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A multivariate logistic regression equation to screen for dysglycaemia: development and validation

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Abstract

Aims To develop and validate an empirical equation to screen for dysglycaemia [impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and undiagnosed diabetes].

Methods A predictive equation was developed using multiple logistic regression analysis and data collected from 1032 Egyptian subjects with no history of diabetes. The equation incorporated age, sex, body mass index (BMI), post-prandial time (self-reported number of hours since last food or drink other than water), systolic blood pressure, high-density lipoprotein (HDL) cholesterol and random capillary plasma glucose as independent covariates for prediction of dysglycaemia based on fasting plasma glucose (FPG) ≥ 6.1 mmol/l and/or plasma glucose 2 h after a 75-g oral glucose load (2-h PG) ≥ 7.8 mmol/l. The equation was validated using a cross-validation procedure. Its performance was also compared with static plasma glucose cut-points for dysglycaemia screening.

Results The predictive equation was calculated with the following logistic regression parameters: $P = 1 + 1/(1 + e^{-X})$ = where X = –8.3390 + 0.0214 (age in years) + 0.6764 (if female) + 0.0335 (BMI in kg/m^2) + 0.0934 (post-prandial time in hours) + 0.0141 (systolic blood pressure in mmHg) – 0.0110 (HDL in mmol/l) + 0.0243 (random capillary plasma glucose in mmol/l). The cut-point for the prediction of dysglycaemia was defined as a probability ≥ 0.38. The equation's sensitivity was 55%, specificity 90% and positive predictive value (PPV) 65%. When applied to a new sample, the equation's sensitivity was 53%, specificity 89% and PPV 63%.

Conclusions This multivariate logistic equation improves on currently recommended methods of screening for dysglycaemia and can be easily implemented in a clinical setting using readily available clinical and non-fasting laboratory data and an inexpensive hand-held programmable calculator.

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Keywords capillary glucose, impaired fasting glucose, impaired glucose tolerance, risk factors, screening, undiagnosed diabetes

Abbreviations EPV, events per variable; FPG, fasting plasma glucose; HDL, high-density lipoprotein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; OAPR, odds of being affected given a positive result; PPV, positive predictive value

Introduction

Recent studies have demonstrated that lifestyle and medication interventions can delay or prevent progression from impaired glucose tolerance (IGT) to Type 2 diabetes [1–5]. Despite the

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lack of randomized controlled clinical trials, there is also growing evidence that earlier detection of Type 2 diabetes, improved glycaemic control and intensified risk factor management may result in clinically important improvements in diabetes-related morbidity and mortality [6,7]. Unfortunately, there is no consensus as to the most effective, efficient and cost-effective means to screen for dysglycaemia defined as impaired fasting glucose (IFG), IGT and previously undiagnosed diabetes. Ideally, any screening test should be safe, acceptable, simple, cheap, sensitive, specific and reliable [6]. Although the 75-g oral glucose tolerance test represents the gold standard for diagnosing dysglycaemia, it is hardly acceptable, simple or cheap for routine use. In this report, we develop, validate and evaluate a simple approach to screening for dysglycaemia that employs data from a brief history, physical examination, routine non-fasting laboratory studies and a random capillary glucose test.

Methods

To assess the likelihood of dysglycaemia, we developed a predictive equation using data from 1032 Egyptian subjects without a history of diabetes who participated in the Diabetes in Egypt Project between July 1992 and October 1993 [8]. The project was approved by the Egyptian Ministry of Health, the US Agency for International Development and the University of Michigan Institutional Review Board. All subjects provided informed consent. On the first visit, all subjects were assessed for age, sex, post-prandial time (self-reported number of hours since last food or drink other than water), family history of diabetes and random capillary whole blood glucose. On a separate day, height, weight, waist circumference, systolic and diastolic blood pressure, fasting total cholesterol, triglycerides, high-density lipoprotein (HDL), fasting plasma glucose (FPG) and plasma glucose 2 h after a 75-g oral glucose load (2-h PG) were measured. Random capillary whole blood glucose was measured using a portable reflectance meter (One Touch II, LifeScan Inc., Milpitas, CA, USA). FPG, 2-h PG and lipids were measured using a Kodak Ektachem DT60II analyser (Eastman Kodak Co., Rochester, NY, USA).

Bivariate logistic regression analysis and stepwise selection procedures were used to select the best possible multivariate model from a panel of risk factors that are available in routine clinical practice. The panel included age, sex, BMI, waist circumference, hip circumference, systolic blood pressure, diastolic blood pressure, total cholesterol, HDL, low-density lipoprotein (LDL), triglycerides, post-prandial time, random capillary plasma glucose and family history of diabetes. Multiple logistic regression analysis was then used to develop an equation to predict dysglycaemia based on FPG $\geq$ 6.1 mmol/l and/or 2-h PG $\geq$ 7.8 mmol/l. Risk factors in the final model included age (years), sex (female), body mass index (BMI) calculated as weight in kg divided by height in meters squared (kg/m^2), post-prandial time (0–8+ h), systolic blood pressure (mmHg), HDL (mmol/l) and random capillary plasma glucose (mmol/l). Capillary plasma glucose values were calculated by multiplying capillary whole blood glucose values by 1.14. Age, BMI, systolic blood pressure, HDL and capillary plasma glucose were modelled as continuous variables; post-prandial time was modelled as a continuous variable between 0 and 8 h (after which random capillary glucose did not vary as a function of post-prandial time); and sex was modelled as a categorical variable (0 = male and 1 = female). The final mathematical equation provides an estimate of a subject's likelihood of dysglycaemia expressed as a probability between 0.0 and 1.0.

The methodology and model-building process are described in detail elsewhere [9]. Briefly, descriptive statistics were obtained for all variables. We assessed multicollinearity and the linearity assumption for logistic regression equation. Accuracy, reliability and precision of regression coefficients were assessed by calculating the number of events per variable (EPV), the ratio of the number of outcome events to the number of predictor variables [10,11]. In general, the validity of a logistic regression equation becomes problematic when the EPV is < 10. The possible interactions among variables were assessed using the Breslow and Day χ^2 test [12].

The –2 Log Likelihood Ratio test was used to test the overall significance of the predictive equation. The significance of the variables in the model was assessed by the Wald χ^2 test, estimated odds ratios and 95% confidence intervals. The fit of the model was assessed by the Hosmer-Lemeshow goodness of fit χ^2 test [13,14].

To select the optimal cut-point to define a positive test, a receiver operating characteristic (ROC) curve was constructed by plotting sensitivity against the false positive rate (1-specificity) over a range of cut-point values. We purposefully selected a cut-point on the ROC curve to ensure a specificity of approximately 90%. To assess the ability of the equation to predict outcome for study subjects, sensitivity, specificity, positive predictive value (PPV), and the odds of being affected given a positive result (OAPR) were calculated.

Concordance and discordance values, derived from the logistic regression analysis, were used to measure the association of predicted probabilities and check the ability of the equation to predict outcome. To evaluate the overall performance of the equation, we considered several measures of predictive performance including discrimination (quantified by the area under the ROC curve) and calibration (quantified by calibration slope) [15–20].

To validate the equation, we randomly divide the data set into two equal parts—a derivation (training) set and a validation (confirmatory) set. The equation was developed and estimated on the derivation set and tested and validated on the confirmatory set using a cross-validation procedure. The average performance was then calculated over two repetitions.

To compare the results obtained with the predictive equation and the results obtained with various recommended and proposed random capillary plasma glucose cut-points, we applied the equation and those cut-points to the validation (confirmatory) dataset. All statistical analyses were performed using SAS software version 6.12 (SAS Institute, Cary, NC, USA).

Results

Table 1 describes the characteristics of the subjects divided into derivation and validation sets. Figure 1(a) shows the distribution of study population by reported post-prandial time (h). Figure 1(b) shows median random plasma glucose

Table 1 Characteristics of the study populations

Variable	Derivation subjects *n* = 516	Validation subjects *n* = 516	Total population *n* = 1032
Age (years) Mean (SD)	44 (15)	45 (14)	45 (15)
Sex (female) *n* (%)	298 (58)	294 (57)	296 (58)
BMI (kg/m^2) Mean (SD)	29.7 (7.1)	29.8 (8.0)	29.8 (7.6)
Post-prandial time (0–8+ h) Mean (SD)	3 (2)	3 (2)	3 (2)
Systolic blood pressure (mmHg) Mean (SD)	130 (23)	129 (22)	130 (23)
HDL (mmol/l) Mean (SD)	1.2 (0.5)	1.2 (0.5)	1.2 (0.5)
Capillary plasma glucose (mmol/l) Mean (SD)	5.9 (2.3)	6.2 (2.7)	6.1 (2.5)
NGT (2-h PG < 7.8 mmol/l and/or FPG < 6.1 mmol/l) *n* (%)	336 (65)	362 (70)	349 (68)
IGT (2-h PG ≥ 7.8 mmol/l) *n* (%)	144 (28)	118 (23)	131 (26)
IFG (FPG ≥ 6.1 mmol/l) *n* (%)	111 (22)	87 (17)	99 (20)
DM (2-h PG ≥ 11.0 mmol/l and/or FPG ≥ 7.0 mmol/l) *n* (%)	77 (15)	58 (11)	68 (13)

DM, diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

levels (and 25–75% intraquartile ranges) by post-prandial time (h). Only 5% of the subjects were fasting (post-prandial time ≥ 8 h). In general, RPG levels were highest 1–2 h post-prandially and decreased thereafter ($P = 0.003$).

The predictive equation was calculated with the following logistic regression parameters: $P = 1 + 1/(1 + e^{-X})$ = where X = –8.3390 + 0.0214 [age (years)] + 0.6764 [if female] + 0.0335 [BMI (kg/m^2)] + 0.0934 [post-prandial time (hours)] + 0.0141 [systolic blood pressure (mmHg)] – 0.0110 [HDL (mmol/l)] + 0.0243 [random capillary plasma glucose (mmol/l)]. Table 2 shows the maximum likelihood estimates for the logistic regression function. The overall significance of the equation by the –2 log-likelihood test was 723.0 ($P = 0.0001$) with 7 degrees of freedom with 82% concordant pairs and 17.5% discordant pairs. The Hosmer-Lemeshow goodness of fit test was 7.98 ($P = 0.44$) with 8 degrees of freedom. The EPV was 159/7 = 23. Because no interactions, either alone or in combination, added significantly to the equation, we did not add any of these parameters. No potential outliers were detected and the equation met the linearity assumption for logistic regression analysis.

The probability level that provided an optimal cut-point was 0.38. Based on the classification table, derived from the

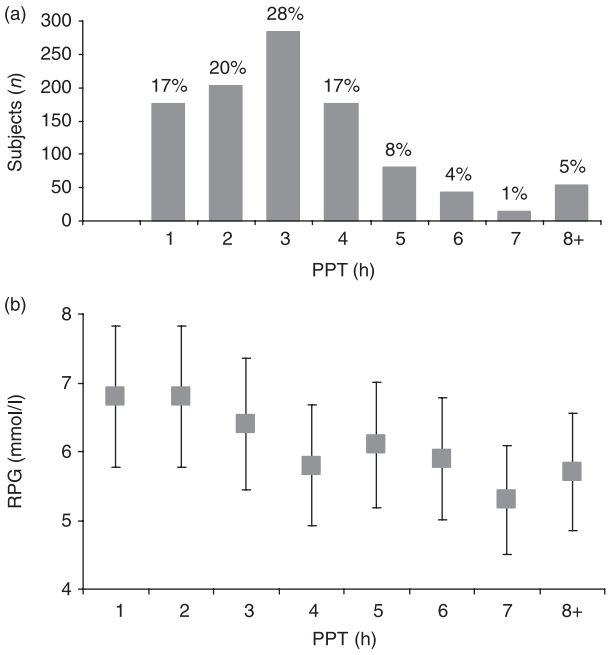

Figure 1 Distribution of study population by post-prandial time (a) and random plasma glucose (median and 25–75% IQR) by post-prandial time (b).

Table 2 Maximum likelihood estimates of logistic regression function

Variable	Estimated regression coefficient	Estimated standard error	Wald χ^2	*P*-value	Estimated odds ratio	95% CI for OR
Intercept	−8.3390	±0.739	—	0.0001	—	—
Age (years)	0.0214	±0.008	7.5	0.006	1.24*	1.06–1.44*
Sex (female)	0.6764	±0.213	10.1	0.002	1.97	1.30–2.99
BMI (kg/m^2)	0.0335	±0.013	6.2	0.01	1.03†	1.01–1.06†
Post-prandial time (0–8 h)	0.0934	±0.053	4.3	0.04	1.10†	1.01–1.21†
Systolic blood pressure (mm/hg)	0.0141	±0.005	9.4	0.002	1.15*	1.05–1.26*
HDL (mmol/l)	−0.0110	±0.005	4.7	0.03	0.998	0.997–0.999‡
Capillary plasma glucose (mmol/l)	0.0243	±0.003	73.5	0.0001	1.28*	1.21–1.35*

*Estimated ORs and 95% CIs for 10 unit increase.
†Estimated ORs and 95% CIs for 1 unit increase.
‡Estimated ORs and 95% CIs for 0.1 unit increase.

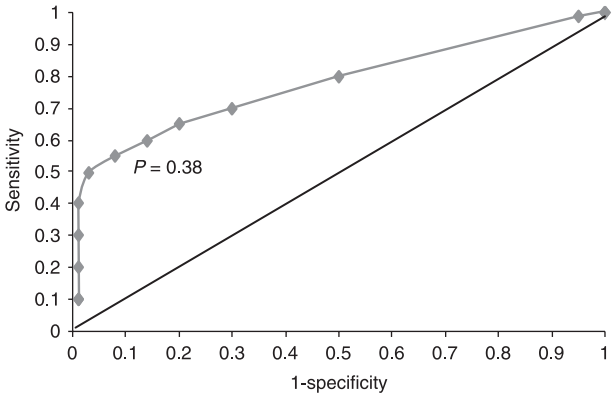

Figure 2 Receiver operator characteristic (ROC) curve. Points on the ROC curve represent the probability levels generated from the logistic regression analysis that was used to select the optimal cut-point. A probability value of 0.38 provided a sensitivity of 55% and a specificity of 90%. The area under the ROC curve was 0.82. Sensitivity and specificity of risk factors for the prediction of dysglycaemia were based on FPG ≥ 6.1 mmol/l and/or 2-h PG ≥ 7.8 mmol/l and were estimated using the multiple regression model described in the text.

logistic regression and ROC curve analysis, sensitivity was 55%, specificity 90% and PPV 65% (Fig. 2). The performance of screening test depends on the cut-point used to define a positive test. We chose the cut-point of 0.38 to optimize specificity. Choosing a probability level of 0.10 optimized sensitivity (sensitivity 91%, specificity 39% and PPV 34%). Choosing a probability of 0.22 produced equal sensitivity and specificity (sensitivity 73%, specificity 73% PPV 49%).

Screening tests that discriminate well between dysglycaemic and non-dysglycaemic individuals aggregate toward the upper left corner of the ROC curve. The area under the curve quantifies how well the screening test correctly distinguishes a dysglycaemic from a non-dysglycaemic person; the greater the area under the curve, the better the performance of the screening test. A diagonal reference line (AUC = 0.50) defines points where a test is no better than chance in identifying persons with dysglycaemia. The area under the ROC curve was 0.82. The calibration slope was 0.99.

When applied to the validation sample, the equation's sensitivity was 53%, specificity 89% and PPV 63%. These represented relatively small decrements from the original equation.

When applied to the validation dataset with a 30% prevalence of dysglycaemia (the prevalence observed in the Egyptian dataset), the predictive equation and a cut-point of 0.38 performed better than static random capillary plasma glucose cut-points (Table 3). In general, the equation yielded higher sensitivity, identified more new cases (true positives) and missed fewer new cases (false negatives) than the static capillary plasma glucose cut-points ≥ 7.2, ≥ 7.8, ≥ 8.3, ≥ 8.9 mmol/l. The equation yielded higher specificity and identified fewer false positive cases than the static capillary plasma glucose cut-points ≥ 5.0, ≥ 5.6, ≥ 6.1, ≥ 6.7, ≥ 7.2 mmol/l. The equation yielded higher PPV than the static capillary plasma glucose cut-points ≥ 5.0, ≥ 5.6, ≥ 6.1, ≥ 6.7, ≥ 7.2, ≥ 7.8 mmol/l. The equation yielded higher OAPR than the static capillary plasma glucose cut-points ≥ 5.0, ≥ 5.6, ≥ 6.1, ≥ 6.7, ≥ 7.2 mmol/l.

Discussion

Behavioural and pharmacological interventions can delay or prevent Type 2 diabetes in high risk populations [1–5,21]. In addition, emerging evidence suggests that earlier diagnosis and treatment of Type 2 diabetes may delay or prevent the development of complications [22]. Based on the results of these studies, it is likely that IFG and IGT will become targets for clinical and public health intervention. Currently, the diagnosis of dysglycaemia requires 2-h 75-g oral glucose tolerance tests. As has been amply documented, oral glucose tolerance tests are not commonly performed in routine clinical practice and alternative approaches to the diagnosis of dysglycaemia must be developed [23–27]. For these reasons, it is desirable to identify subpopulations at increased risk for dysglycaemia and develop quick, non-invasive and inexpensive methods of identifying individuals with dysglycaemia.

Table 3 Comparison of the performance of the predictive equation and capillary plasma glucose cut-points for a hypothetical population of 1000 with a prevalence of IFG, IGT and undiagnosed diabetes of 30%

Screening test	Sensitivity (%)	Specificity (%)	PPV (%)	OAPR (+)	True (+)	False (–)	False
Equation	53	89	63	2.06	159	77	141
Capillary plasma glucose:							
≥ 5.0 mmol/l	94	21	25	0.51	282	553	18
≥ 5.6 mmol/l	90	36	29	0.60	270	448	30
≥ 6.1 mmol/l	73	67	39	0.95	219	231	81
≥ 6.7 mmol/l	57	82	48	1.35	171	126	129
≥ 7.2 mmol/l	46	88	55	1.64	138	84	162
≥ 7.8 mmol/l	40	95	71	3.43	120	35	180
≥ 8.3 mmol/l	37	97	83	5.29	111	21	189
≥ 8.9 mmol/l	35	98	85	7.50	105	14	195

True positive = new cases = prevalence × sensitivity × n; false positive = 1-prevalence × 1-specificity × n; false negative = missed cases = prevalence × 1-sensitivity × n.

We have developed a multivariate predictive equation based on age, sex, BMI, post-prandial time, systolic blood pressure, HDL and capillary plasma glucose levels to access the likelihood of dysglycaemia. The equation was 55% sensitive and 90% specific. In validation testing, the equation was 53% sensitive and 89% specific. The relatively small decrement in sensitivity and specificity on validation testing suggest that the equation has both internal validity and generalizability [28].

A number of recent studies have suggested that risk factor questionnaires [29,30] and risk scores [25,31–36] can be used to screen for dysglycaemia and undiagnosed diabetes. The area under the ROC curves for the published risk scores have ranged from 0.66 to 0.74 for dysglycaemia and from 0.74 to 0.87 for undiagnosed diabetes. The performance of our equation to screen for dysglycaemia, with an area under the ROC curve of 0.82, exceeds that for published risk scores for dysglycaemia and is comparable with published risk scores for undiagnosed diabetes. The sensitivity of the published risk scores have ranged from 51 to 69% for dysglycaemia and from 72 to 81% for undiagnosed diabetes. The specificity has ranged from 63 to 78% for dysglycaemia and 55 to 78% for undiagnosed diabetes. Compared with these risk scores, at the probability level of 0.38, our equation is less sensitive (55%) but more specific (90%) than the risk scores for both dysglycaemia and undiagnosed diabetes.

The application of all screening tests requires a trade-off between sensitivity and specificity. If a lower cut-point value is used to define a positive test, sensitivity increases but specificity decreases. This results in more complete ascertainment of subjects with abnormal glucose tolerance, but substantially more false positive subjects who require follow-up diagnostic testing. The decision regarding acceptable levels of sensitivity and specificity involves weighing the consequences of leaving cases undetected (false negatives) and classifying healthy persons as abnormal (false positives) [37,38]. Highly sensitive tests are preferable if the failure to make an early diagnosis and initiate treatment has dire health consequences. Highly specific tests may be preferred if a disease is uncommon in the population or if a false positive result can harm the subject emotionally, physically or financially. In a substantial minority of subjects, dysglycaemia may revert to normal on follow-up testing [39–44]. In others, dysglycaemia may be slowly progressive but is not likely to be associated with short-term complications. For these reasons, and because dysglycaemia is an uncommon condition and follow-up diagnostic testing is potentially harmful, we believe that specificity should be optimized in screening. To avoid missing individuals with persistent or progressive dysglycaemia, it is imperative that periodic re-screening be performed.

Previously, using data from the same study, we developed an empirical formula to screen for undiagnosed diabetes [9]. The equation's sensitivity was 65% and its specificity was 96%. Compared with the former equation, our present equation for dysglycaemia is less sensitive (55 vs. 65%) and less specific (90 vs. 96%). This indicates that the dysglycaemia equation does not work as well as the equation to predict undiagnosed diabetes. This may be due to the greater overlap of the distributions of random glucose levels between the normal and dysglycaemic populations (IFG, IGT and undiagnosed diabetes) compared with the population with undiagnosed diabetes. Other possible explanations include the variability, poor reproducibility and lack of test-to-test reliability of a 2-h PG of 7.8–11.0 mmol/l for the prediction of IGT [39–44].

When we applied the equation for undiagnosed diabetes to predict dysglycaemia, our dysglycaemia equation was more sensitive (55 vs. 54%) and more specific (90 vs. 84%). This suggests that for the same outcome (prediction of dysglycaemia), the dysglycaemia equation works better than the equation for undiagnosed diabetes. It is likely that the inclusion of additional risk factors in the dysglycaemia equation (systolic blood pressure and HDL cholesterol) account for the improved performance.

Different ethnic groups may vary in their characteristics, which may affect a predictive equation's performance. It is

important to assess the performance of the equation in different ethnic groups [34,35,45,46]. Indeed, some have suggested that ethnic group-specific cut-points may be needed for predictive equations [35]. We applied our predictive equation for undiagnosed diabetes [9], developed in the Egyptian population, to data from 1065 predominantly Caucasian-American subjects. The equation, which was 65% sensitive and 96% specific in the Egyptian population, was 62% sensitive and 96% specific in the US population. Thus, it performed well in another ethnic group. Although the variables included in the equation are routinely available for most adult patients in primary care in the United States, this may not be the case in other settings. This may limit the generalizability of the equation. Further evaluation of the dysglycaemia predictive equation in different populations is needed to further establish its generalizability.

In summary, by incorporating RPG data in combination with simple, available risk factor data, the predictive equation performs better in the general population than any single glucose cut-point. Although exhibiting a specificity of ~90%, use of the equation with a cut-point of 0.38 misses approximately 45% of persons with dysglycaemia. To avoid missing these 'false negative' screenees, it is imperative the repeat screening be performed periodically. The predictive equation has been designed to identify individuals at increased risk for dysglycaemia who require further diagnostic testing. The equation is designed to be used by primary care practitioners in general clinical practice. It can also be used by health systems with access to electronic medical records. The multivariate equation can be implemented with a number of inexpensive, programmable, hand-held calculators. We have programmed the formula and coefficients presented in the statistical methods section into a TI-83 graphic and scientific calculator (Dallas, TX, USA). To obtain a probability value, the user enters the values for age (years), systolic blood pressure (mmHg), HDL (mmol/l), capillary plasma glucose (mmol/l), post-prandial time (0–8+ h), BMI (kg/m^2) and sex (0 for male or 1 for female). The calculator prompts the user by displaying the coefficient for the variable that should be entered next. The result displayed is the calculated probability that a subject has dysglycaemia (a number between 0.0 and 1.0). The programming is available on request. Using this device and a glucose meter, a health-care professional can perform a quick point-of-care assessment of the probability of dysglycaemia to direct further definitive diagnostic testing.

Competing interests

None declared.

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