DOI: 10.1111/j.1464-5491.2011.03392.x

Article: Epidemiology

Predictive value of HbA_{1c} for incident diabetes among subjects with impaired glucose tolerance—analysis of the Indian Diabetes Prevention Programmes

A. Ramachandran, C. Snehalatha, A. Samith Shetty and A. Nanditha

India Diabetes Research Foundation and Dr A. Ramachandran's Diabetes Hospitals, Chennai, India

Accepted 20 July 2011

Abstract

Aims The objectives of the study were to assess the predictive value of baseline HbA_{1c} for incident diabetes among the participants with impaired glucose tolerance in the Indian Diabetes Prevention Programmes 1 and 2.

Methods Data at baseline and at 3-year follow-up were analysed in combined cohorts of the Indian Diabetes Prevention Programmes 1 and 2. Within the 3 years, 324 of the 845 participants developed diabetes (World Health Organization criteria). The predictive value of baseline HbA_{1c} for incident diabetes was determined by logistic regression analysis.

Results Baseline HbA_{1c} values had heterogenous distribution. The distribution was similar in isolated impaired glucose tolerance or in impaired glucose tolerance in combination with impaired fasting glucose. A progressive increase in diabetes occurred with increasing HbA_{1c}. HbA_{1c} showed the strongest association with incident diabetes in the multiple logistic regression analysis (odds ratio 3.548, $P < 0.0001$). The cut-off HbA_{1c} of 43 mmol/mol (6.05%) had 67% sensitivity and 60% specificity to predict future diabetes. The diagnostic sensitivity of HbA_{1c} of ≥ 48 mmol/mol (≥ 6.5%) was only 51%, with a specificity of 87%, when compared with the oral glucose tolerance glucose values.

Conclusions Baseline HbA_{1c} was highly predictive of future diabetes in Asian Indian subjects with impaired glucose tolerance and nearly 60% of the incidence occurred with values ≥ 42 mmol/mol (≥ 6.0). Diagnostic sensitivity of HbA_{1c} ≥ 48 mmol/mol (≥ 6.5%) for new diabetes was only 51% using the oral glucose tolerance test as the standard for comparison.

Diabet. Med. 29, 94–98 (2012)

Keywords HbA_{1c}, prediction, prevention, Type 2 diabetes

Introduction

HbA_{1c} is shown to be significantly associated with the occurrence of diabetic complications and is being recommended by an International Expert Committee [1] and by the American Diabetes Association [2] as a diagnostic tool for diabetes. The American Diabetes Association also suggested that HbA_{1c} values between 39 mmol/mol (5.7%) and 46 mmol/mol (6.4%) identify pre-diabetes [2]. HbA_{1c} is more convenient and reproducible than blood glucose [3]. However, there is a great deal of debate about its optimal cut-off for diagnosing diabetes, as it shows considerable ethnic variations in its sensitivity [3–7].

Correspondence to: Dr A. Ramachandran, President, India Diabetes Research Foundation and Chairman and Managing Director, Dr A. Ramachandran's Diabetes Hospitals, 28 Marshalls Road, Egmore, Chennai—600 008, India. E-mail: ramachandran@vsnl.com

Indian diabetes prevention programmes [8,9] showed that a moderate lifestyle modification or a small dose of metformin (500 mg/day) were equally effective in reducing the risk of diabetes in Asian Indian people with impaired glucose tolerance [8,9]. A combination of lifestyle modification with either metformin or pioglitazone did not improve the efficacy of lifestyle modification in the population. In previous analyses, we tested the predictive value of baseline insulin resistance and β-cell function for incident diabetes [8,10]. The reduction in incident diabetes with intervention occurred as a result of improved insulin action and insulin secretion [11]. The predictive value of baseline HbA_{1c} was not evaluated in these studies.

The primary objective of this analysis was to assess the predictive value of baseline HbA_{1c} for incident diabetes. The secondary objectives were to study the distribution of HbA_{1c} values in subjects with pre-diabetes and to find out whether there were variabilities in HbA_{1c} values among people with isolated impaired glucose tolerance and when impaired glucose tolerance

and impaired fasting glucose coexisted. The diagnostic sensitivity of HbA_{1c} cut-off value of 48 mmol/mol (6.5%) in comparison with the results of an oral glucose tolerance test [12] as the reference method was also studied.

The data from Indian Diabetes Prevention Programmes (IDPP)1 and 2 were combined as the selection criteria and the characteristics of the study participants in both studies were identical. This helped to increase the sample size for the analysis.

Research design and methods

IDPP-1 [8] and IDPP-2 [9] were 3-year prospective, randomized, controlled studies among Asian Indian subjects with persistent impaired glucose tolerance (2-h post-glucose of 7.8–11.0 mmol/l). The IDPP-1 study consisted of: a control group, the participants of which were given standard advice; a group advised on lifestyle modification; and groups on treatment with metformin and a combination of lifestyle modification and metformin [8]. The IDPP-2 study was carried out in a different cohort of subjects with impaired glucose tolerance using lifestyle modification + placebo as the control group and using lifestyle modification + pioglitazone as the intervention group [9]. In both studies, no cases of isolated impaired fasting glucose (fasting plasma glucose 6.1–6.9 mmol/l and 2-h post-glucose < 7.8 mmol/l) were selected and presence of impaired fasting glucose was not an inclusion criterion. In both studies, the primary outcome was development of diabetes detected by a standard oral glucose tolerance test (fasting plasma glucose ≥ 7.0 mmol/l and/or 2-h post-glucose ≥ 11.1 mmol/l) [12]. All subjects underwent annual oral glucose tolerance test. A semi-annual postprandial capillary glucose test was performed. Diabetes detected in any person was confirmed with an oral glucose tolerance test.

HbA_{1c} was analysed using the immunoturbidimetric method (Tina-Quant Reagents; Roche Diagnostics GmbH, Mannheim, Germany). This procedure shows good correlation with the high-performance liquid chromatography method (r = 0.9937) and is an approved procedure by the International Federation of Clinical Chemistry, certified by the National Glycohemoglobin Standardization Procedure and traceable to the Diabetes Control and Complications Trial assay procedure. The intra-batch coefficient variation of HbA_{1c} was < 5% and inter-batch variation was < 7%.

In IDPP-1, the relative risk reductions with all interventions were similar (varying from 26.4 to 28.5%) when compared with the control group [8]. In the IDPP-2 study, the cumulative incidence of diabetes at 36 months were similar in the intervention and placebo group (29.8 and 31.6%, respectively) [9]. BMI, waist circumference and blood pressure were measured at baseline and during each review. Plasma glucose was measured (glucose oxidase method) at fasting, 30 min and 2 h during the oral glucose tolerance test and corresponding plasma insulin was measured using a radioimmunoassay kit from DiaSorin (Saluggia, Italy). Indices of insulin resistance [homeostasis model assessment (HOMA-IR)] [13] and early insulin secretion [(30-min fasting insulin (pmol/l)) divided by 30-min glucose (mmol/l) (ΔI/G)] were calculated [14]. Among the total of 869 followed up for 3 years in both studies, plasma insulin values were not available for 24 individuals. Hence, this analysis was carried out using data of 845 subjects (699 men; 146 women).

Statistical analysis

Mean and standard deviation are shown for normally distributed variables. Student's t-test was used for inter-group comparison. The paired t-test was used for intra-group comparisons. Median values were used for skewed variables and the Mann–Whitney U-test was used for the comparisons. Inter-group proportions were compared using the χ^2-test. Multiple logistic regression (Enter method) was used to identify the baseline variables that predicted incident diabetes. The independent variables included in the equation were baseline age, BMI, waist circumference, fasting plasma glucose, 2-h post-glucose, $HbA_{1c,}$ HOMA-IR, ΔI/G and all intervention vs. control. Receiver operating characteristic curves were drawn with standard methods to identify the cut-off value of baseline HbA_{1c} to predict incident diabetes and also to compare its performance with that of the baseline 2-h post-glucose value. Receiver operating characteristic analysis was also performed to identify the sensitivity of an HbA_{1c} cut-off of 48 mmol/mol (6.5%) to diagnose diabetes, identified by the 2-h post-glucose measurement of ≥ 11.1 mmol/l during the follow-up oral glucose tolerance test.

Analyses were carried out using SPSS version 10.0 (SPSS, Chicago, IL, USA). A P-value of ≤ 0.05 was considered significant.

Results

Table 1 shows the characteristics of the study group at baseline and at the follow-up to 3 years. As expected, the glycaemic variables, including HbA_{1c}, showed significant increases at follow-up. Diastolic blood pressure increased while total cholesterol and LDL cholesterol levels decreased significantly. Baseline values of HbA_{1c} showed a heterogeneous distribution. At baseline, 50.2% of subjects had HbA_{1c} < 42 mmol/mol (< 6.0%), 29.5% had values between 42 mmol/mol (6.0%) and < 48 mmol/mol (< 6.5%) and 20.2% showed values ≥ 48 mmol/mol (≥ 6.5%). During the follow-up, the percentage of those with < 42 mmol/mol (<6.0%) increased significantly. When the American Diabetes Association criteria for HbA_{1c} for diagnosing pre-diabetes [10] were applied, 28.8% had values < 39 mmol/mol (< 5.7%), 45.7% had values of ≥ 39 mmol/mol (≥ 5.7%) to < 46 mmol/mol (< 6.4%) and 25.6% had values ≥ 46 mmol/mol (≥ 6.4%).

There was a progressive increase in incidence of diabetes with increasing levels of baseline HbA_{1c}. The percentages of incident diabetes (n = 324) in HbA_{1c} categories < 42 mmol/mol (< 6.0%), 42–46 mmol/mol (6.0–6.4%) and ≥ 48 mmol/mol (≥ 6.5%) of HbA_{1c} were 25.2% (107 of 426), 38.6% (96 of 249) and 70.3% (121 of 172), respectively. The differences between

Table 1 Characteristics of the study group at baseline and follow-up (n = 845)

Variables	Baseline	Follow-up	*P*-value
Age (years)	45.6 ± 5.9		
Body mass index (kg/m^2)	25.8 ± 3.4	26.0 ± 3.4	0.364
Waist circumference (cm)	90.0 ± 8.2	90.2 ± 8.1	0.235
Blood pressure (mmHg)			
Systolic	120.2 ± 13.4	120.6 ± 12.1	0.450
Diastolic	75.1 ± 9.7	80.5 ± 8.9	< 0.0001
Plasma glucose (mmol/l)			
0 min	5.5 ± 0.7	8.7 ± 0.8	< 0.0001
2-h plasma glucose	6.1 ± 1.4	9.8 ± 3.4	< 0.0001
HbA$_{1c}$ (%)	6.22 ± 0.55	6.73 ± 1.16	< 0.0001
< 42 mmol/mol *n* (%) (< 6.0)	424 (50.2)	354 (41.9)	0.002
≥ 42 to < 48 mmol/mol *n* (%) (≥ 6.0 to < 6.5)	249 (29.5)	245 (29.0)	0.977
≥ 48 mmol/mol *n* (%) (≥ 6.5)	172 (20.2)	234 (27.7)	< 0.0001
Lipid profile (mmol/l)			
Cholesterol	5.2 ± 0.97	5.1 ± 1.0	0.003
Triglycerides*	1.59	1.57	0.302
HDL	1.1 ± 0.23	1.1 ± 0.24	0.979
LDL	3.25 ± 0.80	3.10 ± 0.86	< 0.0001

Values are mean ± SD.
*Median value.

Table 2 Results of multiple logistic regression analyses

Independent variables	β	Odds ratio	95% CI	*P*-value
Waist circumference (cm)	0.04	1.041	1.013–1.069	0.004
2-h plasma glucose	0.022	1.022	1.01–1.033	< 0.0001
HbA$_{1c}$ (%)	1.266	3.548	2.572–4.894	< 0.0001
ΔI/G	−0.012	0.988	0.983–0.994	< 0.0001
Intervention vs. control	−0.653	0.520	0.338–0.801	0.003

Dependent variables—incident diabetes vs. others. Baseline data were used as independent variables. Significant associations are shown
Age, BMI, fasting plasma glucose and HOMA-IR were non-significant.

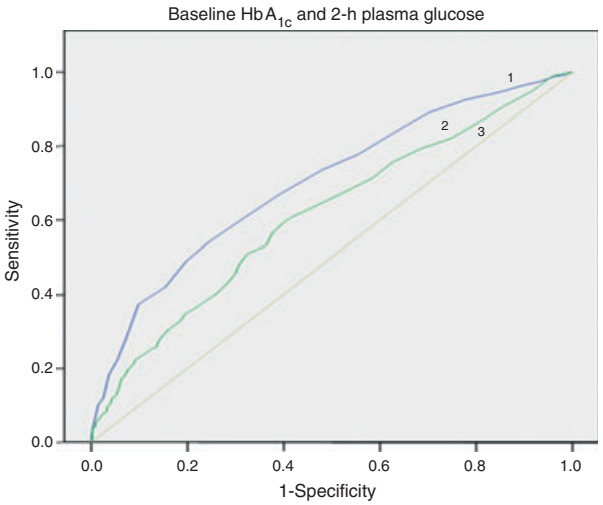

FIGURE 1 Receiver operating characteristic curves showing predictive performance of baseline HbA$_{1c}$ (curve 1) and 2-h plasma glucose (curve 2) for the 3-year incidence of diabetes, identified by oral glucose tolerance test (World Health Organization criteria). HbA$_{1c}$ area under the curve (AUC) = 0.700 (95% CI 0.664–0.737) P < 0.0001. Two-hour plasma glucose AUC = 0.614 (95% CI 0.575–0.653) P < 0.0001. Curve 3 is the reference line.

the first and second and the first and third categories were highly significant (χ^2 = 12.6, P < 0.0001, and χ^2 = 39.9, P < 0.0001, respectively).

Increasing waist circumference, 2-h post-glucose and HbA$_{1c}$ were strongly predictive of incident diabetes. Increasing β-cell function (ΔI/G) and preventive interventions had protective effects (Table 2). Among these, baseline HbA$_{1c}$ had the strongest association with incident diabetes (odds ratio 3.548, P < 0.0001)

The sensitivity of the baseline HbA$_{1c}$ to predict incident diabetes was assessed by the receiver operating characteristic analysis. As shown in Fig. 1, a cut-off value of 42 mmol/mol (5.95%) had 67% sensitivity and 60.8% specificity to predict incident diabetes. The analysis also showed that the baseline 2-h post-glucose of 8.44 mmol/l (152 mg/dl) had both the sensitivity and specificity at the 60% level. The area under the HbA$_{1c}$ curve was higher [0.700 ± SE 0.019 (95% CI 0.664–0.737), P < 0.0001] than the area for 2-h post-glucose [0.0614 ± SE 0.02 (95% CI 0.575–0.653), P < 0.0001].

Among the 324 subjects who developed diabetes in the 3-year period, 224 (69.1%) subjects had isolated impaired glucose tolerance and 100 (30.9%) had impaired glucose tolerance + impaired fasting glucose, at the baseline. The baseline and follow-up HbA$_{1c}$ values (%) were 6.20 ± 0.55 and 6.66 ± 1.09 for the group with isolated impaired glucose tolerance group and 6.25 ± 0.53 and 6.89 ± 1.29 for the group with impaired fasting glucose + impaired glucose tolerance (P < 0.0001 between the groups at follow-up). The distribution of baseline HbA$_{1c}$ in the three categories, as shown in Table 1, was similar in both groups (data not shown).

Among the 324 cases of incident diabetes diagnosed using the oral glucose tolerance test glucose values, only 165 individuals (51%) had HbA$_{1c}$ values of ≥ 48 mmol/mol (≥ 6.5%).

Discussion

In the IDPP studies, baseline HbA_{1c} was strongly predictive of incident diabetes among the subjects with impaired glucose tolerance who were followed-up to 3 years. Among the baseline variables which were predictive of incident diabetes, HbA_{1c} had the highest odds ratio. The HbA_{1c} values were highly heterogeneous; one half of the participants (50.2%) had HbA_{1c} values < 42 mmol/mol (< 6.0%), 29.8% had values between 42 mmol/mol (6.0%) and < 48 mmol/mol (< 6.5%) and the remaining 20.0% had values ≥ 48 mmol/mol (≥ 6.5%). The baseline distribution of subjects with pre-diabetes was also similar when the American Diabetes Association criteria [10] for the diagnosis of pre-diabetes was applied.

The receiver operating characteristic analysis showed that the majority of the incident cases would have occurred where the baseline HbA_{1c} was ≥ 42 mmol/mol (≥ 6.0%). However, the interventions were also effective in the ranges of < 42 mmol/mol (< 6.0%) or ≥ 48 mmol/mol (≥ 6.5%). The power of any prospective study in Asian Indian subjects with impaired glucose tolerance is likely to be enhanced by selecting patients with an HbA_{1c} ≥ 6.0% (≥ 42 mmol/mol) and/or a 2-h post-glucose value of ≥ 8.4 mmol/l (≥ 152 mg/dl).

The International Expert Committee [1] stressed the continuum of risk for diabetes with all glycaemic variables and did not specify an equivalent intermediate category of HbA_{1c}. It was noted that the people with HbA_{1c} in the suggested ranges for 'normal' and 'diabetes' cut-off [42 to < 48 mmol/mol (6.0 – < 6.5%)] had a more than 10-fold higher risk of incident diabetes than the people with lower levels [15–17].

In the Finnish Diabetes Prevention Study (DPS), 14% of the participants had baseline HbA_{1c} values of 42–48 mmol/mol (6.0–6.5%) and 7% had the values ≥ 48 mmol/mol (≥ 6.5%)[18]. The presence of a higher percentage of subjects with baseline HbA_{1c} of ≥ 42 mmol/mol (≥ 6.0%) in the IDPP studies probably was because of ethnic variations in glycation rates. The rate of glycation may be highly variable among the populations and the probability of 'low' and 'high' glycators exist [19]. Among the participants in the Diabetes Prevention Programme (DPP), mean HbA_{1c} levels were found to be higher among the US racial and ethnic minority groups [4]. It was suggested that haemoglobin glycation or red cell survival might differ among racial and ethnic groups. It was concluded that, among patients with impaired glucose tolerance, HbA_{1c} might not be valid for assessing and comparing glycaemic control in these groups [4].

The heterogeneous nature of HbA_{1c} values in subjects with pre-diabetes have been reported in studies in varied ethnic populations [4,18]. A systematic review had suggested that a cut-off of HbA_{1c} > 43 mmol/mol (> 6.1%) might be the optimal for diagnosis of diabetes [20]. The American Diabetes Association criteria for HbA_{1c} in subjects with pre-diabetes did not apply in all populations [21].

In our study, the diagnostic sensitivity of the suggested HbA_{1c} cut-off of ≥ 48 mmol/mol (≥ 6.5%) was 51.0% when the standard oral glucose tolerance test values were used as the reference method. The HbA_{1c} and plasma glucose criteria did not identify the same group of subjects. These observations were in concurrence with the recently published report by the Diabetes Prevention Study group showing that nearly 60% of the incident cases in the study would have been undiagnosed if the HbA_{1c} cut-off of ≥ 48 mmol/mol (≥ 6.5%) had been used [18]. The heterogeneous nature of the HbA_{1c} values in subjects with pre-diabetes was also highlighted in the report.

Using population-based cross-sectional data, Mohan *et al.* [22] suggested that the optimal cut-off point for diagnosing pre-diabetes in Asian Indians was an HbA_{1c} of 38 mmol/mol (5.6%). They also suggested that HbA_{1c} cut-off points of 43 mmol/mol (6.1%) and 46 mmol/mol (6.4%) were optimal for identifying newly diagnosed diabetes in the population using 2-h post-glucose and fasting glucose, respectively, with an accuracy of ≥ 90%. Several population-based studies have shown that an HbA_{1c} cut-off of 48 mmol/mol (6.5%) is highly specific, but has low sensitivity for identification of prevalent undiagnosed diabetes [23–25]. In all these studies, the reference method for diagnosis was the plasma glucose cut-off values.

Most factors that alter the plasma glucose values, such as intra-individual variations, acute illness, recent exercise and food ingestion, timing and type of sample used (whole blood, plasma) and sample handling do not affect measurement of HbA_{1c} values. Measurement of HbA_{1c} in a random blood sample is possible. Intra-individual variations are minimal and HbA_{1c} strongly predicts development of microvascular complications. However, the main disadvantages in measuring HbA_{1c} are the higher cost and lack of widespread availability of standardized procedures in many countries.

The strengths of this study are its prospective nature and the fairly large sample size. As the different intervention methods gave similar relative reductions vs. the control group, we did not analyse the results separately in those groups.

In the IDPP studies, subjects positive for impaired glucose tolerance on two oral glucose tolerance tests were selected, whereby cases of transient impaired glucose tolerance were eliminated [8,9]. Moreover, to a great extend we could also exclude probable diabetic cases. Among the patients with values of HbA_{1c} ≥ 48 mmol/mol (≥ 6.5%), diabetes was excluded by two oral glucose tolerance tests, using the World Health Organization criteria [12].

In conclusion, baseline HbA_{1c} values were the most powerful predictors of incident diabetes in the 3-year study period. Asian Indian subjects with impaired glucose tolerance have a heterogenous distribution of HbA_{1c} values. Fifty per cent of those subjects had values < 42 mmol/mol (< 6.0%), 30% had values of 42 mmol/mol (6.0%) to < 48 mmol/mol (< 6.5%) and 20% had values ≥ 48 mmol/mol (≥ 6.5%). The distribution of HbA_{1c} was similar in isolated impaired glucose tolerance and impaired fasting glucose + impaired glucose tolerance. Preventive interventions were effective in all subgroups. Identification of subjects with abnormal HbA_{1c} appears valuable, as abnormal HbA_{1c} has a strong predictive value for

diabetes and therefore identifies subjects with 'true pre-diabetes' requiring preventive interventions. Inclusion of subjects with impaired glucose tolerance with baseline $HbA_{1c} \geq 42$ mmol/mol (≥ 6.0%) would help to increase the power of prospective studies among Asian Indian subjects.

Competing interests

Nothing to declare.

Acknowledgements

We acknowledge the valuable help given by the following Indian Diabetes Prevention Programme team members in conducting the field survey: Mary Simon, C. K. Sathish Kumar, S. Selvam, A. Catherine Seeli and M. Muruganandam. We thank L. Vijaya for helping in statistical analysis and secretarial help. The secretarial assistance of Bobby Alex is also acknowledged.

References

1 International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care* 2009; **32**: 1327–1334.
2 American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2011; **34**: S62–S69.
3 Lu ZX, Walker KZ, O Dea K, Sikaris KA, Shaw JE. A1C for screening and diagnosis of type 2 diabetes in routine clinical practice. *Diabetes Care* 2010; **33**: 817–819.
4 Herman WH, Ma Y, Uwaifo G, Haffner S, Kahn SE, Horton ES *et al.* the Diabetes Prevention Program Research Group Differences in A1C by race and ethnicity among patients with impaired glucose tolerance in the Diabetes Prevention Program. *Diabetes Care* 2007; **30**: 2453–2457.
5 Eberhardt MS, Lackland DT, Wheeler FC, German RR, Teutsch SM. Is race related to glycemic control? As assessment of glycosylated hemoglobin in two South Carolina Communities. *J Clin Epidemiol* 1994; **47**: 1181–1189.
6 Ziemer DC, Kolm P, Weintraub WS, Vaccarino V, Rhee MK, Twombly JG *et al.* Glucose-independent, Black–White differences in hemoglobin A1c levels. *Ann Intern Med* 2010; **152**: 770–777.
7 Herman WH, Cohen RM. Hemoglobin A1c: teaching a new dog old tricks. *Ann Intern Med* 2010; **152**: 815–817.
8 Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V. Indian Diabetes Prevention Programme (IDPP). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia* 2006; **49**: 289–297.
9 Ramachandran A, Snehalatha C, Mary S, Selvam S, Kumar CK, Seeli AC *et al.* Pioglitazone does not enhance the effectiveness of lifestyle modification in preventing conversion of impaired glucose tolerance to diabetes in Asian Indians: results of the Indian Diabetes Prevention Programme-2 (IDPP-2). *Diabetologia* 2009; **52**: 1019–1026.
10 Ramachandran A, Samith Shetty A, Nanditha A, Snehalatha C. Efficacy of primary prevention interventions when fasting and post-glucose dysglycemia coexist. *Diabetes Care* 2010; **33**: 2164–2168.
11 Snehalatha C, Mary S, Selvam S, Sathish Kumar CK, Shetty SB, Nanditha A *et al.* Changes in insulin secretion and insulin sensitivity in relation to the glycemic outcomes in subjects with impaired glucose tolerance in the Indian Diabetes Prevention Programme-1 (IDPP-1). *Diabetes Care* 2009; **32**: 1796–1801.
12 World Health Organization. *Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications. Part I: Diagnosis and Classification of Diabetes Mellitus*. WHO/NCD/NCS/99.2. Geneva: World Health Organization, 1999.
13 Mathews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostatis model assessment insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1958; **28**: 412–419.
14 Wareham NJ, Philips DIW, Byrne CD, Hales CN. The 30-min insulin increase mental response in an OGTT as a measure of insulin secretion. *Diabet Med* 1995; **12**: 931.
15 Edelman D, Olsen MK, Dudley TK, Harris AC, Oddone EZ. Utility of hemoglobin A1C in predicting diabetes risk. *J Gen Intern Med* 2004; **19**: 1175–1180.
16 Sato KK, Hayashi T, Harita N, Yoneda T, Nakamura Y, Endo G *et al.* Combined measurement of fasting plasma glucose and A1C is effective for the prediction of type 2 diabetes the Kansai Healthcare Study. *Diabetes Care* 2009; **32**: 644–646.
17 Shimazaki T, Kadowaki T, Ohyama Y, Ohe K, Kubota K. Hemogobin A1C (HbA_{1c}) predicts future drug treatment for diabetes mellitus : a follow-up study using routine clinical data in a Japanese university hospital. *Transl Res* 2007; **149**: 196–204.
18 Pajunen P, Peltonen M, Eriksson JG, Ilanne-Parikka P, Aunola S, Keinanen–Kiukaanniemiss S *et al.*, the Finnish Diabetes Prevention Study (DPS) HbA_{1c} in diagnosing and predicting type 2 diabetes in impaired glucose tolerance: the Finnish Diabetes Prevention Study. *Diabet Med* 2011; **28**: 36–42.
19 Kilpatrick ES, Rigby AS, Atkin SL. The effect of glucose variability on the risk of effect of glucose variability on the risk of microvascular complications in type 1 diabetes. *Diabetes Care* 2006; **29**: 1486–1490.
20 Bennett CM, Guo M, Dharmage SC. HbA_{1c} as a screening tool for detection of Type 2 diabetes: a systematic review. *Diabet Med* 2007; **24**: 333–343.
21 Lorenzo C, Lynne E, Wagenknecht , Hanley AJG, Rewers MJ, Karter AJ *et al.* Hemoglobin A_{1c} between 5.7 and 6.4% as a marker for identifying prediabetes, insulin sensitivity and secretion and cardiovascular risk factors: The Insulin Resistance Atherosclerosis Study (IRAS). *Diabetes Care* 2010; **33**: 2104–2109.
22 Mohan V, Vijayachandrika V, Gokulakrishnan K, Anjana RM, Ganesan A, Weber MB *et al.* HbA_{1c} cut points to define various glucose intolerance groups in Asian Indians. *Diabetes Care* 2010; **33**: 515–519.
23 Kramer CK, Araneta MR, Barrett-Connor E. A1C and diabetes diagnosis: The Rancho Bernardo Study. *Diabetes Care* 2010; **33**: 101–103.
24 Selvin E, Brancati FL, Steffes MW, Coresh J, Gregg E. Performance of A1C for the classification and prediction of diabetes. *Diabetes Care* 2011; **34**: 84–89.
25 Cavagnolli G, Comerlato J, Comerlato C, Renzt PB, Gross JL, Camargo JL. HbA_{1c} measurement for the diagnosis of diabetes: is it enough? *Diabet Med* 2011; **28**: 31–35.