Association of A1C With Cardiovascular Disease and Metabolic Syndrome in Asian Indians With Normal Glucose Tolerance

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OBJECTIVE — This study examines the association of A1C with cardiovascular disease (CVD) risk factors, coronary artery disease (CAD), and metabolic syndrome in Asian Indians with normal glucose tolerance (NGT).

RESEARCH DESIGN AND METHODS — This cross-sectional study recruited subjects from phase III of the Chennai Urban Rural Epidemiology Study (CURES), an epidemiological study in a representative population of Chennai (formerly Madras) in South India, conducted between January 2003 and June 2004. Included were 1,644 subjects with NGT, i.e., fasting plasma glucose <100 mg/dl (5.6 mmol/l) and 2-h postload plasma glucose <140 mg/dl (7.8 mmol/l). A1C was measured using the Biorad Variant machine. Metabolic syndrome was defined based on modified Adult Treatment Panel III guidelines.

RESULTS — The mean ± SD A1C value in the study cohort was 5.5 ± 0.4%. A1C showed a significant association with BMI ($\beta = 0.017$, $P < 0.001$), systolic ($\beta = 0.002$, $P = 0.028$) and diastolic ($\beta = 0.202$, $P = 0.017$) blood pressure, waist circumference ($\beta = 0.007$, $P < 0.001$), serum cholesterol ($\beta = 0.002$, $P < 0.001$), triglycerides ($\beta = 0.001$, $P < 0.001$), LDL cholesterol ($\beta = 0.002$, $P < 0.001$), fasting insulin ($\beta = 0.009$, $P < 0.001$), and homeostasis model assessment of insulin resistance ($\beta = 0.047$, $P < 0.001$) after adjusting for age and sex. Regression analysis showed that A1C had a strong association with metabolic syndrome that persisted after adjusting for age and sex (odds ratio [OR] 2.9 [95% CI 2.08–4.00]; $P < 0.001$). A1C also had a strong association with CAD (2.6 [1.23–5.63]; $P = 0.01$), but the significance was lost when adjusted for age and sex.

CONCLUSIONS — There is a strong association of A1C with prevalent CVD risk factors in Asian-Indian subjects with NGT.

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The DCCT (Diabetes Control and Complications Trial) and UKPDS (UK Prospective Diabetes Study) demonstrated the importance of A1C in the development of long-term diabetes microvascular complications (1,2). Further, both studies elegantly demonstrated significant reductions in the risk of developing microvascular complications for every percentage of reduction in A1C levels (1,2). However, the association of A1C with cardiovascular disease (CVD) is less clear (3–8).

CVD is the principal cause of mortality globally, particularly in type 2 diabetic subjects, as their CVD mortality risk is equal to that of subjects without diabetes who had a previous episode of myocardial infarction (9). Recent prospective studies have shown that A1C is associated with CVD and mortality (10). This association has also recently been extended to nondiabetic subjects, as the relationship of CVD with glycemia is believed to be a continuum without a threshold effect (5–8). However, there is uncertainty as to the nature of the relationship, as some studies report no statistically significant association (3) between A1C and CVD in nondiabetic males while others do (4–8).

Asian Indians are known to have very high rates of premature coronary artery disease (CAD) and diabetes (11). This is attributed to the so-called Asian-Indian phenotype (12), characterized by relatively lower prevalence rates of obesity but larger waist measurements indicating abdominal obesity and increased insulin resistance. In keeping with studies in the West (13), we have shown that in Asian Indians also, the risk for CVD starts at the stage of impaired glucose tolerance (IGT) (14). However, to our knowledge, there are no data on the association of A1C with CVD risk in Asian Indians with normal glucose tolerance (NGT). It would be worthwhile to look at the association of A1C with CVD risk factors in Asian Indians, as a recent analysis of global and regional mortality indicated that South Asians had the highest mortality rates due to ischemic heart disease compared with other countries and also had higher mean plasma glucose levels (15). This study examines the association of A1C with CVD risk factors, CAD, and metabolic syndrome in Asian Indians with NGT.

RESEARCH DESIGN AND METHODS

— The Chennai Urban Rural Epidemiology Study (CURES) is a large, cross-sectional study conducted in a representative population of Chennai (formerly Madras), the largest city in Southern India, with a population of approximately 5 million people. The methodology of CURES has been reported elsewhere (16). Briefly, the sampling for

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Abbreviations: ATP, Adult Treatment Panel; CAD, coronary artery diasease; CURES, Chennai Urban Rural Epidemiology Study; CVD, cardiovascular disease; dBP, diastolic blood pressure; HOMA-IR, homeostasis assessment of insulin resistance; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; ROC, receiver-operator characteristic; sBP, systolic blood pressure.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

CURES was based on the model of systematic random sampling, wherein, of the 155 wards in Chennai, 46 were selected to provide a total sample size of 26,001 individuals ≥20 years of age. Phase I of CURES was conducted in the field and involved a door-to-door survey in the selected wards. In Phase II, all the known diabetic subjects and age- and sex-matched nondiabetic subjects were brought to our center for detailed anthropometric measurements and biochemical tests.

This study recruited subjects from Phase III, in which every 10th subject recruited in Phase I were brought to the center for detailed studies, inclusive of oral glucose tolerance in those without self-reported diabetes. Phase III had a 90% response rate (2,350 of 2,600). Subjects with diabetes, (IGT), and impaired fasting glucose (17,18) were excluded from the present study, which deals only with subjects who had NGT (n = 1,644), defined as fasting plasma glucose <100 mg/dl (5.6 mmol/l) and 2-h postload plasma glucose <140 mg/dl (7.8 mmol/l). Of the 1,644 NGT subjects identified in Phase III, A1C tests were conducted in 1,632 (99.3%). Subjects with A1C ≥7.0% were excluded (n = 5).

Anthropometric measurements

Weight, height, and waist measurements were obtained using standardized techniques as detailed elsewhere (16). Height was measured with a tape to the nearest centimeter. Weight was measured with a traditional spring balance that was kept on a firm horizontal surface. Waist size was measured using a nonstretchable fiber measure tape. BMI was calculated as the weight in kilograms divided by the square of height in meters. Blood pressure was recorded in the sitting position using the right arm to the nearest 2 mmHg with a mercury sphygmomanometer (Diamond Deluxe; Pune, India). Two readings were taken 5 min apart, and the mean of the two was taken as the blood pressure.

Biochemical parameters

Fasting plasma glucose (glucose oxidase-peroxidase method), serum cholesterol (cholesterol oxidase-peroxidase-4–aminophenazone method) serum triglycerides (glycerol phosphate oxidase-peroxidase-4–aminophenazone method), and HDL cholesterol (direct method with polyethylene glycol–pretreated enzymes) were measured using the Hitachi-912 Autoanalyser (Hitachi, Mannheim, Germany). The intra- and interassay coefficient of variation (CV) for the biochemical assays ranged between 3.1 and 7.6%. LDL cholesterol was calculated using the Friedewald formula (19) in subjects with triglycerides <400 mg/dl (n = 1,618). Serum insulin concentration was estimated using Dako kits (Dako, Glostrup, Denmark); 1,515 individuals (92.8%) provided a sample for insulin assay. Insulin resistance was estimated using the homeostasis assessment model of insulin resistance (HOMA-IR): fasting insulin (μU/ml) × fasting glucose (mmol/l)/22.5 (20).

Analysis of A1C

A1C was measured using a Variant machine (Biorad, Hercules, CA). Our center participates in the Unity program of Biorad A1C standardization. The CV for A1C assay was 3.5%. The CV for inhouse quality control was <2.5%. In the external quality assessment scheme, bias for A1C analysis was 1.75% and imprecision 2.75%, indicating good reproducibility.

Definitions and diagnostic criteria

Metabolic abnormalities. Hypercholesterolemia (serum cholesterol ≥5.2 mmol/l [≥200 mg/dl] or subjects who self-reported hypercholesterolemia and were on statins), hypertriglyceridemia (serum triglycerides ≥1.7 mmol/l [≥150 mg/dl] or subjects who self-reported hypertriglyceridemia and were on drugs for hypertriglyceridemia), and low HDL cholesterol (male subjects: HDL cholesterol <1.04 mmol/l [< 40 mg/dl] and female subjects: HDL cholesterol <1.3 mmol/l [< 50 mg/dl]) were diagnosed based on Adult Treatment Panel (ATP) III guidelines (21). Metabolic syndrome was diagnosed based on modified ATP III guidelines (21) if any three of the following abnormalities were present: abdominal obesity (defined as waist circumference ≥90 cm for male subjects and ≥80 cm for female subjects, according to modified Asia Pacific World Health Organization guidelines) (22), high blood pressure (systolic blood pressure [sBP] ≥130 mmHg. diastolic blood pressure [dBP] ≥85 mmHg, or subjects who self-reported hypertension and were on antihypertensives), hypertriglyceridemia, or low HDL cholesterol. Obesity was defined as BMI ≥25 kg/m^2 according to the modified Asia Pacific World Health Organization guidelines (22).

CAD. CAD was diagnosed based on a past history of documented myocardial infarction and/or medical therapy (nitrates) or revascularization for CAD, electrocardiographic changes suggestive of Q-wave changes (Minnesota codes 1–1-1 to 1–1-7), and/or ST segment depression (Minnesota codes 4–1 to 4–2).

Statistical analysis

Data management was done via Microsoft Access, and statistical analyses were done using the SPSS statistical package (Version 10.0; Chicago, IL). Subjects with A1C <4.0% were excluded, as this could be due to presence of a variant A1C (n = 5). One-way ANOVA (Tukey's honestly significant difference comparison) were used as appropriate to compare means among different groups. χ^2 test or Fisher's exact test was used to compare proportions among groups. Study subjects were categorized into quartiles of A1C; unequal numbers were found in the quartiles because of decimals. Pearson's correlation analysis was carried out to determine the correlation of A1C with cardiovascular risk factors. Linear regression analysis was done using A1C as the dependent variable and CVD risk factors as independent variables. In multiple linear regression analysis (forward method), HOMA-IR (correlation with fasting insulin CV 0.989), cholesterol (correlation with LDL cholesterol r = 0.924), and CMI (correlation with waist circumference r = 0.823) were not included to avoid intercorrelation between independent variables. Logistic regression analysis was done using CAD and metabolic syndrome as dependent variables and A1C as an independent variable. Receiver-operator characteristic (ROC) curves were constructed to identify the cut point of A1C with maximum accuracy for determining metabolic syndrome and CAD. Sensitivity, specificity, and accuracy for predicting metabolic syndrome were calculated for different cut points of A1C.

RESULTS — The study groups included 1,620 subjects with NGT (734 men and 886 women). Men were older than women (38 ± 13 vs. 36 ± 11 years, respectively, P = 0.007), had lower BMIs (22.3 ± 4.0 vs. 22.8 ± 4.1 kg/m^2, P = 0.026), larger waist circumferences (83 ± 12 vs. 80 ± 11 cm, P < 0.001), and higher sBP (117 ± 16 vs. 114 ± 16 mmHg, P < 0.001), dBP (74 ± 11 vs. 72 ± 11 mmHg, P < 0.001), and serum triglycerides (1.35 ± 0.82 vs. 1.15 ± 0.62

Table 1—*Clinical and biochemical characteristics of the study population according to quartiles of A1C*

Parameters	Quartiles of A1C 1st	2nd	3rd	4th	*P* for trend
n	316	426	426	452	—
A1C (%)	<5.1	5.1–5.4	5.5–5.7	>5.7	—
Age (years)	33 ± 11	34 ± 10	38 ± 11*	42 ± 13†	< 0.001
Sex (male)	147 (46.5)	185 (43.4)	189 (44.4)	213 (47.1)	0.694
BMI (kg/m^2)	21.59 ± 3.96	22.35 ± 4.06	22.58 ± 4.18‡	23.52 ± 3.91§	< 0.001
Waist circumference (cm)	78 ± 12	80 ± 11	81 ± 12¶	85 ± 11‖	< 0.001
sBP (mmHg)	112 ± 15	114 ± 14	116 ± 17‡	119 ± 17**	< 0.001
dBP (mmHg)	70 ± 11	72 ± 11	73 ± 11‡	74 ± 10*	< 0.001
Fasting plasma glucose (mmol/l)	4.51 ± 0.40	4.57 ± 0.36	4.66 ± 0.40§	4.73 ± 0.38††	< 0.001
2-h plasma glucose (mmol/l)	5.43 ± 1.04	5.45 ± 1.08	5.43 ± 1.09	5.79 ± 1.06‖	< 0.001
Total cholesterol (mmol/l)	4.17 ± 0.97	4.38 ± 0.80‡	4.56 ± 0.91*	4.81 ± 1.01‖	< 0.001
Serum triglycerides (mmol/l)	1.04 ± 0.55	1.19 ± 0.64‡	1.26 ± 0.68¶	1.42 ± 0.89**	< 0.001
HDL cholesterol (mmol/l)	1.13 ± 0.26	1.12 ± 0.27	1.14 ± 0.27	1.11 ± 0.23	0.396
LDL cholesterol (mmol/l)	2.56 ± 0.86	2.72 ± 0.68‡‡	2.84 ± 0.78¶	3.05 ± 0.86**	< 0.001
Fasting insulin (μU/ml)	7.3 ± 5.2	7.6 ± 5.0	7.8 ± 5.1	9.0 ± 6.4†	< 0.001
HOMA-IR	1.47 ± 1.07	1.55 ± 1.07	1.63 ± 1.09	1.89 ± 1.34**	< 0.001
Hypertension	51 (16.1)	90 (21.1)	99 (23.2)	147 (32.5)	< 0.001
Obesity	89 (28.2)	148 (34.7)	180 (42.3)	245 (54.2)	< 0.001
High triglycerides	92 (29.2)	182 (42.8)	201 (47.2)	232 (51.4)	< 0.001
Low HDL cholesterol	183 (58.1)	268 (63.1)	270 (63.5)	293 (65.0)	0.262
Metabolic syndrome	10 (3.2%)	26 (6.1%)	35 (8.2%)	45 (10.0%)	< 0.001
CAD	5 (1.6%)	6 (1.5%)	10 (2.5%)	13 (3.1)	0.115

Data are means ± SD or *n* (%) unless otherwise indicated. *$P < 0.001$ compared with 1st quartile and $P < 0.05$ compared with 2nd quartile; †$P < 0.001$ compared with first quartile and $P < 0.01$ compared with 2nd and 3rd quartiles; ‡$P < 0.01$ compared with 1st quartile; §$P < 0.001$ compared with 1st and 2nd quartiles; ¶$P < 0.001$ compared with 1st quartile; ‖$P < 0.001$ compared with 1st, 2nd, and 3rd quartiles; **$P < 0.001$ compared with 1st and 2nd quartile and $P < 0.01$ compared with 3rd quartile; ††$P < 0.001$ compared with 1st and 2nd quartile and $P < 0.05$ compared with 3rd quartile; and ‡‡$P < 0.05$ compared with 1st quartile.

mmol/l, $P < 0.001$) but lower levels of 2-h postload plasma glucose (5.38 ± 1.15 vs. 5.66 ± 1.0 mmol/l, $P < 0.001$) and HDL cholesterol (1.05 ± 0.25 vs. 1.19 ± 0.25 mmol/l, $P < 0.001$). Mean A1C was 5.5 ± 0.4%, range 4.0–6.8%.

The clinical and biochemical characteristics of the NGT group stratified according to quartiles of A1C are shown in Table 1. Age, BMI, waist circumference, sBP and dBP, serum cholesterol, triglycerides, LDL cholesterol, fasting insulin, and HOMA-IR increased significantly with increasing quartiles of A1C values (*P* for trend <0.001). Prevalence of metabolic abnormalities and the metabolic syndrome increase corresponded with increases in quartiles of A1C (*P* for trend <0.001), with the exception of low HDL cholesterol levels (*P* for trend = 0.262). Though the prevalence of CAD increased in the 3rd and 4th quartile compared with the 1st quartile, the difference did not reach statistical significance, probably because of small numbers ($n = 34$). HDL cholesterol failed to show any trend with increasing quartiles of A1C levels, even when categorized sex wise (male subjects: 1st quartile 1.06 ± 0.27 mmol/l, 2nd quartile 1.04 ± 0.24 mmol/l, 3rd quartile 1.05 ± 0.25 mmol/l, and 4th quartile 1.04 ± 0.23 mmol/l; female subjects: 1st quartile 1.19 ± 0.24 mmol/l, 2nd quartile 1.18 ± 0.28 mmol/l, 3rd quartile 1.20 ± 0.26 mmol/l, and 4th quartile 1.17 ± 0.22 mmol/l).

There was a linear increase in the mean values of A1C with an increase in number of components of metabolic syndrome (one metabolic abnormality: 5.5 ± 0.4, two metabolic abnormalities: 5.6 ± 0.5, three or more metabolic abnormalities: 5.7 ± 0.5) compared with subjects with no metabolic abnormalities (5.4 ± 0.4), *P* for trend <0.001).

Table 2 presents the results of the Pearson's correlation analysis of A1C with cardiovascular risk factors. A1C had a significant correlation with age, BMI, waist circumference, sBP and dBP, serum cholesterol, triglycerides, LDL cholesterol, fasting insulin levels, and HOMA-IR ($P < 0.001$).

Table 3 presents the results of linear regression analysis using A1C as a dependent variable and CVD risk factors as independent variables. A1C showed a significant association with BMI ($\beta = 0.017$, $P < 0.001$), sBP ($P = 0.028$), dBP ($P = 0.017$), waist circumference ($P < 0.001$), serum cholesterol ($P < 0.001$), triglycerides ($P < 0.001$), LDL cholesterol ($P < 0.001$), fasting insulin ($P < 0.001$), and HOMA-IR ($P < 0.001$) even after adjusting for age and sex, with the exception of HDL cholesterol, which showed an association with A1C only after adding age and sex into the model ($\beta = -0.003$, $P = 0.006$). However, this

Table 2—*Pearson correlation coefficient of A1C with cardiovascular risk variables*

Correlation	*r*	*P*
Age	0.292	< 0.001
BMI	0.159	< 0.001
Waist circumference	0.216	< 0.001
sBP	0.157	< 0.001
dBP	0.135	< 0.001
Total cholesterol	0.233	< 0.001
Serum triglycerides	0.180	< 0.001
HDL cholesterol	−0.022	0.377
LDL cholesterol	0.205	< 0.001
Fasting insulin	0.117	< 0.001
HOMA-IR	0.138	< 0.001

Table 3—*Association of A1C with metabolic abnormalities in nondiabetic subjects; dependent variable: A1C*

Independent variables	β	*P*
Waist circumference		
Unadjusted	0.008	<0.001
Adjusted for age and sex	0.007	<0.001
sBP		
Unadjusted	0.004	<0.001
Adjusted for age and sex	0.002	0.028
dBP		
Unadjusted	0.005	<0.001
Adjusted for age and sex	0.002	0.017
Total cholesterol		
Unadjusted	0.003	<0.001
Adjusted for age and sex	0.002	<0.001
Serum triglycerides		
Unadjusted	0.001	<0.001
Adjusted for age and sex	0.001	<0.001
HDL cholesterol		
Unadjusted	−0.001	0.377
Adjusted for age and sex	−0.003	0.006
LDL cholesterol		
Unadjusted	0.003	<0.001
Adjusted for age and sex	0.002	<0.001
Fasting insulin		
Unadjusted	0.009	<0.001
Adjusted for age and sex	0.009	<0.001
HOMA-IR		
Unadjusted	0.052	<0.001
Adjusted for age and sex	0.047	<0.001
Multiple linear conclusions regression analysis		
Age	0.008	<0.001
Waist circumference	0.004	<0.001
Serum triglycerides	0.001	0.003
LDL cholesterol	0.002	<0.001
Fasting insulin	0.004	0.026

association lost its significance when triglycerides were added into the model ($\beta = -0.002$, $P = 0.160$). Similar results were obtained even when categorized based on sex (men: $\beta = -0.001$, $P = 0.574$; women: $\beta = -0.002$, $P = 0.199$).

Multiple linear regression analysis revealed that age ($P < 0.001$), waist circumference ($P < 0.001$), triglycerides ($P = 0.003$), LDL cholesterol ($P < 0.001$), and fasting insulin ($P = 0.026$) had a significant association with A1C. The model that used only age as the independent variable had $r^2 = 8.6\%$, which increased to 13.8% when waist circumference, LDL cholesterol, triglycerides, and fasting insulin were incorporated into the model.

Logistic regression using CAD as a dependant variable showed that A1C had a strong association with CAD (odds ratio [OR] 2.6 [95% CI 1.23–5.63], $P = 0.01$). However, this association lost its significance when adjusted for age (1.5 [0.666–3.20], $P = 0.34$), probably because of small numbers of subjects with CAD ($n = 34$). Regression analysis using metabolic syndrome as a dependant variable showed that A1C had a strong association with metabolic syndrome (3.5 [2.53–4.75], $P < 0.001$), and this association persisted even after adjusting for age (2.9 [2.08–4.01], $P < 0.001$) and sex (2.9 [2.08–4.00], $P = < 0.001$).

ROC analysis revealed that an A1C cut point of ≥5.6% had maximum accuracy in determining metabolic syndrome (area under the curve 0.602, $P < 0.001$; accuracy 60%, sensitivity 57.5%, and specificity 60.9%). A1C values of 5.0 and 6.0% were also analyzed to determine their efficiency; a value of 6.0% had a sensitivity of 25.8% and specificity of 87.8%, while a value of 5.0% had a sensitivity of 96.3% and specificity of 9.8%.

With regard to CAD, ROC curves had an area under the curve of 0.605 ($P = 0.036$), and A1C 5.6% had maximum accuracy (56%), optimum sensitivity (67.6%), and optimum specificity (55.7%). A1C 6.0% had a sensitivity of 26.5% and specificity of 86.1%, while a value of 5.0% had a sensitivity of 97.0% and a specificity of 9.2%.

CONCLUSIONS — The main findings of the study are that in Asian Indians with NGT, A1C showed an association with most CVD risk factors, the metabolic syndrome, and CAD; the latter, however, was not significant when age was introduced into the model.

A1C could be considered a good marker for glycated proteins, which play a contributory role in atherosclerosis (23,24) not only in diabetic but also in nondiabetic subjects (25). This is supported by the findings that even nondiabetic subjects with CAD have increased levels of A1C (26).

We observed a trend in prevalence of CAD with an increase in quartiles of A1C; however, the difference in prevalence between quartiles did not reach statistical significance, probably because of small number of subjects with CAD ($n = 34$). While regression analysis revealed that A1C was significantly associated with CAD, this disappeared upon addition of age into the model.

Prospective studies have revealed A1C to be a predictor of total and all-cause mortality (5,6). Indeed, the Rancho Bernardo Study (3) concluded that A1C is a better predictor of CVD mortality than fasting and postload plasma glucose levels. A meta-analysis of several studies concluded that there is a linear relationship between glucose levels and CVD (7). In our population, we reported that the prevalence of CAD is nearly 1.5 times higher among subjects with IGT compared with NGT (14). Further, preclinical atherosclerotic markers like carotid intima media thickness also showed a linear increase with increasing severity of glucose intolerance (27), indicating that the atherosclerotic process starts to get accelerated even before clinical diabetes sets in.

Insulin resistance is considered to be the link between glucose intolerance and CAD (28), and earlier population-based studies demonstrated that plasma insulin levels had a strong association with CAD (29). In the present analysis, we observed a strong association between A1C, fasting insulin, and insulin resistance, independent of age and sex. One could speculate that this association could be through low-grade inflammation, which is strongly associated with insulin resistance (30).

Studies in different ethnic groups have assessed the relation between metabolic abnormalities in terms of CVD risk factors and A1C. Similar to these population studies (31–33), we also found that prevalence of all CVD risk factors increased with increasing quartiles of A1C, and the difference reached statistical significance in the 3rd and 4th quartiles. Similar findings were reported in African Americans (33). However, unlike the Chinese study in which age and sex altered some of these associations (31), in the present analysis adjustments for age and sex did not alter the association of A1C with CVD risk factors.

HDL cholesterol showed an association with A1C when age and sex were incorporated into the model. However, this association disappeared when triglycerides were introduced into the model.

These results are in accordance with those reported in an earlier study by Bakker et al. (34), which suggested that within the metabolic syndrome, disturbances of lipid and glucose coexit (34).

Multiple regression analysis using various CVD risk factors revealed age, waist circumference, triglycerides, LDL cholesterol, and fasting insulin to be associated with A1C. With age, glycation of proteins increases; this supports the association of age with A1C observed in this study. The strong association of waist circumference, fasting insulin, and triglycerides with A1C and the fact that the prevalence of multiple sclerosis increases with increase in A1C quartiles suggest that A1C could be included as a diagnostic criteria for metabolic syndrome instead of fasting plasma glucose, particularly in situations when a fasting sample is difficult to obtain.

The NCEP (National Cholesterol Education Program) ATP III guidelines recognized metabolic syndrome as a risk factor for CAD, and this is confirmed by several studies (21). In this study, A1C levels increased with the number of components of the metabolic syndrome, and NGT subjects with three or more metabolic abnormalities had the highest A1C (5.7%). Moreover, the prevalence of metabolic syndrome per se increases with quartiles of A1C. A study of African Americans suggested A1C to be a surrogate marker for metabolic syndrome (33). In our study, an A1C cut point ≥5.6% was found to have the highest accuracy of predicting both metabolic syndrome and CAD.

The present study supports the EPIC (European Investigation of Cancer and Nutrition)-Norfolk study, which reported an association of A1C with CVD risk even in the nondiabetic range. In that study, 0.1–0.2% reduction in A1C was shown to reduce risk of total mortality by 5.1% (4). Hence, estimation of A1C appears to be a useful measure even among the nondiabetic population in assessing an individual's cardiovascular risk. The advantages of this test are that it can be measured at any time of the day with a very small blood sample (5 μl). The disadvantages are that A1C cannot be measured in the presence of hemoglobin variants by several methods, costs, and the difficulty in standardization (35).

One of the major limitations of this study is that, as a cross-sectional study, it cannot provide evidence for a cause-and-effect relationship between the association of A1C with CAD and its risk factors. The strengths of the study, however, are that it is population based and performed in a population at high risk of diabetes and premature CAD. In summary, this study reports that among Asian Indians who are known to have high risk of premature CAD and diabetes, a linear relationship exists between A1C, CAD, and metabolic syndrome even among nondiabetic subjects.

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