

ARTICLE

Unsuspected glucose abnormalities in patients with coronary artery disease



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JEMDSA

May 2006, Vol. 11, No. 1

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Objectives. To compare the ability of fasting glucose, glycosylated haemoglobin (HbA_{1c}), the American Diabetic Association (ADA) score and measures of the metabolic syndrome (waist circumference, high-density lipoprotein (HDL), and triglycerides) in predicting an initial diagnosis of diabetes mellitus or abnormal glucose tolerance based on the World Health Organization (WHO) criteria.

Design. A cross-sectional, diagnostic study was undertaken of 120 patients admitted to the cardiology wards of Pretoria Academic Hospital for elective coronary angiographic studies.

Main outcome measures. All subjects underwent a modified glucose tolerance test whereby fasting and 2-hour post glucose (75 g) plasma glucose levels were measured. Using the revised WHO criteria, the overall incidence of diabetes was found to be 11.7% (95% confidence interval (CI): 6.5 - 19) and the overall incidence of abnormal glucose tolerance was 46% (CI: 37 - 55).

Results. In univariate analysis for the diagnosis of diabetes, HbA_{1c} ($p < 0.05$) yielded the largest area (0.76) under the receiver operating characteristic (ROC) curve, with a sensitivity of 21%, specificity of 99%, positive predictive value (PPV) of 75% and negative predictive value (NPV) of 91%. For the prediction of abnormal glucose tolerance, applying multivariate analysis using a logistic regression model, the combination of age, ethnic group, serum HDL, serum triglycerides and HbA_{1c} yielded an area under the ROC curve of 0.79, sensitivity of 66%, specificity of 80%, PPV of 76% and a NPV of 71%.

Conclusion. Most subjects with diabetes mellitus (9 of 14) would not have been detected if a 2-hour oral glucose tolerance test had not been done. Addition of either HbA_{1c} or lipid parameters to the model of age and ethnic group were similar in predicting abnormal glucose tolerance.

S Afr Med J 2006; **96**: 216-220.

It is currently estimated that around 194 million people have diabetes mellitus (DM) in the adult population.¹ The prevalence of type 2 DM differs widely in different South African population groups. Previous studies have indicated a prevalence of 28.7% in a mixed population in Cape Town, 13% among Indians in Durban and 8% in urban blacks in Cape Town.² Especially pertinent to our health care environment is that the diagnosis is often made only with the advent of a cardiovascular, cerebral or metabolic event, with one or more microvascular complications already present. Multifactorial aetiologies can be ascribed to the latter, one critical reason being that DM is usually asymptomatic in its early stages. Type 2 DM is usually only recognised 5 - 12 years after hyperglycaemia develops.³

Compared with the general population, morbidity and mortality rates from coronary artery disease (CAD) are two to fourfold higher among patients with type 2 DM

and impaired glucose tolerance (IGT).⁴ In a research study⁵ that assessed mortality associated with the American Diabetic Association (ADA) fasting glucose criteria compared with the World Health Organization (WHO) 2-hour glucose criteria, researchers concluded that abnormalities in 2-hour glucose values are better predictors of mortality than fasting glucose when applied alone in screening. Others,⁶ however, state that the oral glucose tolerance test (OGTT) is poorly reproducible and that measurement of glycosylated haemoglobin (HbA_{1c}) levels represents a reasonable approach in identifying treatment-requiring DM.

In South Africa, studies done on different ethnic groups show varying prevalence rates. The prevalence of DM and IGT in elderly coloured South Africans was found to be 28.7% and 15% respectively.⁷ A study⁸ done on Xhosa factory workers in Transkei showed an age-adjusted prevalence of 4.5% and 5.1% for DM and IGT respectively. In a 10-year follow-up study of

South African Indian subjects, at baseline, the crude prevalences of DM and IGT were found to be 9.8% and 5.8% respectively.⁹ Screening a group of Zulu subjects for DM revealed a prevalence of 5.3% for DM and 7.7% for IGT when adjusted for age and sex.¹⁰ In the surveys conducted in populations in sub-Saharan Africa there was considerable variation in the categorisation of individuals using the ADA and old WHO criteria. The level of agreement between the two ranged from fair to good (kappa statistic 0.71 - 0.86).¹¹ Also, the prevalence of impaired fasting glycaemia (IFG) was lower than that of IGT in 10 of the surveys and the agreement was fair, with kappa \leq 0.26 in all the surveys.¹¹

In a prospective study¹² of glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of DM, the patients had their glucose concentrations recorded during hospitalisation and a standardised OGTT was done at discharge and again at 3-month follow-up. Their results indicated that previously undiagnosed DM (25% at 3 months) and IGT (40% at 3 months) are common in patients with an acute myocardial infarction and that these abnormalities can be detected early in the postinfarction period.

Often the diagnosis of type 2 DM is made on a measurement of fasting hyperglycaemia only. The aim of the current study was to explore the ability of other variables such as HbA_{1c}, ADA score, measures of the metabolic syndrome (waist circumference, high-density lipoprotein (HDL), and triglycerides) to predict an initial diagnosis of DM or abnormal glucose tolerance (a combination of IGT and the diabetic glucose tolerance groups) based on the WHO criteria in subjects with suspected coronary artery disease (CAD).

Methods

Patient selection

Patients with a high index of suspicion of CAD (positive exercise tolerance or positive pyridamole stress test) referred for elective coronary angiograms and those admitted for elective interventions to the cardiology or medical wards and the coronary care unit were included. Self-reported previous diagnosis of DM and use of antidiabetic agents were the only exclusion criteria. The University of Pretoria Ethics Committee approved the study in August 2002 and informed consent was obtained from each participant. Patient recruitment commenced in September 2002 and was completed in May 2003.

Design and measurements

A cross-sectional study was undertaken involving 120 consecutive patients. After an overnight fast of 10 hours, venepuncture was done for fasting

plasma glucose (FPG), fasting lipogram and HbA_{1c}. The lipogram and the HbA_{1c} were measured using the Beckman Coulter (Beckman Coulter, Midrand, Gauteng), while glucose values were measured with the Beckman LX 20 (Beckman Coulter). After initial blood samples were collected, a 2-hour glucose test using a 75 g glucose load (consumed within 10 minutes) was done and this test served as the gold standard. Demographic variables including age, ethnic group, weight, height and blood pressure were recorded. Waist circumference was measured on all participants and the measurement was taken as the centre point of the distance between the last intercostal rib and the superior iliac spine. Patients were also asked to complete a questionnaire that included 7 items, viz. (i) women who delivered a macrosomic baby; (ii) one or more siblings with DM; (iii) one or more parents with DM; (iv) body mass index (BMI) \geq 27 kg/m²; (v) age < 65 and little or no physical activity in most weeks; (vi) age 45 - 64; and (vii) age \geq 65 to score the ADA questionnaire test.¹³ Items *i* to *iii* were worth 1 point each, items *iv* to *vi* 5 points each and item *vii* 9 points. Subjects with a total \geq 10 points were considered to have a positive screening test.

The following diagnostic criteria were used. DM, IFG and normal fasting glucose (NFG) were defined according to the new ADA criteria.¹⁴ NFG was classified as fasting glucose < 5.6 mmol/l, and IFG as fasting glucose \geq 5.6 mmol/l but < 6.9 mmol/l. The diagnosis of diabetes was made on a fasting glucose \geq 7.0 mmol/l. Using the WHO criteria, DM was defined as a 2-hour glucose \geq 11.1 mmol/l, IGT as fasting glucose < 7.0 mmol/l and 2-hour glucose \geq 7.8 mmol/l, normal glucose tolerance (NGT) as fasting glucose < 6.1 mmol/l and 2-hour glucose < 7.8 mmol/l. The category of impaired fasting glycaemia based on the WHO classification of a fasting glucose \geq 6.1 mmol/l but < 7.0 mmol/l and 2-hour glucose < 7.8 mmol/l was not used in this study. The category of abnormal glucose tolerance was defined as IFG, IGT and DM based either on the ADA or WHO criteria.

Statistical analysis

All statistical calculations were done using Stata version 8.0. Baseline characteristics were compared in 3 groups as classified by the WHO criteria. Continuous data were compared using the Kruskal-Wallis test and proportions were compared using the chi-square test. The kappa statistic was calculated to assess the agreement between the 2 criteria. Owing to the relatively few cases with DM, multivariate models were not estimated to predict DM and only univariate models were evaluated. For abnormal glucose tolerance (IFG, IGT or DM) multivariate models were evaluated with univariate predictors that had *p*-values < 0.25. The models were constructed based on: (i) only demographic variables (ethnic group, age); (ii) the latter plus lipid measures (HDL and triglycerides); (iii)

the latter plus HbA_{1c}; and (iv) demographic variables plus HbA_{1c}. Models were evaluated with Hosmer-Lemeshow goodness of fit tests and diagnostic ability (sensitivity, specificity, predictive value and receiver operating characteristic (ROC) curves). The various ROC curves were compared non-parametrically (no adjustment was made for multiple testing). *p*-values less than 0.05 were regarded as statistically significant.

Results

The participants comprised 9 blacks (7.5%), 13 Indians (10.8%), 5 coloureds (4.2%) and 93 whites (77.5%). The overall mean age was 58 years, with 37 subjects (30.8%) being female and 83 (69.2%) male. Other characteristics are shown in Table I.

The distribution of the 120 participants by glucose concentrations and their classifications according to the 2 sets of criteria are shown in Table II. While the ADA criteria diagnosed 95 subjects (79.1%) as normal, the WHO criteria only classified 65 (54.2%) as having normal glucose tolerance. The prevalence of DM according to the WHO criteria was 11.7%; in contrast the ADA criteria diagnosed only 5 subjects, with a prevalence of 4.2%.

A poor agreement exists between the criteria, as the kappa value was 0.26 ($p < 0.00001$).

Predicting diabetes mellitus

As shown in Table II, only 14 subjects were diagnosed as having DM according to the criteria used. This was deemed unsatisfactory for multivariate logistic regression and only univariate logistic regression was done.¹⁵ The 2-hour glucose value predicted diabetes 100% correctly in this sample (all subjects with diabetic fasting values also had diabetic 2-hour values). The univariate associations with DM are given in Table III. HbA_{1c} was the only statistically significant predictor.

Predicting abnormal glucose tolerance

Details are given in Fig. 1 and Table IV. The variable ethnic group was classified into 2 groups, with whites and blacks collectively as the reference group and the other 2 groups (coloureds and Indians) as the risk group. The motivation for this classification was evident after the completion of tabular analysis revealed that abnormal glucose homeostasis was far more common in the Indians and coloureds. Even though the number of Indians ($N = 13$) and coloureds ($N = 5$) was relatively small, the frequency of IGT was 77% and 80% respectively, while in the blacks IGT frequency was 44% and in whites 40%. Statistics of the univariate variables for abnormal glucose tolerance are given in Table IV.

The multivariate models are shown in Table V and Fig. 1. The basic model (model 1) using only ethnic group and age yielded an AUC of 0.66 (66% of individuals would be correctly classified using ethnic group and age). Adding lipid parameters (model 2) to the basic model improved the AUC from 0.66 to 0.75 ($p = 0.05$) (Fig. 1). Likewise, adding HbA_{1c} to the basic model (model 4) improved the AUC from 0.66 to 0.74 ($p = 0.046$). When HbA_{1c} and lipids were both added to the basic model (model 3) increases in the AUC of the ROC, and in sensitivity and specificity were minimal. The *p*-value for comparing the ROC curves for model 2 (AUC of 0.75) versus model 3 (AUC of 0.79) was 0.14. Although significant as univariate variables, when included in the basic model and dropped stepwise with the aid of the likelihood ratio test, body mass index (BMI), waist circumference and ADA scores were shown to be non-contributory (*p*-value of likelihood ratio test > 0.05). On evaluating leverage and outliers, 2 observations with high leverage were identified. Deleting the outliers improved the AUC from 0.74 to 0.76 for model 4 and from 0.75 to 0.78 for model 2.

Table I. Baseline characteristics of patients according to WHO criteria categories (mean (SD))

Variable	NGT (<i>N</i> = 65)	IGT (<i>N</i> = 41)	DGT (<i>N</i> = 14)	<i>p</i> -value
Age (yrs)	56.69 (10.63)	58.29 (9.79)	62.07 (10.56)	0.16
Systolic BP (mmHg)	126.38 (15.32)	128.32 (19.69)	130.36 (17.92)	0.70
Diastolic BP (mmHg)	77.31 (9.33)	78.37 (12.11)	81.00 (14.71)	0.65
BMI (kg/m ²)	27.32 (4.79)	28.55 (4.14)	27.77 (3.98)	0.28
Waist circumference (cm)	95.35 (12.44)	98.46 (11.31)	100.07 (14.93)	0.17
LDL (mmol/l)	3.03 (1.01)	2.96 (0.76)	3.07 (0.76)	0.86
HDL (mmol/l)	1.03 (0.28)	0.94 (0.29)	0.87 (0.33)	0.03
Cholesterol (mmol/l)	4.64 (1.17)	4.74 (1.18)	4.66 (0.93)	0.90
Triglycerides (mmol/l)	1.30 (0.57)	1.74 (0.93)	1.81 (1.05)	0.01
HbA _{1c} (%)	5.06 (0.68)	5.23 (0.37)	6.10 (1.36)	0.00
FPG (mmol/l)	4.87 (0.48)	5.17 (0.60)	6.94 (2.12)	0.00
ADA score	8.49 (3.67)	9.32 (3.59)	9.64 (4.16)	0.34

BP = blood pressure; BMI = body mass index; LDL = low-density lipoprotein, HDL = high-density lipoprotein, cholesterol = total cholesterol, FPG = fasting plasma glucose; ADA = American Diabetic Association.

Table II. Number of subjects in each glucose category according to ADA and WHO diagnostic categories at baselining to WHO criteria categories (mean (SD))

WHO criteria	NFG (N = 95)	IFG (N = 20)	DFG (N = 5)	Total %
NGT (N = 65)	61	4	0	54.2
IGT (N = 41)	32	9	0	34.2
DGT (N = 14)	2	7	5	11.7
Total %	79.1	6.7	4.2	

NGT = normal glucose tolerance; IGT = impaired glucose tolerance; DGT = diabetic glucose tolerance; NFG = normal fasting glucose; IFG = impaired fasting glucose; DFG = diabetic fasting glucose.

Table III. Univariate odds ratios of determinants of diabetes mellitus

Variable	Odds ratio	p-value	Confidence interval
Age	1.05	0.11	0.99 - 1.11
Gender	0.58	0.42	0.15 - 2.03
Ethnic group	1.65	0.49	0.41 - 6.63
Systolic BP	1.01	0.51	0.98 - 1.04
Diastolic BP	1.03	0.30	0.98 - 1.08
Body mass index	0.10	0.99	0.88 - 1.13
Waist circumference	1.02	0.32	0.98 - 1.07
LDL cholesterol	1.09	0.80	0.58 - 2.05
HDL cholesterol	0.20	0.14	0.21 - 1.89
Total cholesterol	0.98	0.94	0.60 - 1.60
Triglycerides	2.49	0.14	0.75 - 8.31
HbA _{1c}	3.31	0.00	1.56 - 7.05
ADA score	1.06	0.43	0.91 - 1.24

BP = blood pressure; LDL = low-density lipoprotein; HDL = high-density lipoprotein; ADA = American Diabetic Association.

Table IV. Univariate odds ratios of predictors for abnormal glucose tolerance

Variable	Odds ratio	p-value	Confidence interval
Age	1.02	0.18	0.99 - 1.06
Gender	1.41	0.39	0.65 - 3.08
Ethnic group	4.43	0.01	1.37 - 14.40
Systolic BP	1.00	0.61	0.98 - 1.02
Diastolic BP	1.01	0.49	0.98 - 1.05
Body mass index	1.06	0.18	0.97 - 1.15
Waist circumference	1.03	0.09	0.91 - 1.06
LDL cholesterol	1.11	0.60	0.74 - 1.67
HDL cholesterol	0.32	0.08	0.87 - 1.15
Total cholesterol	1.17	0.32	0.85 - 1.61
Triglycerides	4.86	0.00	1.79 - 13.25
HbA _{1c}	2.46	0.00	1.23 - 4.91
ADA score	1.08	0.11	0.98 - 1.20

BP = blood pressure; LDL = low-density lipoprotein; HDL = high-density lipoprotein; ADA = American Diabetic Association.

yielded a prevalence of 4.2% only, as shown in Table II. Will lowering the cut-off value of 5.6 mmol/l improve the diagnostic value of the fasting glucose concentration? Adopting the OGTT as the gold standard and using ROC analysis an 'optimal' cut-off/score for fasting glucose and HbA_{1c} was determined. 'Optimal' is meant only in the sense that it indicates the value of the new diagnostic test yielding the highest combination of sensitivity and specificity. For fasting glucose, the optimal value was 5.6 mmol/l with a sensitivity of 85.7% (95% CI: 57.29 - 98.2) and specificity of 87.7% (95% CI: 79.9 - 93.3). For HbA_{1c} it was 5.3% with a sensitivity of 71.4% (95% CI: 41.9 - 91.6) and specificity of 67.9% (95% CI: 58.1 - 76.7).

Discussion

In a clinical situation diagnosing DM means much more than making a biochemical diagnosis. It encompasses managing hyperglycaemia and hyperlipidaemia, hypertension and obesity (if present). Diagnosing DM as soon as possible after admission is important. With the implementation of a simplified approach to diagnosing DM, it is envisaged that an increasing number of patients who need treatment will be identified to prevent the development and progression of this disease.

In this study, a significant number of patients (9 out of 14) would not have been detected if the OGTT had not been performed. Also the IFG category included substantially fewer people than the IGT category, i.e. 20 (16.7%) compared with 41 (34.2%).

This study did not demonstrate differences in findings on coronary arteriography between subgroups according to glucose tolerance.

It has been stated previously that the OGTT is not performed frequently in the clinical setting. Apart from being deemed poorly reproducible, it is described as inconvenient to administer and unpleasant for patients, and must be performed twice to confirm the

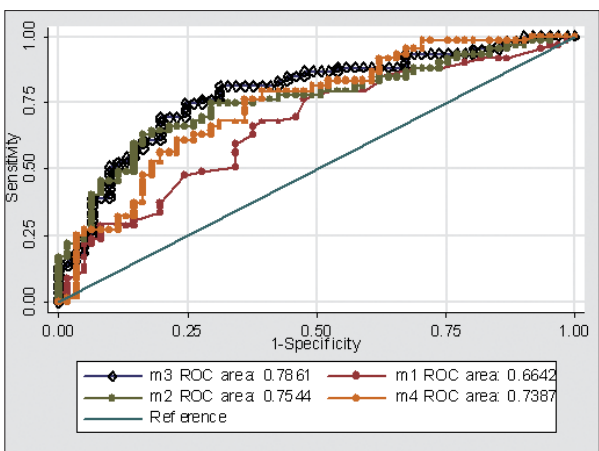


Fig. 1. ROC curves for prediction of abnormal glucose tolerance (m1= model 1 (ethnic group and age), m2 = model 2 (ethnic group, age, HDL, and triglycerides), m3 = model 3 (ethnic group, age, HDL, triglycerides and HbA_{1c}), m4 = model 4 (ethnic group, age and HbA_{1c}).

Optimal cut-off values for fasting glucose and HbA_{1c} given the reference test (OGTT)

Currently, according to the ADA criteria a fasting glucose of 5.6 mmol/l is considered diagnostic of DM. Coincidentally in this study a value of 5.6 mmol/l

Table V. Sensitivity and specificity of significant predictors and combinations thereof for diagnosing abnormal glucose tolerance

Predictors and combinations	Sensitivity (%)	Specificity (%)	PPV (%)	NPV(%)	AUC	p-value: fit of model	p-value
Ethnic group, age	49.2	72.1	63.0	59.5	0.66	0.83	0.007
Ethnic group, age, HDL and triglycerides	66.1	77.1	73.6	70.2	0.75	0.76	< 0.0001
Ethnic group, age, HDL, triglycerides, HbA _{1c}	66.1	80.3	76.5	71.0	0.79	0.34	< 0.0001
Ethnic group, age and HbA _{1c}	52.5	80.3	72.1	63.7	0.74	0.27	0.0004

PPV = positive predictive value; NPV = negative predictive value; AUC = area under the ROC curve; HDL = high-density lipoprotein.

diagnosis of DM.¹⁶ This perception is going to demand intensive reconsideration since this study showed an almost threefold increase in prevalence of DM using the OGTT compared with ADA fasting glucose (11.7% versus 4.2% respectively).

Most crucial is the evidence provided by the Decode study¹⁷ that fasting glucose alone does not identify individuals at increased risk of death associated with hyperglycaemia. The OGTT provides additional prognostic information and enables detection of individuals with IGT who have the greatest attributable risk of death.¹⁷

Although clinical diagnosis requires a confirmatory test, in this study classification of patients was done on the basis of the first test. Follow-up glucose measurements were done, but not on all patients. Of the 14 patients diagnosed, 12 had at least either a repeat fasting glucose or an OGTT. One patient died 2 days after admission and 1 gave an incorrect contact number and could not be contacted. Of the 5 patients diagnosed using the fasting ADA criteria, all had follow-up fasting glucoses done and the repeat results differed slightly. Three of the 5 were still classified as diabetic, while 2 were now classified as having NFG. In total, 12 repeat 2-hour glucose tests were performed. Seven of the 12 were still classified as diabetic; 3 were classified as IGT and the remaining 2 were changed to NGT.

Even though the measurement of blood pressure was not used as an outcome measure it should be noted that measurements were done using a single cuff and only one reading was recorded.

In the study by Dinneen *et al.*,¹⁸ individuals with an initial FPG between 5.6 and 6.0 mmol/l demonstrated an approximately threefold higher risk of progressing to overt DM than individuals with an initial fasting glucose < 5.6 mmol/l. In this study, a fasting glucose of 5.6 mmol/l was found to yield optimal sensitivity and specificity.

In an article that looked at the impact of new diagnostic criteria for DM,¹⁹ the influence of age was not clear-cut and was only significant when

comparing those ≥ 64 years of age. These older people were more likely to be in the WHO group, in keeping with recent findings on older Americans, among whom 14.8% were diabetic on WHO criteria but only 7.7% according to the ADA fasting criteria. Similar findings were found in this study, with the mean age of patients in the DGT group being 62 years.

In this study the 2-hour glucose value predicted DM 100% correctly. The second best predictor was HbA_{1c} with an AUC of 0.76 and low sensitivity (21%) but a high specificity (99%). Lowering the HbA_{1c} to 5.3% would improve the sensitivity to 71%. For the diagnosis of abnormal glucose tolerance other predictive variables, with the exception of fasting glucose, included age, ethnic group, HbA_{1c}, HDL and triglycerides.

Conclusion

The purpose of screening is to identify asymptomatic individuals who are likely to have DM, even though there are no randomised trials demonstrating benefits of early diagnosis.²⁰ More telling are the most recent therapeutic guidelines from the National Cholesterol Education Program which equate the cardiovascular risk associated with DM with that of patients with documented CAD.²¹ In summary, the results of this study show that the fasting ADA criteria defined fewer individuals as having abnormal glucose concentrations than the WHO criteria. The combination of 2-hour glucose and FPG provides more information than either alone. The measures of the metabolic syndrome did not prove to have any predictive power in diagnosing DM. However, the findings of this study indicate a need for future studies with larger sample sizes, and suggest that cardiologists should apply the same rigour in screening for DM as for the other modifiable risk factors.

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Reprinted from the *South African Medical Journal* (2006; **96**: 216-220).