. Values are number (row %).

	ADA fasting criteria				HbA_{1c} (mmol/mol)		
	Normal	IFG	Diabetes	Total	<39	39-<48	≥ 48
WHO criteria							
European	Weighted kappa 0.37 (0.30-0.45)				Weighted kappa 0.27 (0.22-0.33)		
Normal	1,384 (85.3)	45 (2.8)	0	1,429 (88.1)	1,126 (69.4)	300 (18.5)	3 (0.2)
IGT	127 (7.8)	24 (1.5)	0	151 (9.3)	65 (4.0)	81 (5.0)	5 (0.3)
Diabetes	9 (0.6)	15 (0.9)	18 (1.1)	42 (2.6)	10 (0.6)	22 (1.4)	10 (0.6)
Total	1,520 (93.7)	84 (5.2)	18 (1.1)	1,622 (100.0)	1,201 (74.0)	403 (24.9)	18 (1.1)
HbA_{1c} (mmol/mol)	Weighted kappa 0.21 (0.16-0.26)						
< 39	1,172 (72.3)	344 (21.2)	4 (0.2)	1,520 (93.7)			
39-<48	27 (1.7)	50 (3.1)	7 (0.4)	84 (5.2)			
≥ 48	2 (0.1)	9 (0.4)	7 (0.4)	18 (1.1)			
Total	1,201 (74.0)	403 (24.9)	18 (1.1)	1,622 (100.0)			

WHO criteria

Māori	Weighted kappa 0.44 (0.35-0.53)				Weighted kappa 0.25 (0.19-0.31)		
Normal	694 (81.0)	31 (3.6)	0	725 (84.6)	448 (52.3)	272 (31.7)	5 (0.6)
IGT	76 (8.9)	23 (2.7)	0	99 (11.6)	28 (3.3)	59 (6.9)	12 (1.4)
Diabetes	7 (0.8)	11 (1.3)	15 (1.8)	33 (3.9)	5 (15.2)	11 (3.2)	17 (50.0)
Total	777 (90.7)	65 (7.6)	15 (1.8)	857 (100.0)	481 (56.1)	342 (39.9)	34 (4.0)

HbA_{1c} (mmol/mol)	Weighted kappa 0.19 (0.14-0.25)			
< 39	464 (59.7)	302 (38.9)	11 (1.4)	1,520 (93.7)
39-<48	17 (26.2)	39 (60.0)	9 (13.9)	84 (5.2)
≥ 48	0 (0.0)	1 (6.7)	14 (93.3)	18 (1.1)
Total	481 (56.1)	342 (39.9)	34 (4.0)	857 (100.0)

WHO criteria

Pacific	Weighted kappa 0.60 (0.52-0.67)				Weighted kappa 0.27 (0.22-0.32)		
Normal	569 (76.3)	37 (5.0)	0	606 (81.2)	285 (38.2)	301 (40.3)	20 (2.7)
IGT	60 (8.0)	22 (3.0)	0	82 (11.0)	13 (1.8)	47 (6.3)	22 (2.9)
Diabetes	5 (0.7)	14 (1.9)	39 (5.2)	58 (7.8)	2 (3.5)	17 (29.3)	39 (67.2)
Total	634 (85.0)	73 (9.8)	39 (5.2)	746 (100.0)	300 (40.2)	365 (48.9)	81 (10.9)

HbA_{1c} (mmol/mol)	Weighted kappa 0.25 (0.20-0.30)			
< 39	294 (39.4)	318 (42.6)	22 (3.0)	634 (85.0)
39-<48	6 (0.8)	40 (5.4)	27 (3.6)	73 (9.8)
≥ 48	0 (0.0)	7 (0.9)	32 (4.3)	39 (5.2)
Total	300 (40.2)	365 (48.9)	81 (10.9)	746 (100.0)

WHO criteria

Asian	Weighted kappa 0.50 (0.34-0.66)				Weighted kappa 0.37 (0.25-0.49)		
Normal	196 (81.7)	8 (3.3)	0	204 (85.0)	152 (63.3)	51 (21.3)	1 (0.4)
IGT	15 (6.3)	7 (2.9)	0	22 (9.2)	8 (3.3)	11 (4.6)	3 (1.3)
Diabetes	5 (2.1)	3 (1.3)	6 (2.5)	14 (5.8)	1 (0.4)	6 (2.5)	7 (2.9)
Total	216 (90.0)	18 (7.5)	6 (2.5)	240 (100.0)	161 (67.1)	68 (28.3)	11 (4.6)

HbA_{1c} (mmol/mol)	Weighted kappa 0.31 (0.18-0.43)			
< 39	156 (65.0)	58 (24.2)	2 (0.8)	216 (90.0)
39-<48	5 (2.1)	9 (3.7)	4 (1.7)	18 (7.5)
≥ 48	0 (0.0)	1 (0.4)	5 (2.1)	6 (2.5)
Total	161 (67.1)	68 (28.3)	11 (4.6)	240 (100.0)

IGT = impaired glucose tolerance; IFG = impaired fasting glucose.

Only 35.7% of European, 33.3% of Māori, 24.1% of Pacific, and 21.4% of Asian participants with diabetes by WHO criteria would have been classified as IFG by ADA criteria.

Diagnostic rates of diabetes were lower using the ADA FPG criteria compared to WHO oGTT criteria in all ethnic groups (Appendix 1). Using a FPG cut-off of 7.0 mmol/L (126 mg/dL) only would miss 46.9% of participants with WHO diagnosed diabetes, comprising 57.1% of Europeans, 54.5% of Māori, 32.8% of Pacific and 57.1% of Asian people. This indicates that using a FPG (ADA) criterion alone is relatively more sensitive for Pacific people, compared with those of other ethnicities.

Using an HbA_{1c} cutoff of ≥ 48 mmol/mol as the sole criterion would miss 59.2% of participants with WHO diagnosed diabetes, comprising 76.2% Europeans, 88.4% Māori, 50.0% Pacific, and 88.4% of Asian people. This indicates that the HbA_{1c} cutoff is particularly insensitive in Māori and Asian people, but relatively more sensitive for Pacific people.

The percentage agreements between the two diagnostic criteria were similar between ethnic groups, being 87.9% in European, 85.4% in Māori, 84.5% in Pacific, and 87.1% in Asian people. Prevalence rates of IGT compared with IFG were slightly higher in all ethnic groups.

The weighted κ's were 0.44 (0.35-0.53) for Māori, 0.60 (0.52-0.67) for Pacific, and 0.50 (0.34-0.66) for Asian participants, indicating moderate agreement, and 0.37 (95% CI 0.30-0.45) for Europeans, indicating fair agreement.

Appendix 2: AUC's (95% CI) from receiver operator curves for impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG).

	AUC (95% CI)
IGT	
HbA_{1c}	0.76 (0.73, 0.78)
FPG	0.76 (0.73, 0.79)
IFG	
HbA_{1c}	0.76 (0.72, 0.81)
2-hr PG	0.67 (0.61, 0.72)

The areas under the curves predicting IGT for HbA_{1c} and FPG were moderately predictive (Appendix 2). FPG and HbA_{1c} were not significantly different ($P = 0.7420$). The AUC's predicting IFG for HbA_{1c} was moderately predictive, whereas the AUC's for 2-hr PG was less predictive. All tests were significantly different from each other (all $P < 0.0001$).