A1C Cut Points to Define Various Glucose Intolerance Groups in Asian Indians

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OBJECTIVE — To determine A1C cut points for glucose intolerance in Asian Indians.

RESEARCH DESIGN AND METHODS — A total of 2,188 participants without known diabetes were randomly selected from the Chennai Urban Rural Epidemiology Study. All had fasting plasma glucose (FPG) and 2-h postload plasma glucose measurements after a 75-g load and were classified as having impaired fasting glucose (IFG) (American Diabetes Association [ADA] criteria, FPG ≥5.5 and <7 mmol/l, and World Health Organization [WHO] criteria, FPG ≥6.1 and <7 mmol/l), impaired glucose tolerance (IGT) (2-h postload plasma glucose ≥7.8 and <11.1 mmol/l), or diabetes (FPG ≥7 mmol/l and/or 2-h postload plasma glucose ≥11.1 mmol/l). A1C was measured using the Bio-Rad Variant machine. Based on receiver operating characteristic curves, optimum sensitivity and specificity were derived for defining A1C cut points for diabetes, IGT, and IFG.

RESULTS — Mean ± SD values of A1C among subjects with normal glucose tolerance, IGT, and diabetes were 5.5 ± 0.4, 5.9 ± 0.6, and 8.3 ± 2.0%, respectively ($P_{trend} < 0.001$) with considerable overlap. To identify diabetes based on 2-h postload plasma glucose, the A1C cut point of 6.1% had an area under the curve (AUC) of 0.941 with 88.0% sensitivity and 87.9% specificity. When diabetes was defined as FPG ≥7.0 mmol/l, the A1C cut point was 6.4% (AUC = 0.966, sensitivity 93.3%, and specificity 92.3%). For IGT, AUC = 0.708; for IFG, AUC = 0.632 (WHO criteria) and 0.708 (ADA criteria), and the A1C cut point was 5.6%.

CONCLUSIONS — In Asian Indians, A1C cut points of 6.1 and 6.4% defined diabetes by 2-h postload plasma glucose or FPG criteria, respectively. A value of 5.6% optimally identified IGT or IFG but was <70% accurate.

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A1C is an indicator of the average blood glucose concentrations over the preceding 2–3 months and is currently considered the best index of metabolic control in individuals with diabetes (1). The Diabetes Control and Complications Trial and the UK Prospective Diabetes Study (UKPDS) have demonstrated that lowering A1C can reduce the risk of diabetes microvascular complications (2,3). An association between A1C and cardiovascular risk factors in subjects with normal glucose tolerance (NGT) was also reported (4).

Until recently, A1C had not been recommended as a diagnostic or a screening tool because of several factors: lack of standardization, low sensitivity, and high cost (5). However, after efforts to improve standardization of the A1C assay and the introduction of the new International Federation of Clinical Chemists (IFCC) standards, A1C is now being considered for diagnostic and screening purposes (6). A1C does not need to be measured in a fasting state or with a glucose load and, therefore, offers potential ease and convenience. A recent American Diabetes Association (ADA) International Expert Committee proposed an A1C cut point of 6.5% as a diagnostic test for diabetes (7). It is important to investigate whether these cut points for A1C apply to all populations worldwide. The normative distribution for A1C levels has been described in western populations in subjects with NGT as well as those with impaired glucose tolerance (IGT) (8). However, there are no reports of the normative A1C distributions, to our knowledge, from India, which currently has the largest number of individuals with diabetes in the world. Here, we examine the distribution of A1C in a south Indian population and explore optimal cut points for identifying diabetes and high-risk pre-diabetic groups.

RESEARCH DESIGN AND METHODS

— The Chennai Urban Rural Epidemiology Study (CURES) is a cross-sectional population-based study representative of Chennai (formerly Madras), the largest city in southern India, with a population of ~5 million people. The details of CURES have been reported previously (9). In brief, CURES was based on the model of systematic stratified random sampling, wherein, for phase 1 of the study, 46 of the 155 wards in Chennai were selected for sampling, providing a total sample size of 26,001 individuals aged ≥20 years.

In a subsequent phase, every 10th subject recruited in phase 1 (n = 2,600) was invited for detailed testing, including an oral glucose tolerance test (OGTT) in those without self-reported diabetes, and the response rate was 90% (2,350 of 2,600 subjects) (Fig. 1). Anthropometric measurements including weight, height, and waist measurements were obtained using standardized techniques (9). BMI was calculated using the formula, weight in kilograms divided by the square of height in meters. Blood pressure was recorded in the sitting position in the right arm to the nearest 2 mmHg with a mercury sphygmomanometer (Diamond Deluxe BP apparatus; Pune, India). Two readings were taken 5 min apart, and the mean of the two was used.

Fasting plasma glucose (FPG) and 2-h postload (75-g) plasma glucose (glucose oxidase-peroxidase method), serum cho-

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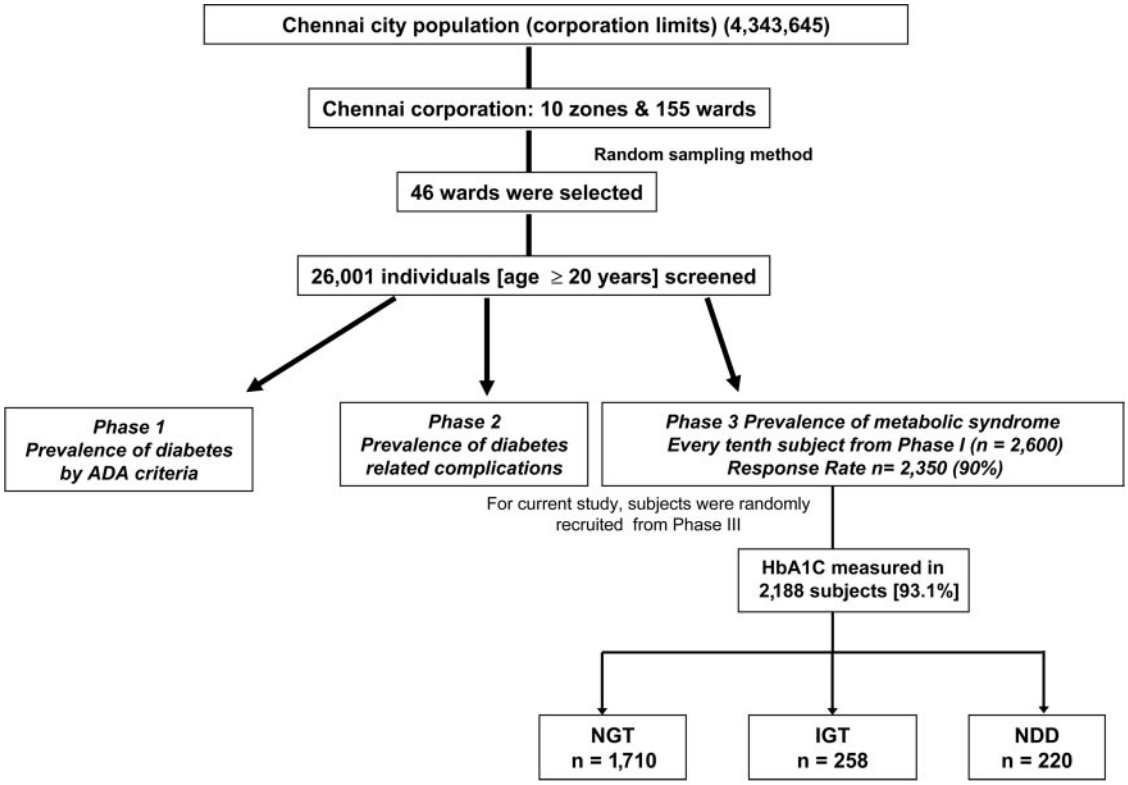

Figure 1—*CURES methodology.*

lesterol (cholesterol oxidase-peroxidase-amidopyrine method) serum triglycerides (glycerol phosphate oxidase-peroxidase-amidopyrine method), and HDL cholesterol (direct method, polyethylene glycol-pretreated enzymes) were measured using a Hitachi-912 Autoanalyzer (Hitachi, Mannheim, Germany). The intra- and interassay coefficients of variation (CVs) for the biochemical assays ranged from 3.1 to 7.6%. LDL cholesterol was calculated using the Friedewald equation.

Of the 2,350 subjects who received an OGTT, A1C was measured in 2,188 subjects (Response rate 93.1%). A1C was measured using the Variant machine (Bio-Rad Laboratories, Hercules, CA). Our center participates in the Unity program of Bio-Rad A1C standardization. The CV for the A1C assay was 3.5%. The CV for in-house quality control was <2.5%. In the external quality assessment scheme, bias for the A1C analysis was 1.75%, and imprecision was 2.75%, indicating good reproducibility.

Definitions and diagnostic criteria

Diabetes. Diabetes was diagnosed based on the World Health Organization (WHO) Consulting Group Criteria (10), i.e., FPG ≥126 mg/dl (7 mmol/l) and/or 2-h plasma glucose after an OGTT ≥200 mg/dl (11.1 mmol/l).

IGT. IGT was defined as 2-h postload plasma glucose ≥140 mg/dl (7.8 mmol/l) and <200 mg/dl (11.1 mmol/l) by WHO criteria (10).

Impaired fasting glucose. Impaired fasting glucose (IFG) was defined using ADA criteria (11) if FPG was ≥100 mg/dl (5.5 mmol/l) and <126 mg/dl (7 mmol/l) and using WHO criteria (10) if FPG was ≥110 mg/dl (6.1mmol/l) and <126 mg/dl (7 mmol/l).

NGT. NGT was defined as FPG <100 mg/dl (5.5 mmol/l) and 2-h postload plasma glucose <140 mg/dl (7.8 mmol/l) by WHO criteria (10).

Statistical analysis

Student's *t* test or one-way ANOVA (with the Tukey honestly significant difference) were used to compare groups for continuous variables and the χ^2 test or Fisher exact test were used to compare proportions. Receiver operating characteristic curves were plotted using sensitivity and 1 − specificity for different cut points of A1C, taking the diagnosis of diabetes, IGT, or IFG based on various plasma glucose criteria as the gold standard. Sensitivity was defined by the proportion of subjects with a given risk factor who were identified correctly by a A1C value greater than or equal to the cut point. Specificity was defined by the proportion of subjects without the risk factor who were identified by a A1C value below the cut point. The area under the curve was constructed, and by interpolation from the area under the curve, the point closest to the upper left-hand corner, which maximized sensitivity and specificity, was selected as the optimal cut point; this identified the highest number of subjects with or without diabetes, IGT, or IFG (12). Positive and negative predictive values and accuracy for predicting diabetes, IGT, and IFG were calculated for different cut points of A1C.

RESULTS — Among the 2,188 subjects who had both OGTT and A1C tests, 1,710 (78.2%) had NGT, 258 (11.8%) had IGT, and 220 (10.1%) had newly diagnosed diabetes (NDD). Subjects with glucose intolerance (i.e., IGT or NDD) were older than subjects with NGT ($P <$ 0.01). Waist circumference, systolic and diastolic blood pressure, FPG, 2-h postload plasma glucose, A1C, serum cholesterol, serum triglyceride, and LDL cholesterol were also higher among sub-

Table 1—*Clinical and biochemical characteristics of study subjects*

	NGT	Pre-diabetes (IFG and IGT)	NDD
n	1,710	258	220
Age (years)	37 ± 12	43 ± 13*	45 ± 11*
BMI (kg/m^2)	22.6 ± 4.0	24.2 ± 3.5*	24.2 ± 3.1*
Waist circumference (cm)	81.6 ± 11.4	86.9 ± 10.3*	88.5 ± 9.0*
Systolic blood pressure (mmHg)	115 ± 16.3	126.4 ± 19.9*	128.2 ± 21.2*†
Diastolic blood pressure (mmHg)	72.7 ± 10.8	77.4 ± 11.4*	78.8 ± 11.6*
Fasting plasma glucose (mmol/l)	4.6 ± 0.4	5.2 ± 0.8*	8.6 ± 3.3*†
2-h postload plasma glucose (mmol/l)	5.5 ± 1.1	8.8 ± 1.0*	15.5 ± 3.7*†
A1C (%)	5.5 ± 0.4	5.9 ± 0.6*	8.3 ± 2.0*†
Serum cholesterol (mmol/l)	4.5 ± 0.9	4.8 ± 1.0*	5.0 ± 0.9*
Serum triglycerides (mmol/l)	1.2 ± 0.7	1.6 ± 1.0*	2.1 ± 1.4*†
HDL cholesterol (mmol/l)	1.1 ± 0.2	1.0 ± 0.2‡	1.0 ± 0.2*
LDL cholesterol (mmol/l)	2.8 ± 0.8	3.0 ± 0.9*	3.0 ± 0.8*

Data are means ± SD. *$P < 0.001$ compared with NGT. †$P < 0.001$ compared with IGT. ‡$P < 0.01$ compared with IGT.

jects with glucose intolerance (IGT and NDD) than in those with NGT. Mean ± SD values of A1C among subjects with NGT, IGT, and NDD were 5.5 ± 0.4, 5.9 ± 0.6, and 8.3 ± 2.0%, respectively ($P_{trend} < 0.001$) (Table 1).

As shown in Table 2, for diabetes, using the 2-h postload plasma glucose ≥200 mg/dl (11.1 mmol/l) criterion, the A1C cut point of 6.1% had the highest sensitivity and specificity. Using the FPG ≥126 mg/dl (7.0 mmol/l) criterion for diabetes, the optimal A1C cut point was 6.4% and for the 2-h postload plasma glucose ≥200 mg/dl and FPG ≥126 mg/dl criterion, the optimal A1C cut point was 6.5%. The accuracy of correctly differentiating a person with NDD selected at random from the population varied from 90.2 to 95.9% (Table 2), depending on the definition of diabetes and the respective cut point. For IGT, the optimal A1C cut point was 5.6%. For IFG, defined by either the WHO criterion of FPG ≥110 (6.1 mmol/l) and ≤126 mg/dl (7.0 mmol/l) or the ADA criterion of FPG ≥100 mg/dl (5.6 mmol/l) and ≤126 mg/dl (7.0 mmol), the optimal A1C cut point was 5.6%. The accuracy of identifying these pre-diabetic states was ~70%.

Figure 2 shows the distribution of A1C in those with NGT, IGT, and diabetes. It can be seen that there is considerable overlap among the three categories with respect to the A1C levels. The percentage of subjects with NGT, IGT and/or IFG, and diabetes identified using various A1C cut points is shown in Table 3. Using a cut point of 5.6%, 73.6% of those with IGT and/or IFG (using WHO criteria) and 72.8% of subjects with IFG (using ADA criteria) would be correctly identified. Using the cut point of 6.5%, 78.2% of subjects with diabetes would bet correctly identified; however, 19.4% of subjects with IGT and/or IFG (using ADA criteria), 18.1% of subjects with IGT and/or IFG (using WHO criteria), and 3.0% of subjects with NGT would be included in this category.

CONCLUSIONS — Our population-based data suggest that A1C cut points of 6.1 and 6.4% are optimal for identifying NDD in Asian Indians by 2-h postload plasma glucose and FPG criteria, respectively. These cut points can identify subjects with diabetes with >90% accuracy in this population. In addition, our data suggest that an A1C cut point of 5.6% would identify subjects with IGT and/or IFG with optimal specificity and sensitivity, but the accuracy is only 69–74%.

A large meta-analysis using data from 10 different studies concluded that a A1C cut point of 7.0%, could identify diabetes requiring pharmacological therapy (13). A population-based study of 3,190 adults of Malay ethnicity concluded that A1C levels in the range 6.6–7% were optimal for detecting microvascular complications (14). Studies have also demonstrated that a A1C threshold of 6.0% discriminates well between OGTT-diagnosed diabetic and nondiabetic subjects (15,16).

A recent report by an International Expert Committee has proposed that a diagnosis of diabetes can be made if the A1C level is ≥6.5%, but the diagnosis should be confirmed with a repeat A1C test, unless clinical symptoms or glucose levels >200 mg/dl (>11.1 mmol/l) are present (7). However, this decision was based on

Table 2—*A1C cut points with respect to diabetes, IGT, and IFG*

Condition	Criteria	*n* (%)	A1C (%)	Optimal A1C cut point	Sensitivity	Specificity	PPV	NPV	AUC	Accuracy
Diabetes	2-h PG ≥200 mg/dl or FPG ≥126 mg/dl (10)	225 (10.3)	8.3 ± 2.0	6.1	88.0	87.9	45.5	98.5	0.941	90.2
Diabetes	2-h PG ≥200 mg/dl (10)	220 (10.1)	8.3 ± 2.0	6.1	88.6	87.8	44.8	98.6	0.944	90.5
Diabetes	FPG ≥126 mg/dl (10)	134 (6.1)	9.2 ± 1.9	6.4	93.3	92.3	44.2	99.5	0.966	95.5
Diabetes	2-h PG ≥200 mg/dl and FPG ≥126 mg/dl (10)	122 (5.6)	9.2 ± 1.6	6.5	92.6	93.7	46.3	99.5	0.978	95.9
IGT	2-h PG ≥ 140 mg/dl and <200 mg/dl (10)	248 (12.6)	5.9 ± 0.6	5.6	65.6	62.1	19.9	92.6	0.708	74.1
IFG (WHO)	FBG ≥110 mg/dl and <126 mg/dl (10)	10 (0.6)	5.7 ± 0.3	5.6	60.0	56.5	0.8	99.6	0.632	69.9
IFG (ADA)	FBG ≥100 mg/dl and <126 mg/dl (11)	83 (4.8)	5.8 ± 0.5	5.6	65.1	63.4	8.3	97.3	0.708	70.0

Data are means ± SD. AUC, area under the curve; FBG, fasting blood glucose; NPV, negative predictive value; PG, plasma glucose; PPV, positive predictive value.

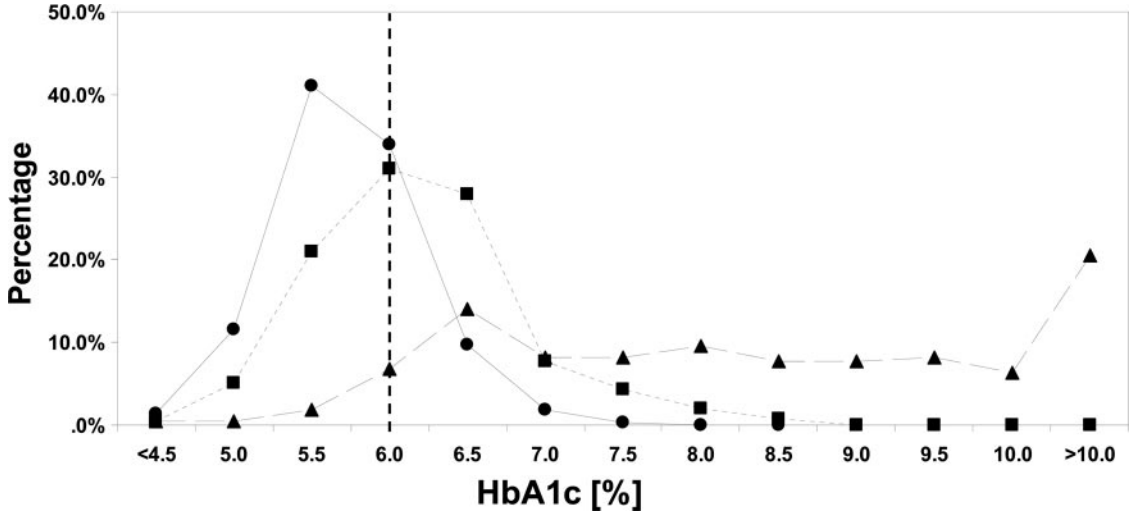

Figure 2—*A1C distribution among subjects with NGT, IGT, and NDD. ●, normal glucose tolerance; ■, impaired glucose tolerance; ▲, diabetes.*

cross-sectional data on the relationship between A1C and risk of future complications (retinopathy) from western populations. Our data from an Asian Indian population, based on the normative distribution of A1C and on its receiver operator characteristics compared with the gold standard test (OGTT), indicates that the A1C cut point appropriate for diagnosing diabetes may be different for nonwestern populations. Our data suggest an optimal A1C cut point of 5.6% in Asian Indians to identify IGT or IFG, which are considered to be pre-diabetes states, and, therefore, to target groups for diabetes prevention. The differences in A1C cut points in different populations could be due to potential racial and ethnic differences (17–19). Other factors such as aging, hemoglobin glycation (17,18,20), and/or erythrocyte survival (17,18,21,22) could affect the A1C assay in addition to heritable factors (23).

The advantages of the A1C test are that it can be measured at any time of the day with a small sample of blood and that it also does not require the cumbersome glucose load. The disadvantages are the difficulty in standardization, cost, and the fact that A1C cannot be measured in the presence of hemoglobin variants (6).

The International Expert Committee suggests a cut point of 6.0% only as an indication for high-risk pre-diabetes states but not as a strict cutoff point. Because there is now strong evidence that lifestyle management of those with IGT can reduce the rate of progression to diabetes (24), it is important to correctly identify those with pre-diabetes so that prevention efforts may be implemented, without missing those who would benefit from intervention. Our data suggest that despite optimal specificity and sensitivity, the A1C cut point of 5.6% only has 69–74% accuracy of identifying IGT or IFG. The cut point would have to be as low as 5% to identify 97% of all IGT and/or IFG.

One of the strengths of this study is that it is population-based and from an Asian Indian population, an ethnic group that has a high susceptibility to type 2 diabetes. Another advantage is the high response rates: 90% of the subjects participated in phase 3 of CURES, of whom A1C could be measured in 93.1%. Thus, it is unlikely that there is any significant selection bias. One limitation of our study is that because it is cross-sectional, we cannot assess the ability of A1C to predict future diabetes or its micro- and macrovascular complications. Our focus, however, was to evaluate A1C as a screening and diagnostic tool to identify NDD or IGT or IFG. Although diabetes was newly diagnosed in the subjects in the present study, many had high glycemic and A1C values as shown in Fig. 2. Had the diagnosis been made earlier, the cut points would perhaps not have been so clear-cut or accurate.

In summary, our population-based data indicate that for Asian Indians a A1C value of ≥6.0% may be optimal for diagnosing diabetes with a very high level of accuracy. On the other hand, use of even a cut point as low as 5.6% may miss a

Table 3—*Proportion of subjects with NGT, IGT, and/or IFG and type 2 diabetes identified using different A1C cut points*

A1C cut points	NGT	Subjects with IGT and/or IFG: Using ADA criteria	Subjects with IGT and/or IFG: Using WHO criteria	NDD
≥4.5	1,621 (99.0)	257 (99.6)	329 (99.4)	224 (99.6)
≥5.0	1,490 (91.0)	249 (96.5)	320 (96.7)	223 (99.1)
≥5.5	890 (54.3)	205 (79.5)	264 (79.8)	220 (97.8)
≥5.6	733 (44.7)	190 (73.6)	241 (72.8)	218 (96.9)
≥5.7	599 (36.6)	167 (64.7)	216 (65.3)	213 (94.7)
≥5.8	463 (28.3)	154 (59.7)	200 (60.4)	213 (94.7)
≥5.9	350 (21.4)	136 (52.7)	177 (53.5)	208 (92.4)
≥6.0	244 (14.9)	121 (46.9)	156 (47.1)	203 (90.2)
≥6.1	171 (10.4)	110 (42.6)	142 (42.9)	202 (89.8)
≥6.2	124 (7.6)	90 (34.9)	116 (35.0)	198 (88.0)
≥6.3	91 (5.6)	71 (27.5)	90 (27.2)	191 (84.9)
≥6.4	62 (3.8)	57 (22.1)	68 (20.5)	184 (81.8)
≥6.5	49 (3.0)	50 (19.4)	60 (18.1)	176 (78.2)

Data are *n* (%).

substantial proportion of individuals at high risk of diabetes who would benefit from proven prevention interventions. Although there are merits for a simple and convenient test such as A1C to screen for and diagnose diabetes and/or high-risk states (such as IGT and/or IFG), it is important that proposals for cut points to define diabetes and high-risk states take into account population differences in A1C levels and for this, more studies are clearly needed in nonwestern populations. Thus, there is a need for more studies, including the cost-effectiveness of A1C versus plasma glucose testing, before A1C can be universally recommended as a diagnostic test for diabetes in developing countries. The recommendation for A1C to diagnose high-risk states is even less clear. Moreover, recognition of individuals with a high risk of diabetes can be made on criteria other than glucose regulation only; for example, overweight, increased waist circumference, or other elements of the metabolic syndrome, which can help to identify individuals who would need lifestyle modification advice. Indeed, an Indian Diabetes Risk Score was shown to be very effective to screen not only for undiagnosed diabetes but also for metabolic syndrome and coronary artery disease and is one of the strongest predictors of incident diabetes in an Asian Indian population (25).

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