High Incidence of Glucose Intolerance in Asian-Indian Subjects With Acute Coronary Syndrome

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OBJECTIVE — The risk of diabetes and coronary heart disease is high in Asian Indians. In this study, we aim to assess 1) the prevalence of hyperglycemia in incident acute coronary syndrome (ACS), 2) the effect of glycemia on the outcome, and 3) the association of plasma levels of insulin and proinsulin with ACS.

RESEARCH DESIGN AND METHODS — A total of 146 nondiabetic subjects (121 men, 25 women) with ACS admitted to two hospitals in 1 year were enrolled. Random blood glucose at admission and a standard oral glucose tolerance test within 3 days were done. Glucose tolerance was categorized as normal glucose tolerance, impaired glucose tolerance (IGT) or impaired fasting glucose, and diabetes. Diabetes was arbitrarily classified further as undiagnosed (HbA₁c >6.0%) or possibly stressed diabetes (A₁c <6.0%). Subjects not on antidiabetic treatment were reassessed with a glucose tolerance test between 1 and 2 months. Fasting plasma specific insulin, proinsulin, their molar ratios, and insulin resistance (homeostasis model assessment) were estimated at baseline.

RESULTS — Mean age of the cohort was 55 ± 10.6 (SD) years. At baseline, 24 (16.4%) had normal glucose tolerance, 67 (45.9%) had IGT or impaired fasting glucose, and 55 (37%) had diabetes (35 [24%] were undiagnosed and 20 [13.7%] had stress diabetes). At follow-up, 53 of 92 responders (57.6%) continued to have IGT or diabetes. Mean baseline plasma insulin, proinsulin and its ratios, and insulin resistance were higher than normal in all subgroups.

CONCLUSIONS — Nondiabetic Asian Indians showed a high prevalence of hyperglycemia following ACS. ACS was associated with insulin resistance and increased levels of specific insulin, proinsulin, and high proinsulin-to-insulin ratios.

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the physician were allowed initiation of treatment. All of the remaining subjects underwent an oral glucose tolerance test with a 75-g glucose load 1 day before discharge from the hospital.

Subjects who had elevated glucose values at fasting (≥6.0 mmol/l) or at 2 h after glucose load (≥7.8 mmol/l) were classified using the World Health Organization criteria (14). Subjects with glucose values in diabetic range (fasting ≥7.0 and/or 2 h ≥11.1 mmol/l) were subdivided based on the A1C values. Undiagnosed preexisting diabetes was considered possible if the A1C values were ≥6.0%, and stress-induced hyperglycemia was considered if the A1C values were <6.0%.

All of the patients were reviewed between 5 and 8 weeks after discharge from the hospital. At the review, clinical parameters were recorded, and a repeat oral glucose tolerance test was performed. The glycemic status was reclassified, and appropriate medical treatment was advised for glycemic control. Biochemical parameters, including plasma insulin and proinsulin, were estimated in the baseline samples.

Plasma glucose was estimated by glucose oxidase-peroxidase method. Estimations of specific insulin and proinsulin were done using radio immunoassay methods (Linco reagents; Linco, St. Louis, MO). The lowest detection limit for specific insulin was 12.0 pmol/l; for proinsulin, it was 2.0 pmol/l. The assays had 100% specificity for human specific insulin and proinsulin. Intra- and interassay variations were <7–11% for both assays. The serum samples were stored at −70 °C until the assays were done. Insulin resistance was estimated by using the homeostasis model assessment (HOMA) procedure (15). HOMA of insulin resistance ≥4.1 was considered to indicate high insulin resistance in our laboratory (16). Capillary blood glucose was tested using Accutrend sensor meter and test strips (Roche Diagnostics, Mannheim, Germany). A1C (by immunoturbidimetric procedure) and lipid parameters were tested using (enzymatic) kits from Roche Diagnostics. The normal value for A1C varied from 4 to 6% in our laboratory.

**Statistical procedures**

Means ± SD are reported for normally distributed variables. Group comparisons were done by one-way ANOVA. For skewed variables, median and range are reported; median test was used for group comparisons. A multiple logistic regression analysis was done to look for variables associated with abnormal glucose tolerance.

The association of proinsulin with insulin resistance was studied using a multiple linear regression analysis, in which other variables such as age, sex, BMI, waist circumference, and hypertension were also included.

Molar ratios of proinsulin to specific insulin were calculated using values corrected for BMI using a linear regression equation.

**RESULTS** — During a 1-year recruitment period, 151 cases of ACS without known history of diabetes were identified, among whom 146 consented to participate in the study. The study group included 121 men (82.9%) and 25 (17.1%) women. Mean age of the total
group was 45 ± 6 years, and mean BMI was 25.0 ± 3.0 kg/m². Hypertension (blood pressure >140/90 mmHg monthly and/or on antihypertensive treatment) was present in 74 (50.7%) participants, 31.5% were regular smokers, and 26% consumed alcohol daily. Hypolipidemic drugs were being used by 39.7%. Among the acute coronary events, 70% had myocardial infarction, 27% had unstable angina pectoris, and the remaining 3% had other acute cardiac events such as congestive heart failure.

Of the 146 subjects, 4 had unequivocal diabetes and were started on antidiabetic treatment. The remaining 142 subjects underwent oral glucose tolerance tests. A total of 83.6% of subjects had glycose intolerance. The breakdown of glucose tolerance according to the plasma glucose and A1C values was as follows: normal glucose tolerance in 16.4%, IFG or IGT in 46%, undiagnosed diabetes in 24%, and possible stress-induced hyperglycemia in 13.7%.

The flow chart showing the recruitment of patients, basal glucose tolerance test outcome, and the number followed up is shown in Figure 1. There were three deaths, one before and two after discharge from the hospital. The remaining 98 subjects were requested to report for a follow-up glucose tolerance test within 5–8 weeks; 92 subjects responded to the request.

Table 1 shows the characteristics of the groups in relation to the glucose tolerance at entry. Age, BMI, waist circumference, and lipid parameters were not significantly different among the subgroups. As expected, the A1C and plasma glucose values were significantly higher in the newly diagnosed diabetic subjects.

Table 2 shows the status of glucose tolerance at review in relation to the initial status. A total of 57.6% continued to have abnormal glucose tolerance. Among the IGT subjects, four cases developed diabetes during the follow-up period.

The fasting concentrations of specific insulin, proinsulin, and their molar ratios were significantly higher in the subjects with ACS, irrespective of the status of glucose tolerance (Table 3). Insulin resistance was also significantly higher in the total group.

In the multiple logistic regression analysis, baseline 2-h plasma glucose was a strong indicator of odds ratios (95% CI), 1.04 (1.02–1.06) (P = 0.0001) of abnormal glucose tolerance.

Proinsulin was a strong determinant of insulin resistance because it explained 27.7% (R² = 27.7%, P < 0.0001) of the variations of HOMA of insulin resistance of a total of 31.3% contributed by age, sex, BMI, waist circumference, and presence of hypertension. None of the other tested variables were significantly associated with insulin resistance.

**CONCLUSIONS** — This study showed that among the Asian-Indian subjects admitted with ACS, abnormal glucose tolerance was present in a majority (84%) after the exclusion of those with known history of diabetes. Based on the presence of an elevated A1C value, it was estimated that nearly a quarter of the cases had undiagnosed diabetes. Another 13.7% no longer showed diabetes at the follow-up and could be considered as stress-induced hyperglycemia during the acute phase of the cardiac event. On the other hand, in many cases, such an improvement in glucose tolerance could be due to the regression-to-the-mean phenomenon that happens in repeat testing of subjects with high values in the initial assessment. It is, however, important to note that the majority of these patients had IGT at the repeat testing.

In the urban adult population in India, 12.1% have diabetes, and ~4% of them are undiagnosed (6). Therefore, it was not surprising that 24% of subjects have undiagnosed diabetes in this group of patients with ACS. The maximum age-specific prevalence of diabetes in the population cohort was 29.1% in the age-group of 60–69 years, among whom only approximately one-third (~10%) were newly diagnosed cases of diabetes (6).
IGT and/or IFG were detected in approximately half of the ACS patients. In the urban Indian population, the age-specific prevalence of IGT varied from 11.5% in the age-group of 20–29 years to a maximum of 19.3% in those aged >69 years, with no sex difference (6). The overall age-adjusted prevalence of IGT was 14.0%. The high prevalence of diabetes (37.7%) and impaired glucose regulation (45.9%) in the study group demonstrates that the majority of Indian patients with ACS have abnormal glucose metabolism.

The prevalence of abnormal glucose tolerance in urban Indians with ACS is higher than in European countries (2,3). Norhammar et al. reported that <35% of subjects had normal glucose tolerance either at admission to the hospital or 3 months after follow-up after excluding those with known diabetes (3), whereas we found <16% had normal glucose tolerance at the time of the events. Other striking variations in our study were the younger mean age of the cohort (55 ± 10.6 vs. 62.6 ± 9.3 years) and a higher prevalence of hypertension (30.7 vs. 37%) and treated hyperlipidemia (39.7 vs. 16%). The number of deaths were not high in our study given the small number of ACS patients included, and thus no attempt was made to analyze the risk of mortality due to hyperglycemia compared with nondiabetic cases. It has been reported by other investigators that the risk was 2.8-fold higher in nondiabetic ACS patients who had hyperglycemia on admission than those without after adjusting for age (17).

The baseline 2-h glucose value was the predictor of abnormal glucose tolerance, including diabetes and IGT at follow-up. Our observations differed from the results of Norhammar et al. (3) in that the 2-h glucose concentration, but not the fasting value, was a predictor of future abnormal glucose tolerance. This is consistent with our observation that the postchallenge glucose, rather than the fasting glucose, is a more sensitive index of abnormal glucose tolerance in our population (18) and in Asian populations in general (19).

In the present study, specific insulin and proinsulin levels were elevated irrespective of the glycemic status at the time of the acute cardiac event. Insulin resistance was also higher than the control values in both diabetic and nondiabetic groups. This confirms our earlier report showing an association of proinsulin and insulin resistance with coronary artery disease proven by angiography in normoglycemic men (13). We noted that elevated proinsulin levels explained 27.7% of the variations of insulin resistance, thereby indicating a strong link between the two parameters. A study by Zethelius et al. (12) had reported that elevated proinsulin levels were a good surrogate marker of insulin resistance.

A higher proportion of proinsulin to insulin is indicative of an abnormal metabolism of insulin, and this is uniformly observed in cases of ACS irrespective of the glucose concentration. It had been suggested by Haffner et al. (10) in the San Antonio Heart Study that the level of proinsulin was strongly predictive of several metabolic and hemodynamic variables in nondiabetic subjects. Similarly, Yudkin et al. (11) found that proinsulin-like molecules were a marker of vascular disease, although it was unlikely to be involved directly in the etiology of coronary artery disease. Their study group included nondiabetic European and South Asian subjects.

In summary, we observed that the majority of the Asian-Indian ACS patients without history of diabetes show dysglycemia, with a small proportion probably being stress-induced diabetes. The occurrence of ACS was at a younger age than currently typical in Western counterparts. On a short-term follow-up, it was noted that nearly two-thirds of the subjects continued to have abnormal glucose metabolism. In addition, increased levels of plasma insulin, proinsulin, and insulin resistance were associated with ACS regardless of glycemia status.

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