

A Rational Alternative for the Diagnosis of Diabetes Mellitus in High Risk Individuals

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Abstract

Introduction: To facilitate early, accurate diagnosis, tests should be easy, cheap and reproducible. We studied volunteers with an increased risk of developing diabetes mellitus (DM) to see if HbA_{1c} levels could replace the oral glucose tolerance test (OGTT) in diagnosing DM. **Materials and Method:** One hundred and eleven individuals were studied, using the standard oral glucose tolerance test, and simultaneous measurement of HbA_{1c} levels. Receiver operator characteristic (ROC) analysis was performed to assess the sensitivity and specificity of various HbA_{1c} cut-off levels for diagnosing DM. The relationship between fasting plasma glucose (FPG) and DM diagnosis was also investigated. **Results:** The majority of DM and impaired glucose tolerance (IGT) cases were diagnosed on the basis of two-hour OGTT glucose values. If FPG alone had been used, 29% of the study population with DM or IGT would have been missed. HbA_{1c} cut-off of 6.2% or 6.3% gives the optimal sensitivity and specificity. In linear regression analysis, FPG was found to be a significant predictor of 2-hour OGTT, but only accounted for 45% of the variability of 2-hour OGTT glucose value. **Conclusions:** Our data support the view that although HbA_{1c} alone cannot replace the OGTT in the diagnosis of DM, it can still provide a useful guide to rational, cost-effective screening for diabetes mellitus.

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Key words: Diabetes mellitus, Diagnosis, HbA_{1c}, Oral glucose tolerance test,

Introduction

The “gold standard” for the diagnosis of diabetes mellitus has all along been the oral glucose tolerance test (OGTT). As diabetes mellitus defines a group of individuals at high risk for macrovascular and microvascular disease, it is essential that the diagnosis be made promptly. In newly diagnosed patients with diabetes, about 20% had retinopathy, suggesting that the disease had been existent for at least 7 to 10 years.^{1,2} Apart from a lack of suspicion of the diagnosis of diabetes mellitus, another reason for the delay in diagnosis in asymptomatic patients is the fact that the OGTT is inconvenient to perform. The OGTT is considered to be unnecessary in most cases, costly and time-consuming to perform, and lacks reproducibility, with a coefficient of variation in non-pregnant adults ranging from 20% to 35%.^{3,4} Besides, patients find the 75 g glucose drink unpleasant and the need for 2 venepunctures in two hours unacceptable.

In the light of the above, it has always been the dream of diabetologists to find a simple one-off diagnostic test. A single measurement of glycosylated haemoglobin (HbA_{1c}) has been suggested as the successor to the OGTT. Data from Peters et al⁵ seem encouraging. They showed that using an HbA_{1c} of greater than 7.0% as a cut-off to diagnose diabetes mellitus had a 99% sensitivity, and a specificity of 99.6%. Taking this together with the results of the Diabetes Control and Complications Trial (DCCT)⁶, where an HbA_{1c} greater than 7.0% was associated with an increased risk of microvascular complications, using the HbA_{1c} of 7.0% as cut-off to define diabetes mellitus appears as a rational approach.

The prevalence of type 2 diabetes mellitus is high in Asian countries, being 8.6% in Singapore.⁷ Impaired glucose tolerance is seen in 14% of Singaporeans.⁷ In addition to preventing complications, early glycaemic control appears to slow the rate of deterioration of β -cell function, and thus

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further improves the outcome of type 2 diabetes mellitus patients.^{8,9} As such, with an aim to simplify the diagnosis of diabetes mellitus, we performed a clinical study in an Asian population to help define the correlation between HbA_{1c} and OGTT. This study attempts to determine if different cut-off levels of HbA_{1c} can be used to define diabetes mellitus, impaired glucose tolerance and normal glucose tolerance.

Materials and Methods

Subjects below 55 years of age, with a high risk of glucose intolerance were included in the study. High risks include a) positive family history of diabetes mellitus, hypertension, b) hyperlipidaemia, especially with a low HDL cholesterol of <0.9 mmol/L, and c) obese individuals with a body mass index (BMI) greater than 25 kg/m².

Subjects with underlying renal, liver, or cardiac disease were excluded from the study. Also excluded were those who had history of malabsorption syndrome, or previous gastrectomy. Known diabetics and pregnant women were also excluded.

The subjects were required to undergo an OGTT. All had non-restricted diet for 3 days before the test and were subjected to a 10-hour overnight fast before the test was carried out. A fasting blood sample for glucose, insulin, lipids and HbA_{1c} was collected. An oral 75 g anhydrous glucose load was taken with a standard volume of 250 mL of water. Blood samples for glucose and insulin were repeated 1 and 2 hours later. All tests were performed on the same day except for the test of insulin levels. Blood for insulin levels was collected in plain tubes, spun at 3900 rpm on the same morning, and the serum stored at -60°C till a day when the test could be performed.

Although we had intended to repeat the OGTT in these patients, as 2 abnormal readings are required before diabetes mellitus can be diagnosed in asymptomatic patients, this was not possible as the majority who had normal results did not consent to have their tests repeated.

Glucose was measured bichromatically using a Technicon RA[®] Systems analyser (interassay CV 2.0%). Fasting lipids were also measured colorimetrically using the Technicon RA[®] Systems analyser (interassay CV 3.0%). HbA_{1c} was measured using the DCA 2000[®] Reagent Kit by Bayer. This system had CV of 3.3%, and the range was 4.2% to 6.5%.

Statistical Analysis

Statistical analysis was performed using the STATA 5.0 package. Subjects' glucose tolerance were classified as Normal, impaired glucose tolerance (IGT) and DM based on the WHO criteria.¹⁰ The relationship of HbA_{1c} with diabetes mellitus was explored graphically. A ROC analysis

was performed to assess the sensitivity and specificity of various HbA_{1c} cut-off levels for diagnosing diabetes mellitus. The relationship between fasting plasma glucose and diabetes mellitus diagnosis was also investigated using graphical and ROC methods.

Results

Profile of Study Sample

A total of 111 subjects were studied. The mean age was 43.2 years (SD 8.0 years), and the median age was 45 years (inter-quartile range 37 to 50). Females outnumbered males in our study, making 65% of our study population. This was largely due to the fact that large proportions of our volunteers were nurses from our hospital. Chinese made up 60% of subjects, Malays 19%, Indians 20% and 1% Others. Our subjects were of a large frame, with a mean BMI of 26.7 (SD 4.4), and median of 25.4 (interquartile range 24.3 to 29.1). Twenty-one per cent of our subjects were hypertensive. The mean total cholesterol level was 5.5 mmol/L, low-density lipoprotein level 3.3 mmol/L, high density lipoprotein level 1.2 mmol/L and triglyceride elevated at 2.3 mmol/L.

Diabetes Mellitus and Diagnostic Criteria

Using the WHO criteria,¹⁰ 24 fulfilled the criteria for IGT (22%), and 19 had diabetes mellitus (17%). In our cohort, there was good agreement between the WHO criteria¹⁰ and the new American Diabetes Association (ADA) criteria¹¹ for diabetes mellitus as shown in Table I.

Table II illustrates well the fact that the majority of diabetes mellitus and IGT cases were diagnosed on the basis of 2-hour OGTT glucose values. It clearly shows that of the 99 patients defined as "Normal" based on fasting plasma glucose (FPG) alone, 32 patients (29% of the study population) with diabetes mellitus or IGT would have been missed.

HbA_{1c} and Diabetes Mellitus

Across the categories of normal, IGT and diabetes mellitus, there was a rise in HbA_{1c} values. Table III gives

TABLE I: COMPARISON OF THE GLUCOSE TOLERANCE USING ADA AND WHO CRITERIA

	WHO criteria for DM			Total
	Normal	IGT	DM	
ADA criteria				
Normal	67	0	0	67
IFG/IGT	1	22	0	23
DM	0	2	19	21
Total	68	24	19	111

ADA: American Diabetic Association; DM: diabetes mellitus; IFG: impaired fasting glucose; IGT: impaired glucose tolerance

TABLE II: DISTRIBUTION OF 2-HOUR POST-LOAD GLUCOSE VALUES

	2-hour post-load plasma glucose			
	Normal	IGT	DM	Total
Fasting plasma glucose				
Normal	67	21	11	99
IFG	1	1	6	8
DM	0	2	2	4
Total	68	24	19	111

DM: diabetes mellitus; IFG: impaired fasting glucose; IGT: impaired glucose tolerance

the mean and median HbA_{1c} values in each category.

Receiver operating characteristic (ROC) analysis was used to assess HbA_{1c} as a predictor of diabetes mellitus status. The estimated area under the ROC curve in Figure 1 was 0.89 (SE = 0.041). From Table IV it can be seen that a HbA_{1c} cut-off of 6.2% or 6.3% gives the optimal sensitivity and specificity.

Figure 2 shows the scatter-plot of HbA_{1c} values against 2-hour OGTT glucose. The correlation of HbA_{1c} with 2-hour OGTT glucose was 0.75, suggesting that 56% of the variability in the HbA_{1c} value could be explained by 2-hour OGTT glucose value.

FPG and 2-hour Post-load Glucose

Figure 3 illustrates the relationship between FPG and 2-hour OGTT glucose. The correlation was found to be 0.67. In linear regression analysis, FPG was found to be a significant predictor of 2-hour OGTT, but only accounted for 45% of the variability of 2-hour OGTT glucose value.

Cut-off values for FPG as a predictor of diabetes mellitus were studied using ROC analysis as illustrated in Figure 4 and Table V. Cut-off values of as low as 5.8 mmol/L had poor sensitivity for picking up diabetes mellitus in this

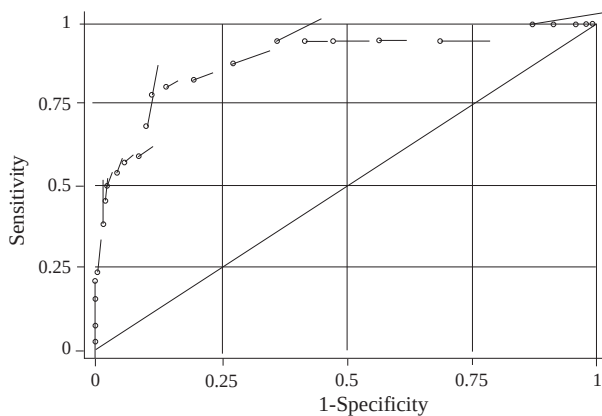


Fig. 1. Empirical ROC plot for HbA_{1c}: AUC = 0.89 (group variable: pure DM).

TABLE III: DISTRIBUTION OF HbA_{1c} ACCORDING TO GLUCOSE TOLERANCE

	HbA _{1c}				
	Mean	Standard deviation	Median	Interquartile range	Range
Normal	5.6	0.4	5.5	5.3-5.8	4.6-6.5
IGT	6.1	0.6	6	5.4-6.7	5.1-7.4
DM	7.0	1.1	6.9	6.4-7.3	5.3-10.3

DM: diabetes mellitus; IGT: impaired glucose tolerance

TABLE IV: HbA_{1c} LEVELS IN COMPARISON TO OGTT RESULTS FOR THE DIAGNOSIS OF DM

HbA _{1c} cut-off value (%)	Sensitivity (%)	Specificity (%)
≥5.9	95	67
≥6.0	90	69
≥6.1	81	84
≥6.2	81	88
≥6.3	81	88
≥6.4	76	90
≥6.5	62	90
≥6.6	57	96
≥6.7	52	97
≥6.8	52	97
≥6.9	52	98
≥7.0	48	98

DM: diabetes mellitus; OGTT: oral glucose tolerance test

study.

It was noted, much to our surprise that FPG for diabetics ranged down to 4.2 mmol/L, and 45% of DM had FPG <5.5 mmol/L. Table VI takes a closer look at these subjects.

The clinical course of subjects who were diabetes mellitus on criteria but had a low FPG will be reviewed with repeat OGTT. The insulin levels, which will be measured in the near future, will give a further insight as to whether these patients have insulin resistance.

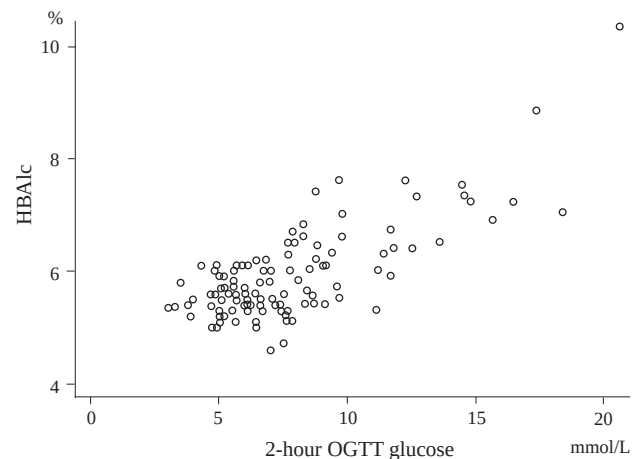


Fig. 2. Scatter-plot of HbA_{1c} versus 2-hour OGTT glucose: coefficient of correlation, $r = 0.75$, $r^2 = 0.56$.

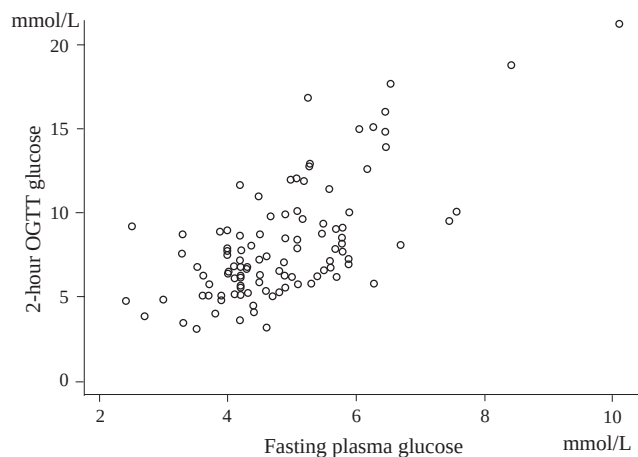


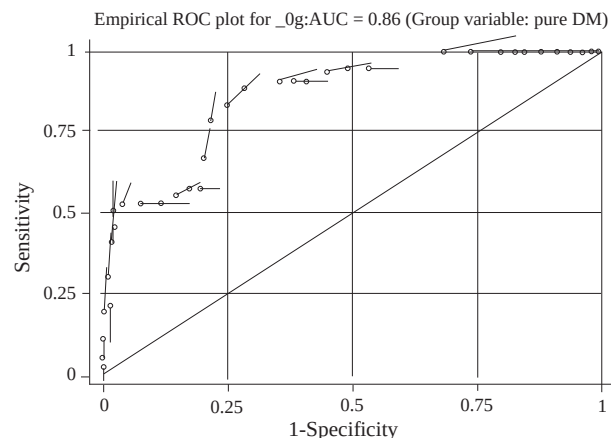
Fig. 3. Scatter-plot of fasting plasma glucose and 2-hour OGTT values: coefficient of correlation, $r = 0.67$, $r^2 = 0.45$.

TABLE V: USE OF FASTING PLASMA GLUCOSE ALONE TO PREDICT DM

Fasting glucose cut-off value (mmol/L)	Sensitivity (%)	Specificity (%)
≥ 7.0	19	100
≥ 6.9	19	100
≥ 6.8	19	100
≥ 6.7	19	100
≥ 6.6	19	99
≥ 6.5	38	99
≥ 6.4	38	99
≥ 6.3	43	98
≥ 6.2	43	98
≥ 6.1	48	98
≥ 6.0	52	98
≥ 5.9	52	94
≥ 5.8	52	90

Discussion

The oral glucose tolerance test has been used as the “gold standard” for diagnosing diabetes mellitus. However, in a survey on primary care physicians, greater than two-thirds of the doctors did not think of ordering an OGTT to diagnose diabetes mellitus.¹² Another study revealed that only less than 20% of diabetics are diagnosed by OGTT.^{13–15} Although sometimes useful, the OGTT has several limitations and confounding factors, which restrict its universal use. As such an alternative approach is desirable and the HbA_{1c} may be the answer to this problem. The main disadvantage of the use of glycated haemoglobin as a diagnostic test is that several biochemical assay methods are used and there is no universal reference standard for interlaboratory calibration.¹⁶ However, these limitations should be overcome in the near future, thus allowing us to justify its widespread use.



AUC = 0.86
SE of AUC = 0.04

Fig. 4. ROC curve of FPG as a predictor of DM status.

TABLE VI: OGTT AND HbA_{1c} PROFILE OF DM SUBJECTS WITH LOW FASTING GLUCOSE

Fasting plasma glucose (mmol/L)	2-hour OGTT glucose (mmol/L)	HbA _{1c} (%)
4.2	11.4	6.3
5.0	11.7	5.9
5.1	11.8	6.4
5.2	11.7	6.7
5.3	12.5	6.4
5.3	16.5	7.2
5.3	12.5	6.4
5.3	12.7	7.3
5.6	11.2	6

OGTT: oral glucose tolerance test

There are strong grounds for maintaining HbA_{1c} below 7.0%. In the DCCT, patients intensively treated had a mean HbA_{1c} of 7.2% and this was associated with decreased development and progression of the microvascular complications and neuropathy. Similar data are available on patients with type 2 diabetes treated intensively.^{9,17} A study by McCance et al¹⁸ showed that HbA_{1c} was useful for predicting microvascular complications, as were fasting and 2-hour plasma glucose, and suggested its benefits as a diagnostic tool as well.

In our study, all our subjects were previously undiagnosed to have diabetes mellitus, and were screened as they were assessed as having a high risk of developing the disease. We noticed that FPG was not a good predictor of diabetes mellitus in our cohort. A total of 45% of our subjects with diabetes mellitus had a FPG level of below 5.5 mmol/L. This low level FPG is indeed surprising and way below the 7.0 mmol/L recommendation by the latest ADA guidelines. In a previous study done in Singapore, the optimally sensitive and specific cut-off for FPG to diagnose diabetes

mellitus was found to be 5.7 mmol/L.¹⁹ It was suggested that the FPG levels were low in our subjects with diabetes mellitus because the hepatic glucose output was still restrained in them. The reason for them having high post glucose levels was due to the loss of first phase insulin secretion, seen early in most patients with type 2 diabetes.

It is well appreciated that the diagnosis of diabetes mellitus in asymptomatic patients requires two abnormal plasma glucose levels before labelling them as having diabetes mellitus. The diagnosis not only carries medical implications but may also affect them economically e.g. in terms of excess loading on insurance policy premiums and occupational biases and restrictions. As such, we would indeed need a second abnormal glucose value before we can categorically state whether an asymptomatic person has DM or not. However, we have earlier explained the limitations of our study and were unable to repeat the OGTT for our entire cohort.

From our data, we found the use of HbA_{1c} cut-off levels of 7.0% was associated with a high specificity of 98%, but only had a sensitivity of 48%. The sensitivity for a cut-off level of 7.0% is low compared to that of 99.6% reported by Peters et al.⁵ One reason could be due to the fact that our study population was small and that the results might be different in a larger sample population. Using ROC analysis, HbA_{1c} cut-off levels of 6.2% and 6.3% were found to have optimal specificity and sensitivity. These levels are lower than those recommended in most other studies. We, however, believe these levels can help guide the diagnosis of diabetes mellitus, as well as deciding on follow-up plans.

From our data, we would like to make the following recommendations:

- Screen all patients with high risk for developing diabetes mellitus with HbA_{1c} and FPG levels.
- Patients with FPG below 6.0 mmol/L and HbA_{1c} below 6.0% can be discharged as they are at reduced risk of developing diabetes mellitus.
- Patients with FPG 6.0 to 6.9 mmol/L, and/or HbA_{1c} from 6.0% to 6.9% will require an OGTT to confirm diabetes mellitus status, and if confirmed, treated by non-pharmacological means of dietary restriction, exercise and lifestyle modifications, as long as the HbA_{1c} remains below 7.0%.
- Patients with FPG greater than 6.9 mmol/L, and HbA_{1c} greater than 6.9% have diabetes mellitus, and require pharmacological therapy if HbA_{1c} remains greater than 7.0% after 3 months of lifestyle modifications.
- Patients with FPG greater than 6.9, but with HbA_{1c} less than 7.0% will fall into the category of diabetes mellitus according to the new ADA guidelines. These patients can be managed by non-pharmacological measures.

With this strategy, based on our data, we would have missed 10% of patients with diabetes mellitus, followed-up 40%, and treated 50% of patients with diabetes mellitus. These data provide a rationale for adhering to HbA_{1c} cut-off levels, and a justification to avoid doing the OGTT. However, larger studies are required to verify and fine-tune the guidelines. After all, the aim in the prompt and accurate diagnosis of diabetes mellitus is towards achieving prevention of its complications, and with a threshold to treat pharmacologically set at an HbA_{1c} 7.0%, we will certainly accomplish this aim.

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