Acta Diabetol (2012) 49 (Suppl 1):S73–S79
DOI 10.1007/s00592-011-0260-6

ORIGINAL ARTICLE

# Incidence of type 2 diabetes by $HbA_{1c}$ and OGTT: the Isfahan Diabetes Prevention Study

**Mohsen Janghorbani · Masoud Amini**

Received: 20 October 2010 / Accepted: 13 December 2010 / Published online: 22 February 2011


**Abstract** The aim of this study was to estimate the incidence of type 2 diabetes using newly proposed hemoglobin $A_{1C}$ ($HbA_{1c}$) and current oral glucose tolerance test (OGTT) definition in an Iranian non-diabetic population. A total of 923 non-diabetic first-degree relatives (FDRs) of patients with type 2 diabetes 30–70 years old in 2003–2005 were followed through 2009 for the occurrence of type 2 diabetes. At baseline and through follow-ups, participants underwent a standard 75 g 2-h OGTT and $HbA_{1c}$ measurements. Prediction of progression to type 2 diabetes by OGTT-defined or $HbA_{1c}$-defined diabetes was assessed with area under the receiver operating characteristic (ROC) curves based upon measurement of fasting plasma glucose, 2-h post-load glucose values, and $HbA_{1c}$. The prevalence of type 2 diabetes was 9.2% (95% CI: 8.2, 10.2) by OGTT-defined diabetes and 7.9% (95% CI: 6.9, 9.0) by $HbA_{1c}$ $\geq$6.5. The incidence of type 2 diabetes was 2.0% (95% CI: 1.6, 2.4) (1.8% men and 2.1% women) per year by the current OGTT definition, whereas the incidence rates were 1.7% (95% CI: 1.3, 2.0) (1.6% men and 1.7% women) per year by $HbA_{1c}$ $\geq$6.5%. Of those diagnosed with type 2 diabetes by OGTT, 69.6% had $HbA_{1c}$ <6.5% and therefore would not have been classified as having type 2 diabetes. The incidence and prevalence of diabetes using newly proposed $HbA_{1c}$ threshold in this FDRs of patients with type 2 diabetes were slightly lower than using current OGTT definition.

**Keywords** Type 2 diabetes · First-degree relatives · Diagnostic test · $HbA_{1c}$ · Glucose tolerance test

M. Janghorbani (✉)
Department of Epidemiology and Biostatistics, School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran
e-mail: janghorbani@yahoo.com

M. Janghorbani · M. Amini
Department of Epidemiology and Isfahan Endocrine and Metabolism Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

## Introduction

The most widely used diagnostic and/or screening test for the detection of diabetes includes fasting plasma glucose (FPG) and the oral glucose tolerance test (OGTT). FPG is a more commonly used test, compared with OGTT, due to its logistical advantages. Hemoglobin $A_{1C}$ ($HbA_{1c}$) has been suggested as an alternative screening test for type 2 diabetes [1, 2]. However, the significance of $HbA_{1c}$ in identifying persons with a future risk of diabetes remains unknown [3, 4]. The question then arises whether FPG is a better predictor of diabetes risk than post-load glucose values or $HbA_{1c}$. Although measuring FPG is less expensive, more convenient, and more reproducible than performing an OGTT, various studies have shown that FPG has a sensitivity of only 40–60% for detecting patients with type 2 diabetes [4–7]. In contrast, the OGTT has been the preferred test for diagnosing diabetes in epidemiological studies for over 40 years, despite the widely recognized costs and inconvenience of the test, and has poor reproducibility. In addition, OGTT is time-consuming and shows considerable intra-individual variation, with up to 20% of OGTT-diagnosed patients reclassified as not having diabetes when retested [8–10]. Use of $HbA_{1c}$ has some logistical advantages over both the FPG and the OGTT. It can be measured at any time of day with a small sample of blood and is convenient and easy to do [8]. The disadvantages are the difficulty in standardization and the fact

that $HbA_{1c}$ cannot be measured in the presence of certain form of anemia and hemoglobin variants [11], which may also have unique ethnic or geographic distributions.

Although concerns about the standardization of assay have largely been resolved in developed world [12], the standardization difficulty still exists in some regions of developing world. The limited access to standardized laboratory $HbA_{1c}$ methods makes unfeasible the inclusion of the $HbA_{1c}$ criteria among the diagnostic criteria of diabetes in these parts of the developing world. This discordance points out that the question of optimally predicting diabetes risk is still unsolved and needs further clarification. No study has examined diabetes incidence using repeated measures of $HbA_{1c}$ in Iran.

The objectives of this study, therefore, were to estimate the prevalence and incidence of type 2 diabetes by current OGTT definition and the newly proposed $HbA_{1c}$-defined diabetes in an Iranian FDRs of patients with type 2 diabetes.

Racial disparities in $HbA_{1c}$ values exist [13]. Comprehensive data for developing countries have not been reported. Therefore, at an ethnological level, the study contributes by characterizing the occurrence of diabetes in a specific population from central Iran.

## Patients and methods

### Study area

Our investigation was conducted in Isfahan, a very large area situated in central Iran, located on 1,590 m height above sea level, between latitudes 30 and 34° north of the equator and longitude 49–55° east, with a population of almost four and half million (4,559,256 in 2006 (men 2,335,399, women 2,223,857)) and a high proportion of young people. The total area is 107,029 $Km^2$. The climate is dry temperate and quite wide temperature differences between the summer and the winter with a mean daily temperature of 3.0° Celsius in January and February, 29.0° Celsius in July and August, and 16.5° Celsius in September and October. The population structure and socioeconomic status of Isfahan are similar to the rest of the country. Private physicians and hospitals, district health centers, and government and university hospitals and clinics provide the health services. Fifteen endocrinologists and 3 diabetes centers serve the study area. Residency in remote and mountain areas and economical status may affect accessibility to the endocrinological expertise.

### Participants and data collection

The Isfahan Diabetes Prevention Study (IDPS) is an ongoing cohort study in central Iran to assess the efficacy of intensive diet and exercise to prevent or delay the onset of type 2 diabetes in the FDRs of patients with type 2 diabetes. The study was performed between 2003 and 2005. A total of 3,176 (826 men and 2350 women) FDRs of a consecutive sample of patients with type 2 diabetes attending clinics at Isfahan Endocrine and Metabolism Research Center were included in the study. The participants completed laboratory tests including standard 75 g 2-h OGTT, $HbA_{1c}$ and a questionnaire on their health status and on various potential risk factors for diabetes. Participants received follow-up tests according to a medical care standard in diabetes [14] to update information on demographic, anthropometric, and lifestyle factors and on newly diagnosed diabetes. Accordingly, if OGTT was normal at baseline, repeated testing was carried out at least at 3-year intervals. Otherwise, repeat testing was carried out annually. The IDPS baseline methods have been described in detail elsewhere [15]. The participants included siblings and children. The tenants of the Declaration of Helsinki were followed, institutional ethical committee approval was granted, and an informed consent form was signed by each participant.

### Ascertainment of diabetes

Cases of diabetes were identified from baseline and follow-up OGTTs and $HbA_{1c}$ according to American Diabetes Association criteria [2]. Pregnant women were excluded. This study used data of 923 FDRs (216 men and 707 women) who were free of diabetes at registration and had at least one subsequent review in mean (standard deviation [SD]) follow-up period of 5.0 (1.5) years and who were aged 30 years and over (Fig. 1).

### Procedures

Participants reported to clinics in the morning after overnight fast. Subjects were asked to abstain from vigorous exercise in the evening before and in the morning of the investigations. Smokers were encouraged to abstain from smoking in the morning of the investigations. First on arrival at the clinic, the information given by the participants in the

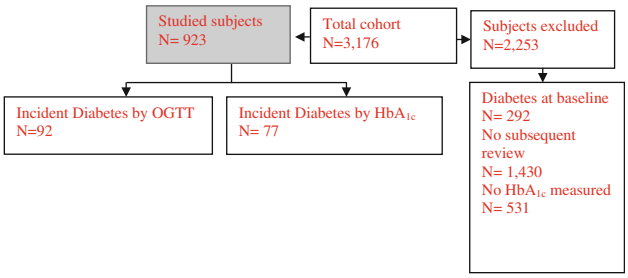


**Fig. 1** Schematic diagram of the study population

questionnaire on family history was verified. Then, with the subjects in light clothes and without shoes, height, weight, waist, and hip circumference were measured using standard apparatus. Weight was measured to the nearest 0.1 kg. Height, waist, and hip circumference were measured to the nearest 0.5 cm. Waist was measured midway between the lower rib margin and the iliac crest at the end of a gentle expiration. Hip circumference was measured over the greater trochanter directly over the underwear. Resting blood pressure (BP) was measured after subjects had been seated for 10 min, using standard techniques. FPG was measured using the glucose oxidase method. All subjects underwent a standard OGTT (75 g 2-h glucose), including FPG assessment, at baseline and the follow-ups. Venous blood was sampled at fasting, 30, 60, and 120 min after oral glucose administration. Plasma samples obtained after centrifugation were analyzed the same day.

$HbA_{1c}$ (measured by ion-exchange chromatography), total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol (calculated by the Friedewald equation provided total triglycerides did not exceed 400 mg/dl [16]) were also assessed at the baseline and through follow-ups. All blood sample procedures were performed in the central laboratory of the Isfahan Endocrine and Metabolism Research Center using enzyme-linked method. The same methodology was used for both the prevalence and incidence studies.

### Definitions

Diabetes was defined if: (i) FPG $\geq$126 or (ii) 2-h plasma glucose of $\geq$ 200 mg/dl or (iii) $HbA_{1c}$ $\geq$6.5%. Pre-diabetes was defined as having IFG (FPG: 100–125 mg/dl and 2-h plasma glucose <140 mg/dl) or IGT (FPG <126 mg/dl, but with 2-h plasma glucose concentration $\geq$140 and <200 mg/dl) or $HbA_{1c}$ 6.0–6.49% [17]. Whereas if the FPG was below 100 mg/dl and 2-h plasma glucose smaller than 140 mg/dl and $HbA_{1c}$ <6.0%, it was considered a sign of normal glucose tolerance (NGT) [14, 18].

### Determination of diabetes incidence

Incidence of diabetes was expressed as the number of type 2 diabetes cases per 100 person-years of follow-up. As the relevant period was considered the date of completion of the baseline examination between 2003 and 2005 until the either (i) occurrence of diabetes, (ii) the date of the last completed follow-up, (iii) death, or (iv) end of follow-up on December 31, 2009, whichever came first. For ease of interpretability, we report the incidence rates in terms of percent per year.

### Statistical analysis

Statistical methods used included the Student's *t*-test, chi-squared test, analysis of variance, or Kruskal–Wallis tests for normally or non-normally distributed continuous variables, respectively, and Cox's proportional hazards model. Univariate and multivariate Cox's proportional hazards models were fitted to identify the predictors of new-onset diabetes using SPSS version 18 for Windows (SPSS Inc., Chicago, IL, USA). Variables age, BMI, waist circumference, triglyceride, LDL, HDL, total cholesterol, and BP were entered in the multivariate-adjusted analyses as continuous variables, while gender, IGT, and IFG were categorical. Adjustment for age and gender was made in separate models. Age-adjusted means were calculated and compared using general linear models. The ability of FPG, 2-h glucose values, and $HbA_{1c}$ to predict the incidence of diabetes according to current OGTT definition or newly proposed $HbA_{1c}$-defined diabetes was examined by ROC curve and their respective areas under the curve, in which sensitivity was plotted as a function of 1-specificity. Areas under the ROC curves were compared by the algorithm developed by DeLong et al. [19]. All tests for statistical significance were two-tailed, confidence intervals (CI) were set at 95%, and $P < 0.05$ was considered significant.

## Results

### Characteristics

The baseline characteristics of the study participants by different $HbA_{1c}$ categories are shown in Table 1. In age-adjusted comparisons of variables at baseline, age, follow-up duration, number of follow-up visits, plasma glucose at 30 and 60 min., $HbA_{1c}$, and diastolic BP were more likely to increase and HDL was more likely to decrease across the four subject groups. The mean (SD) age of participants was 42.9 (6.3) years and 76.6% were women.

### Prevalence

Of the 3,176 subjects who received an OGTT, $HbA_{1c}$ was measured in 2,645 (83.3%) at baseline. Of the 3,176 participants, 292 had diabetes at baseline by OGTT and the prevalence of diabetes was 9.2% (95% CI: 8.2, 10.2). Of the 2,645 participants who had $HbA_{1c}$, 210 had diabetes at baseline by $HbA_{1c}$ $\geq$6.5 and the prevalence of diabetes was 7.9% (95% CI: 6.9, 9.0). Among these cases, 103 (49.0%) had diabetes according to both OGTT- and $HbA_{1c}$-defined diabetes, while 107 (51.0%) did not have diabetes by OGTT criteria. A total of 1,236 (38.9%) participants had pre-diabetes, including 655 (20.6%) IGT only and 581

**Table 1** Age, age-adjusted, and proportion characteristics of first-degree relatives of patients with type 2 diabetes by $HbA_{1c}$ categories in the Isfahan Diabetes Prevention Study

| Characteristics | Total | $HbA_{1c}$ level (%) | | | |
|---|---|---|---|---|---|
| | | <5.0 | 5.0–5.4 | 5.5–5.9 | 6.0–6.4 |
| Number (%) | 923 (100) | 446 (48.3) | 240 (26.0) | 150 (16.3) | 87 (9.4) |
| Age (year) | 42.9 (0.21) | 42.3 (0.30) | 43.0 (0.40) | 43.7 (0.51) | 43.8 (0.67)* |
| Height (cm) | 159.0 (0.26) | 158.8 (0.38) | 159.4 (0.52) | 159.0 (0.65) | 159.3 (0.86) |
| Weight (kg) | 73.1 (0.38) | 72.6 (0.55) | 73.7 (0.75) | 72.6 (0.94) | 75.0 (1.25) |
| Waist circumference (cm) | 88.6 (0.31) | 88.2 (0.44) | 89.2 (0.60) | 88.3 (0.76) | 89.4 (1.00) |
| Hip circumference (cm) | 107.6 (0.29) | 107.6 (0.42) | 107.4 (0.58) | 107.6 (0.73) | 108.4 (0.96) |
| Waist-to-hip ratio | 0.82 (0.002) | 0.82 (0.003) | 0.83 (0.004) | 0.82 (0.005) | 0.83 (0.007) |
| Body mass index ($kg/m^2$) | 28.9 (0.14) | 28.9 (0.20) | 29.0 (0.27) | 28.7 (0.34) | 29.6 (0.45) |
| Follow-up duration (year) | 5.0 (0.05) | 4.9 (0.07) | 4.9 (0.09) | 5.2 (0.12) | 5.3 (0.15)* |
| Number of follow-up visit | 2.6 (0.03) | 2.6 (0.05) | 2.5 (0.06) | 2.7 (0.08) | 2.8 (0.10) |
| FPS (mg/dl) | 96.6 (0.42) | 95.8 (0.59) | 96.9 (0.80) | 97.2 (1.02) | 98.2 (1.33) |
| PG 30 min (mg/dl) | 147.4 (1.09) | 144.0 (1.54) | 150.0 (2.11) | 153.1 (2.69) | 148.3 (3.59)* |
| PG 60 min (mg/dl) | 152.4 (1.44) | 147.3 (2.04) | 155.7 (2.78) | 157.2 (3.52) | 161.0 (4.65)** |
| PG 120 min (mg/dl) | 123.0 (1.16) | 120.6 (1.66) | 125.3 (2.26) | 124.6 (2.86) | 126.4 (3.75) |
| $HbA_{1c}$ (%) | 5.0 (0.02) | 4.4 (0.01) | 5.2 (0.02) | 5.7 (0.02) | 6.2 (0.03)*** |
| Cholesterol (mg/dl) | 195.9 (1.36) | 194.5 (1.92) | 199.8 (2.60) | 195.6 (3.31) | 192.7 (4.38) |
| LDL (mg/dl) | 118.5 (1.19) | 117.9 (1.67) | 121.4 (2.27) | 117.0 (2.92) | 115.7 (3.83) |
| HDL (mg/dl) | 44.9 (0.40) | 45.7 (0.58) | 45.2 (0.79) | 44.5 (1.00) | 41.0 (1.32)* |
| Triglyceride (mg/dl) | 167.3 (3.55) | 162.6 (5.12) | 170.6 (6.96) | 171.0 (8.94) | 176.4 (11.76) |
| Systolic BP (mm Hg) | 115.2 (0.56) | 113.8 (0.08) | 115.8 (0.10) | 117.1 (0.13) | 117.2 (0.18) |
| Diastolic BP (mm Hg) | 74.6 (0.04) | 73.4 (0.06) | 75.1 (0.08) | 76.4 (0.10) | 76.5 (0.13)* |
| Women, no (%) | 707 (76.6) | 345 (77.4) | 1182 (75.8) | 115 (76.7) | 65 (74.7) |
| Obesity, no (%) | 329 (36.1) | 157 (35.8) | 83 (34.9) | 56 (37.3) | 33 (38.8) |

Age-adjusted means were calculated using general linear models. Data are expressed as mean (SE) or number (%)

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ comparison across all four groups

(18.3%) IFG only by OGTT criteria, and 204 (7.7%; 95% CI: 6.7, 8.8) had pre-diabetes by $HbA_{1c}$ in the range 6.0–6.49%.

## Incidence

During 4,600 (1,078 men and 3,522 women) person-years of follow-up, 92 (10.0%) (19 men and 73 women) incident cases of type 2 diabetes occurred according to current OGTT definition, while 77 individuals had diabetes by the $HbA_{1c}$ ≥6.5. The overall incidence of subsequent diabetes was 2.0% (95% CI: 1.6, 2.4) (1.8% (95% CI: 1.1, 2.7) men and 2.1% (95% CI: 1.6, 2.6) women) per year by OGTT criteria, while incidence of diabetes was 1.7% (95% CI: 1.3, 2.0) (1.6% (95% CI: 0.9, 2.5) men and 1.7% (95% CI: 1.3, 2.2) women) per year by $HbA_{1c}$ ≥6.5. Among participants with $HbA_{1c}$ ≥6.5, 31.2% had diabetes, 20.8% had IGT, 26.0% had IFG, and 22.1% had NGT by OGTT criteria.

Table 2 shows the incidence of diabetes by baseline $HbA_{1c}$ levels. The incidence of diabetes increased across the four subject groups, from 1.2% per year in the $HbA_{1c}$ <5.0 group to 3.3% per year in the $HbA_{1c}$ = 6.0–6.4% group. Compared with participants with $HbA_{1c}$ <5.0%, the risk of diabetes was 2.75 times higher in those with $HbA_{1c}$ = 6.0–6.4% at baseline (hazard ratio (HR) 2.75; 95% CI: 1.5, 5.1) and 95% higher in those with $HbA_{1c}$ = 5.5–5.9% (HR 1.95; 95% CI: 1.1, 3.5) in unadjusted models. Controlling for age and gender slightly reduced the HR compared with the unadjusted model. In a multivariate model, the additional adjustment for other time-dependent covariates did not appreciably alter the HR compared with the model adjusted for age and gender (Table 2). Over 80% of incident cases arose among subjects with a baseline $HbA_{1c}$ of <6.0%.

The areas under the ROC curves for incidence of type 2 diabetes by $HbA_{1c}$ ≥6.5% were 0.636 (95% CI: 0.573, 0.698), 0.639 (95% CI: 0.568, 0.709), and 0.684 (95% CI: 0.619, 0.749) for the $HbA_{1c}$, fasting, and 2-h glucose values, respectively. The areas under the ROC curves for incidence of type 2 diabetes by OGTT-defined diabetes were 0.650

**Table 2** Incidence rates and relative risks of diabetes by $HbA_{1c}$ level and OGTT at baseline, the Isfahan Diabetes Prevention Study

| | $HbA_{1c}$ level (%) at baseline | | | |
|---|---|---|---|---|
| | <5.0 | 5.0–5.4 | 5.5–5.9 | 6.0–6.4 |
| Number of cases (%) | 26 (5.8) | 18 (7.5) | 18 (12.0) | 15 (17.2) |
| Person-year | 2,179 | 1,186 | 776 | 459 |
| Incidence/100 person-year (95% CI) | 1.2 (0.8, 1.7) | 1.5 (0.9, 2.4) | 2.3 (1.4, 3.6) | 3.3 (1.8, 5.3) |
| Unadjusted HR (95% CI) | 1.00 | 1.28 (0.70, 2.31) | 1.95 (1.07, 3.53) | 2.75 (1.46, 5.13) |
| Age- and gender-adjusted HR (95% CI) | 1.00 | 1.23 (0.68, 2.25) | 1.73 (0.95, 3.17) | 2.47 (1.30, 4.70) |
| Multivariate-adjusted HR[†] (95% CI) | 1.00 | 1.04 (0.53, 2.01) | 1.73 (0.92, 3.26) | 2.10 (1.00, 4.40) |

*CI* confidence interval, *HR* hazard ratio

[†] Hazard ratios (with 95% CI) calculated by Cox's proportional hazards model. Adjusted for age, gender, BMI, WC, triglyceride, LDL, HDL, total cholesterol, and blood pressure

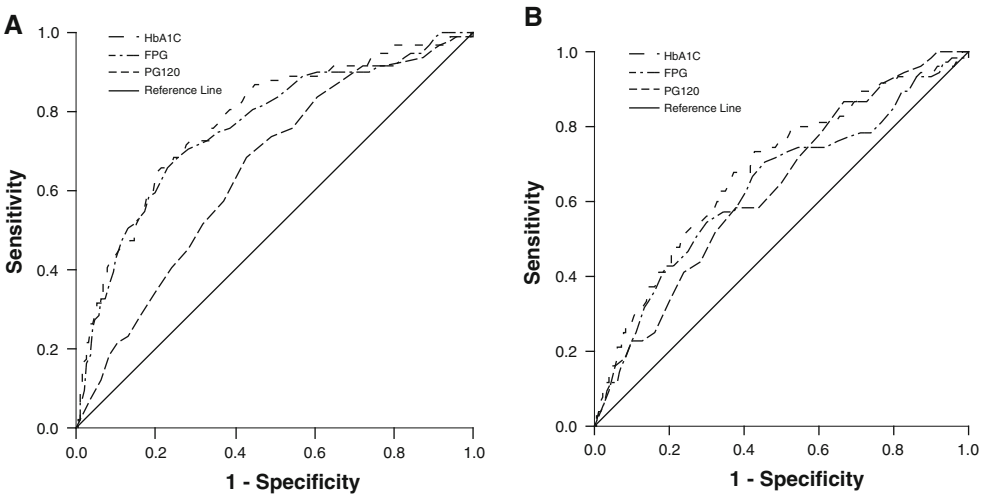


**Fig. 2** Receiver operating characteristic (*ROC*) curves for fasting, 2-h glucose, and $HbA_{1c}$ for prediction of type 2 diabetes by **a** OGTT- and **b** $HbA_{1c}$-defined diabetes in non-diabetic first-degree relatives of patients with type 2 diabetes. The estimates of the area under the ROC curves and their 95% confidence intervals are shown

**Area under the curve (95% Confidence Interval)**

| | |
|---|---|
| $HbA_{1C}$ 0.650 (0.594, 0.706) | $HbA_{1C}$ 0.636 (0.573, 0.698) |
| Fasting plasma glucose 0.760 (0.705, 0.815) | Fasting plasma glucose 0.639 (0.568, 0.709) |
| 2-hour plasma glucose 0.776 (0.724, 0.829) | 2-hour plasma glucose 0.684 (0.619, 0.749) |

(95% CI: 0.594, 0.706), 0.760 (95% CI: 0.705, 0.815), and 0.776 (95% CI: 0.724, 0.829) for the $HbA_{1c}$, fasting, and 2-h glucose values, respectively (Fig. 2). All plasma glucose concentrations were significant predictors for future risk of type 2 diabetes by either OGTT- or $HbA_{1c}$-defined diabetes ($P < 0.001$). The areas under the curves for 2-h PG concentration were significantly greater than those of $HbA_{1c}$ by OGTT-defined diabetes ($P < 0.001$). 2-h PG concentration had an area slightly but not significantly larger than that of $HbA_{1c}$ by $HbA_{1c}$-defined diabetes.

## Discussion

This is the first follow-up study among the non-diabetic FDRs of patients with type 2 diabetes that reports the incidence and prevalence of type 2 diabetes and relative risk for progression to diabetes according to the newly proposed $HbA_{1c}$-defined diabetes compared with those detected using current OGTT definition in Iran. We found an overall incidence of diabetes of 1.7% per year (77 patients) over an average follow-up of 5.0 years by $HbA_{1c} \geq 6.5$, while incidence of diabetes was 2.0% per year (92 patients) by OGTT criteria. It seems that the lower the $HbA_{1c}$ levels at baseline, the lower the risk of progression to diabetes. Almost half of those identified by the OGTT-defined diabetes had the $HbA_{1c} \geq 6.5\%$, confirming observations from other studies [20–22]. These findings clearly demonstrate that subjects identified by $HbA_{1c} \geq 6.5\%$ are different from those classified by the OGTT criteria. Our study showed that the discriminating power of FPG and 2-h post-load plasma glucose values to distinguish between individuals at diabetes risk and

those not at risk was almost similar to that of $HbA_{1c}$. Even though fasting, 2-h PG, and $HbA_{1c}$ value had approximately the same predictive power in our study, $HbA_{1c}$ is superior in clinical practice because it is a simple test and does not need fasting state. Choosing $HbA_{1c}$ as diabetes test avoids cost and inconveniences associated with OGTT [1].

This study shows that the prevalence and incidence rate of type 2 diabetes were lower when replacing the OGTT-defined diabetes with $HbA_{1c}$-defined. A recent study observing the impact of using $HbA_{1c}$ $\geq$6.5 for detecting type 2 diabetes instead of an OGTT found four populations with a decrease in prevalence and three populations with an increase [23, 24]. The first four populations had a relatively lower mean $HbA_{1c}$, similar to that within this cohort, which generally favors a lower proportion of the population with $HbA_{1c}$ $\geq$6.5%.

Only two studies have examined the incidence and relative risk of diabetes using repeated measure of $HbA_{1c}$ in individuals defined by different baseline $HbA_{1c}$ levels. Selvin et al. examined the incidence of self-reported diabetes in American men and women with different baseline $HbA_{1c}$ values [13]. The 15-year cumulative incidence of diabetes was 6, 12, 21, and 44% in individuals with a $HbA_{1c}$ of <5.0, 5.0–5.4, 5.5–5.9, and 6.0–6.4%, respectively. Chamnan et al. [25] also estimated the incidence of type 2 diabetes defined by the newly proposed diagnostic criteria and/or clinically in EPIC-Norfolk Cohort categorized by different $HbA_{1c}$ levels. The 3-year cumulative incidence of diabetes was 0.4, 0.3, 1.1, and 2.4% in individuals with a $HbA_{1c}$ of <5.0, 5.0–5.4, 5.5–5.9, and 6.0–6.4%, respectively. In our study, the estimated annual incidence was higher than those observed across all $HbA_{1c}$ categories. Our study sample was addressed to individuals at increased risk of developing type 2 diabetes, because they had FDRs with the disease and it might be explained by the differences in the levels of other risk factors and in particular the different definitions of diabetes used in each study. Different studies have found that the incidence and prevalence of type 2 diabetes are greater in those persons who have a family history of the disease [26–32]. A Swedish study was found that persons with a family history of diabetes have a 2–3 times higher prevalence of both diabetes and impaired glucose metabolism than one without (27).

Similar to our findings, an international expert committee reported that people with a $HbA_{1c}$ value of at least 6% but less than 6.5% are likely to be at highest risk for progression to diabetes [17].

Our findings are also compatible with Tsuji et al.'s; in screening test for diabetes by using the ROC curve analysis, they found that $HbA_{1c}$ has almost the same discriminatory power as FPG [33].

A few studies [34, 35] suggest that the combined use of FPG and $HbA_{1c}$ predicts the incidence of diabetes more effectively than either test alone in individuals at risk of diabetes. This warranted further study.

The strengths of the present study include the prospective cohort design, the sample consisting of both men and women of a wide age range from an Iranian population, diagnosis of diabetes based on both repeat standard OGTT and $HbA_{1c}$, and information on potential determinants of diabetes. All participants underwent a full OGTT and $HbA_{1c}$, which was repeated in each follow-up visit. Selection and information bias is considered unlikely by virtue of the prospective design. Our study was addressed to individuals at increased risk of developing type 2 diabetes, because they had FDRs with the disease. The $HbA_{1c}$ value reflects mean glycemia over the preceding 2–3 months, so people with a history of diabetes of less than 3 months might not be identified by $HbA_{1c}$ testing. However, this is extremely unlikely given that on average a seven-year gap exists between the actual onset of diabetes and its diagnosis [36]. In addition, conditions that shorten the survival of erythrocytes, such as hemolytic anemia, will decrease the concentration of $HbA_{1c}$. Conversely, conditions that prolong the age of erythrocytes, such as splenectomy and aplastic anemia, will increase the concentration of $HbA_{1c}$ independent of glycemia. Hemoglobinopathies such as hemoglobin S (sickle-cell) interfere with some assays. Thus, the use of $HbA_{1c}$ may be inappropriate for such disorders.

However, there is a need for more studies in developing countries, including the cost-effectiveness of $HbA_{1c}$ versus plasma glucose testing, before $HbA_{1c}$ can be universally recommended as a diagnostic test for diabetes in developing world.

In conclusion, our study indicates that the incidence and prevalence of diabetes using newly proposed $HbA_{1c}$ threshold in this FDRs of patients with type 2 diabetes were slightly lower than using current OGTT definition. The $HbA_{1c}$ was almost similar to FPG and post-load glucose values for predicting new-onset diabetes. However, $HbA_{1c}$ is superior in clinical practice because of clinical convenience and superior precision. $HbA_{1c}$ appeared to miss a proportion of OGTT-defined diabetes cases.

**Acknowledgments** This work was supported by grants from the Isfahan Endocrine and Metabolism Research Center, Iran. The authors are grateful to Mr. Majid Abyar for computer technical assistance. This study could not have been conducted without the contribution of the FDRs of patients with type 2 diabetes who consented to participate.

**Conflict of interest** None.

## References

1. Bennett CM, Guo M, Dharmage SC (2007) $HbA_{1c}$ as a screening tool for detection of Type 2 diabetes: a systematic review. Diabet Med 24:333–343

2. American Diabetes Association (2010) Diagnosis and classification of diabetes mellitus. Diabetes Care 33(Suppl 1):S62–S69
3. Davidson MB, Schriger DL, Lorber B (2001) $HbA_{1c}$ measurements do not improve the detection of Type 2 diabetes in a randomly selected population. Diabetes Care 24:2017–2018
4. Perry RC, Shankar RR, Fineberg N, McGill J, Baron AD (2001) $HbA_{1c}$ measurement improves the detection of Type 2 diabetes in high-risk individuals with non-diagnostic levels of fasting plasma glucose: the Early Diabetes Intervention Program (EDIP). Diabetes Care 24:465–471
5. Tanaka Y, Atsumi Y, Asahina T, Hosokawa K, Matsuoka K, Kinoshita J et al (1998) Usefulness of revised fasting plasma glucose criterion and characteristics of the insulin response to an oral glucose load in newly diagnosed Japanese diabetic subjects. Diabetes Care 21:1133–1137
6. Barr RG, Nathan DM, Meigs JB, Singer DE (2002) Tests of glycaemia for the diagnosis of type 2 diabetes mellitus. Ann Intern Med 137:263–272
7. Engelgau MM, Narayan KM, Herman WH (2000) Screening for type 2 diabetes. Diabetes Care 23:1563–1580
8. Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M (2002) Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 48:436–472
9. Selvin E, Crainiceanu CM, Brancati FL, Coresh J (2007) Short-term variability in measures of glycemia and implications for the classification of diabetes. Arch Intern Med 167:1545–1551
10. Mooy JM, Grootenhuis PA, de-Vries H, Kostense PJ, Popp-Snijders C, Bouter LM et al (1996) Intra-individual variation of glucose, specific insulin and proinsulin concentrations measured by two oral glucose tolerance tests in a general caucasian population: the Hoorn Study. Diabetologia 39:298–305
11. Sacks DB, ADA/EASD/IDF Working Group of the HbA1c Assay (2005) Global harmonization of haemoglobin A1C. Clin Chem 1:681–683
12. Kahn R, Fonseca V (2009) Translating the A1C assay. Diabetes Care 31:1704–1707
13. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J et al (2010) Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med 362:800–811
14. Executive summary (2008) Standard of medical care in diabetes-2008. Diabetes Care 31:S5–S11
15. Amini M, Janghorbani M (2007) Diabetes and impaired glucose regulation in first degree relatives of patients with type 2 diabetes in Isfahan, Iran: prevalence and risk factors. Rev Diabetes Stud 4:169–176
16. Friedewald WT, Levy RI, Fredrickson DS (1972) Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 18:499–502
17. The International Expert Committee (2009) International Expert Committee Report on the role of the $A_{1c}$ assay in the diagnosis of diabetes. Diabetes Care 32:1327–1334
18. Expert Committee on the Diagnosis, Classification of Diabetes Mellitus (2003) Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care suppl 1:S5–S20
19. DeLong ER, DeLong DM, Clarke-Pearson DL (1988) Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 44:837–845
20. Borg R, Vistisen D, Witte DR, Borch-Johnsen K (2010) Comparing risk profiles of individuals diagnosed with diabetes by OGTT and HbA1c the Danish Inter99 study. Diabet Med 27:906–910
21. DECODE Study Group on behalf of the European Diabetes Epidemiology Study Group (1998) Will new diagnostic criteria for diabetes mellitus change phenotype of patients with diabetes? Reanalysis of European epidemiological data. BMJ 317:371–375
22. Engelgau MM, Thompson TJ, Herman WH, Boyle JP, Aubert RE, Kenny SJ et al (1997) Comparison of fasting and 2-h glucose and HbA1c levels for diagnosing diabetes. Diagnostic criteria and performance revisited. Diabetes Care 20:785–791
23. Christensen DL, Witte DR, Kaduka L, Jørgensen ME, Borch-Johnsen K, Mohan V et al (2010) Moving to an A1C-based diagnosis of diabetes has a different impact on prevalence in different ethnic groups. Diabetes Care 33:580–582
24. Mostafa SA, Davies MJ, Webb D, Gray LJ, Srinivasan BT, Jarvis J et al (2010) The potential impact of using glycated haemoglobin as the preferred diagnostic tool for detecting Type 2 diabetes mellitus. Diabet Med 27:762–769
25. Chamnan P, Simmons RK, Forouhi NG, Luben RR, Khaw KT, Wareham NJ et al (2010) Incidence of type 2 diabetes using proposed HbA1c diagnostic criteria in the EPIC-Norfolk cohort: implications for preventive strategies. Diabetes Care Publish Ahead of Print, published online 9 July 2010
26. Janghorbani M, Amini M (2009) Diabetes risk among first-degree relatives of patients with type 2 diabetes in Isfahan, Iran. Obes Metab 5:114–120
27. Kuhl J, Hilding A, Ôstenson CG, Grill V, Efendic S, Båvenholm P (2005) Characterisation of subjects with early abnormalities of glucose tolerance in the Stockholm Diabetes Prevention Programme: the impacts of sex and type 2 diabetes heredity. Diabetologia 48:35–40
28. Grill V, Persson G, Carlsson S, Norman A, Alvarsson M, Ostensson CG et al (1999) Family history of diabetes in middle-aged Swedish men is a gender unrelated factor which associates with insulinopenia in newly diagnosed diabetic subjects. Diabetologia 42:15–23
29. Park HS, Yim KS, Cho SI (2004) Gender differences in familial aggregation of obesity-related phenotypes and dietary intake pattern in Korean families. Ann Epidemiol 14:486–491
30. Li JK, Ng MC, So WY, Chiu CK, Ozaki R, Tong PC et al (2006) Phenotypic and genetic clustering of diabetes and metabolic syndrome in Chinese families with type 2 diabetes mellitus. Diabetes Metab Res Rev 22:46–526
31. Meigs JB, Cupples LA, Wilson PWF (2000) Parental transmission of type 2 diabetes mellitus: the Framingham Offspring Study. Diabetes 49:2201–2207
32. Klein BE, Klein R, Moss SE, Cruickshanks KJ (1996) Parental history of diabetes in a population-based study. Diabetes Care 19:827–830
33. Tsuji I, Nakamoto K, Hasegawa T, Hisashige A, Inawashiro H, Fukao A et al (1991) Receiver operating characteristic analysis on fasting plasma glucose, HbA1c, and fructosamine on diabetes screening. Diabetes Care 14:1075–1077
34. Ko GT, Chan JC, Tsang LW, Cockram CS (2000) Combined use of fasting plasma glucose and HbA1c predicts the progression to diabetes in Chinese subjects. Diabetes Care 23:1770–1773
35. Inoue K, Matsumoto M, Kobayashi Y (2007) The combination of fasting plasma glucose and glycosylated hemoglobin predicts type 2 diabetes in Japanese workers. Diabetes Res Clin Pract 77:451–458
36. Harris MI (1993) Undiagnosed NIDDM: clinical and public health issues. Diabetes Care 16:642–652