Relationship of Glucose and Insulin Levels to the Risk of Myocardial Infarction: A Case-Control Study

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OBJECTIVE
To assess the relationship between dysglycemia and myocardial infarction in nondiabetic individuals.

BACKGROUND
Nondiabetic hyperglycemia may be an important cardiac risk factor. The relationship between myocardial infarction and glucose, insulin, abdominal obesity, lipids and hypertension was therefore studied in South Asians—a group at high risk for coronary heart disease and diabetes.

METHODS
Demographics, waist/hip ratio, fasting blood glucose (FBG), insulin, lipids and glucose tolerance were measured in 300 consecutive patients with a first myocardial infarction and 300 matched controls.

RESULTS
Cases were more likely to have diabetes (OR 5.49; 95% CI 3.34, 9.01), impaired glucose tolerance (OR 4.08; 95% CI 2.31, 7.20) or impaired fasting glucose (OR 3.22; 95% CI 1.51, 6.85) than controls. Cases were 3.4 (95% CI 1.9, 5.8) and 6.0 (95% CI 3.3, 10.9) times more likely to have an FBG in the third and fourth quartile (5.2–6.3 and >6.3 mmol/l); after removing subjects with diabetes, impaired glucose tolerance and impaired fasting glucose, cases were 2.7 times (95% CI 1.5–4.8) more likely to have an FBG >5.2 mmol/l. A fasting glucose of 4.9 mmol/l best distinguished cases from controls (OR 3.42; 95% CI 2.42, 4.83). Glucose, abdominal obesity, lipids, hypertension and smoking were independent multivariate risk factors for myocardial infarction. In subjects without glucose intolerance, a 1.2 mmol/l (21 mg/dl) increase in postprandial glucose was independently associated with an increase in the odds of a myocardial infarction of 1.58 (95% CI 1.18, 2.12).

CONCLUSIONS
A moderately elevated glucose level is a continuous risk factor for MI in nondiabetic South Asians with either normal or impaired glucose tolerance. (J Am Coll Cardiol 1999;33:612–9) © 1999 by the American College of Cardiology

Diabetes mellitus and hypercholesterolemia are well-established risk factors for coronary artery disease (CAD). Patients with CAD also have a high rate of glucose intolerance, hypertriglyceridemia, low high density lipoprotein (HDL) levels, insulin resistance and hyperinsulinemia, in addition to abdominal obesity and hypertension. The observation that different ethnic groups have different rates of CAD suggests that these groups may differ with respect to the frequency or nature of predisposing metabolic risk factors, and/or with respect to their susceptibility to these risk factors.

South Asians constitute one sixth of humanity and experience much higher rates of coronary heart disease than other ethnic groups in the world (1–6). The World Bank estimates that the death rate from coronary heart disease will increase dramatically in the Indian subcontinent and is expected to contribute to more quality-adjusted life years lost over the next 20 years than in any other part of the world (7). South Asians also have up to a five-fold (8,9) higher rate of type 2 diabetes mellitus, as well as a higher rate of glucose intolerance, low HDL, high triglycerides and abdominal obesity than people of European ancestry. Despite the high prevalence of both CAD and metabolic risk factors for CAD in the South Asian Indian population, there are sparse data linking the two in these populations. This article reports the relationship between myocardial infarction and body fat distribution, hypertension, glucose tolerance status, glucose, insulin and lipid levels in a case-control study completed in India.

METHODS
Subjects. Details of the design of this hospital-based case-control study have been reported previously (10). This
glucose, as defined by the recently revised diagnostic criteria for the classification of diabetes (11). Cases were defined as consecutive patients between the ages of 30 and 60 years (inclusive) who were admitted to the coronary care unit of the hospital with a first acute MI. The diagnosis of acute MI required a history of typical chest pain lasting at least 20 min, a standard 12 lead electrocardiogram (ECG) showing ST elevation of 2 mm or more in two or more contiguous leads and subsequent evolution of cardiac enzymes. Controls were selected from outpatients attending the hospital clinic for refraction, otorhinolaryngology evaluation or a general physical examination or from inpatients admitted for cataract extraction or herniorrhaphy. Both cases and controls were excluded if they had any previous diagnosis of heart disease, clinical evidence of liver disease (jaundice, ascites or prominent abdominal veins), or a history of dietary modification in the month prior to admission. They were also excluded if a fasting blood sample could not be drawn within 24 h of the onset of chest pain because the effect of acute MI on lipid levels occurs after this period (12). Controls were also excluded if their 12 lead ECG showed pathological Q waves, ST segment deviation, T wave inversion, bundle branch or atrioventricular block, tachyarrhythmia (other than isolated atrial ectopic beats) or chamber hypertrophy. Controls were matched to cases for age (within 5 years) and gender. A subject was classified as having diabetes if they reported a history of diabetes, or if the fasting blood glucose (FBG) or postprandial blood glucose (PPBG) was ≥7.0 mmol/l (126 mg/dl) or ≥11.1 mmol/l (200 mg/dl) respectively (11). A subject was classified as having impaired glucose tolerance (IGT) if the PPBG was ≥7.78 mmol/l (140 mg/dl) and <11.1 mmol/l (200 mg/dl) and the FBG was <7.0 mmol/l (126 mg/dl); impaired fasting glucose (IFG) was diagnosed if the FBG was ≥6.1 mmol/l (110 mg/dl) and <7.0 mmol/l (126 mg/dl). Subjects without known diabetes who did not have a glucose tolerance test were classified on the basis of their fasting glucose alone.

Variables measured. Age, gender, religion, monthly income, educational level, dietary details, smoking habits, alcohol use and a history of diabetes mellitus and hypertension were recorded for all subjects. Weight, height, and waist and hip circumference were determined for each subject; waist circumference was measured at the narrowest diameter between the costal margin and the iliac crest, and hip circumference was measured at the greatest diameter over the glutei.

Fasting total cholesterol, HDL cholesterol, low density lipoprotein (LDL) cholesterol, and total triglyceride were measured within 24 hours of the onset of chest pain for cases and prior to any surgery for controls. Fasting blood glucose in plasma was measured on the 9th or 10th day after admission for cases and at the time of lipid measurement for controls. In addition those subjects without a previous history of diabetes had blood drawn for fasting insulin levels at this time; they then had a PPBG measured two hours after drinking 75 grams of glucose. Patients were not on any intravenous therapy when glucose levels were measured.

Total cholesterol and triglycerides were estimated by enzymatic methods (cholesterol oxidase/peroxidase-aminophenazone for cholesterol, glycerol phosphate oxidase/peroxidase-aminophenazone for triglycerides) on an automated system using standard kits (Boehringer Mannheim GmbH). High density lipoprotein cholesterol was estimated using a precipitation method and LDL cholesterol was calculated (total cholesterol–HDL cholesterol–triglycerides/5). Glucose was assayed by the glucose oxidase method and serum insulin was estimated by radioimmunoassay (kit manufactured by the Board of Radiation and Isotope Technology, Bombay). All biochemical analyses were conducted without knowledge of the clinical information.

Statistical methods. For the analyses in which all cases were compared to all controls, cases were matched with the next control subject recruited and estimates of odds ratios (ORs) and 95% confidence intervals were based on analyses of matched-pair data. Unmatched analyses were used to compare nondiabetic or diabetic cases to nondiabetic or diabetic controls because cases were not matched to controls on the basis of diabetes status. Because of the skewed distribution of continuous variables, nonparametric univariate analyses were used. Univariate comparisons of frequencies were done using chi square tests.

For multivariate model building, all nonnormal variables were transformed and stepwise multiple logistic regression analyses were performed to identify the best independent determinants of myocardial infarction (MI). Case-control matching was used for analyses of all cases and controls. For nondiabetic and non-IGT subgroups, an unmatched model was used with age and sex added as covariates. Based on these logistic regression models, cutoffs for the receiver operating curve (ROC) analyses were those that optimized the cross-product ratio.
The following variables were included in all of the multivariate analyses: fasting glucose, postprandial glucose (in nondiabetic subjects), waist/hip ratio, cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, cholesterol/HDL and smoking status. In addition, diabetes status (yes/no) was entered in the regression analysis of all cases and controls; IGT status (yes/no), postprandial glucose and insulin level in the regression analysis of nondiabetic cases and controls; and impaired fasting glucose status (yes/no), postprandial glucose and insulin levels in the regression analysis of non-IGT cases and controls. BMDP LR (step-wise logistic regression) with a p-value for entry of a variable into the model of \( p < 0.10 \) and \( p < 0.15 \) to remove variables was used for this analysis.

Figures illustrating the unadjusted relationship between glucose values and odds ratios for all subjects and for nondiabetic subjects were constructed from univariate logistic regression coefficients. The SAS and BMDP statistical packages were used for all statistical analyses. p values are two-tailed.

**RESULTS**

Table 1 describes the clinical and biochemical characteristics of the 300 cases and 300 controls. Overall, there was a higher prevalence of previously diagnosed diabetes and hypertension in cases. Moreover, cases had a higher waist/hip ratio (\( p = 0.0001 \)), higher FBG (\( p = 0.0001 \)) and PPBG (\( p = 0.0001 \)) and higher fasting insulin (\( p = 0.003 \)). There was no difference in either body mass index or lipid values.

**Diabetes and impaired glucose tolerance.** A history of diabetes was obtained in 87 subjects (61 cases, 26 controls) at the time of presentation. No glucose levels were recorded in 6 subjects (4 cases, 2 controls) no PPBG levels were recorded in 59 subjects (43 cases, 16 controls) and no FBG was recorded in 1 case who was classified with diabetes on the basis of a PPBG of 11.7 mmol/l. On the basis of their recorded glucose levels, 66 subjects (49 cases, 17 controls) were diagnosed with diabetes, 82 subjects (54 cases, 28 controls) were classified as having impaired glucose tolerance and 41 subjects (25 cases, 16 controls) were classified as having impaired fasting glucose (IFG). Therefore, a total of 189 cases (63.9%) and 87 controls (29.2%) had either diabetes, impaired glucose tolerance or IFG. The distribution and odds ratios for each of these diagnoses is listed in Table 2.

The results for subjects with and without diabetes were analyzed separately to explore the relationship between nondiabetic levels of glycemias and myocardial infarction. Both diabetic and nondiabetic cases had a higher waist/hip ratio than controls (\( p = 0.05 \) and \( p = 0.0001 \), respectively). Nondiabetic cases also had higher FBG and PPBG levels
than nondiabetic controls ($p = 0.0001$ for both); fasting insulin levels (available in 150 nondiabetic cases and 218 nondiabetic controls) were marginally lower in cases (133.4 pmol/l and 134.1 pmol/l for cases and controls, respectively; $p = 0.03$).

**Continuous relationship between glucose and risk of myocardial infarction.** The odds ratios for MI in all subjects increased with increasing FBG quartiles (Fig. 1) and was greater than 1 at FBG levels clearly below the nondiabetic and impaired glucose tolerance range. For example, cases were 3.4 times (95% CI 1.9–5.8) more likely to have an FBG between 5.2 mmol/l (94 mg/dl) and 6.3 mmol/l (114 mg/dl) than controls. This continuous relationship was maintained in the analysis of nondiabetic subjects and was also clearly maintained after removing all subjects with diabetes, IGT and IFG (Fig. 1D). Compared to subjects with an FBG $\geq$4.5 mmol/l (81 mg/dl), the odds

<table>
<thead>
<tr>
<th>Glucose Tolerance Status</th>
<th>Cases (%)</th>
<th>Controls (%)</th>
<th>Odds Ratios (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>153†</td>
<td>110 (37.2)</td>
<td>43 (14.4)</td>
</tr>
<tr>
<td>Impaired Glucose Tolerance</td>
<td>82</td>
<td>54 (18.2)</td>
<td>28 (9.4)</td>
</tr>
<tr>
<td>Impaired Fasting Glucose</td>
<td>41</td>
<td>25 (8.4)</td>
<td>16 (5.4)</td>
</tr>
<tr>
<td>Normal Glucose Tolerance</td>
<td>318</td>
<td>107 (36.2)</td>
<td>211 (70.8)</td>
</tr>
<tr>
<td>Total</td>
<td>594</td>
<td>296</td>
<td>298</td>
</tr>
</tbody>
</table>

*These odds ratios and 95% confidence intervals were derived from a logistic regression of the matched cases and controls; $p < 0.0001$. †This category includes subjects with an established diagnosis of diabetes as well as subjects with a fasting glucose $\geq$7.0 mmol/l (126 mg/dl) or a postprandial glucose $\geq$11.1 mmol/l (200 mg/dl).

![Figure 1](https://example.com/fig1.png)

**Figure 1.** Fasting glucose quartiles and the risk of myocardial infarction in all subjects. The odds of a myocardial infarction increase with glucose quartile (A) even after subjects with diabetes are excluded (B), subjects with both diabetes and impaired glucose tolerance are excluded (C) and subjects with diabetes, impaired glucose tolerance and impaired fasting glucose are excluded (D). (D) only includes subjects whose fasting glucose is $<6.1$ mmol/l (i.e., those with no IFG). The actual odds ratios and 95% confidence intervals are above the bars.
ratio for MI in subjects in this latter group with an FBG of 5.2 to 6.3 mmol/l (94 to 114 mg/dl) was 2.7 (95% CI 1.5–4.8).

Receiver operating curve analysis: distinguishing cases from controls. To further explore the observed relationship between FBG, PPBG, insulin levels and CAD, and to determine the extent to which these biochemical markers discriminated between cases and controls, the distributions of these values were plotted (Fig. 2) and subjected to ROC analysis (Table 3). An FBG of 4.9 mmol/l (89 mg/dl) best differentiated all cases from controls. Seventy percent of cases had an FBG $\leq 4.9$ mmol/l (89 mg/dl); these patients were 3.42 times more likely to be a case than a control (95% CI 2.42–4.83). Similar analyses for the postprandial glucose level yielded a cutpoint of 7.0 mmol/l (126 mg/dl; OR = 5.3; 95% CI 3.0–9.4). When the analysis was restricted to nondiabetic patients, similar fasting and postprandial glucose cutpoints of 5.1 mmol/l (91 mg/dl) and 7.1 mmol/l (128 mg/dl) were obtained (Table 3). A waist/hip ratio $\geq 0.89$ best differentiated all cases from controls (OR = 3.24; 95% CI = 2.24–4.69; 81% of cases’ waist/hip ratios were $\geq 0.89$). No fasting insulin level clearly separated cases from controls.

Multiple logistic regression. A matched multiple logistic regression analysis that included the variables (transformed for normality where appropriate) measured in all subjects (i.e., diabetes status, history of hypertension, inverse of FBG, waist/hip ratio, lipid levels, smoking status and presence or absence of diabetes or IGT) was done to identify the independent determinants of myocardial infarction. Current smoking ($p < 0.001$), waist/hip ratio ($p < 0.001$), total cholesterol/HDL cholesterol ratio ($p = 0.01$) and presence or absence of diabetes ($p < 0.001$) or hypertension ($p = 0.02$) independently differentiated cases from controls.
Because PPBG was not measured in the diabetic subjects, this variable was not included in this analysis. Similar findings were noted when the analysis was restricted to nondiabetic subjects and subjects without impaired glucose tolerance, in whom both FBG and PPBG as well as fasting insulin levels were measured and entered into the regression in addition to all of the other variables listed above. Insulin levels were not independent variables in any model tested.

Table 4 lists the odds ratios for an increase in 1 standard deviation of the variables included in the regression models for all subjects, nondiabetic subjects and non-IGT subjects. After adjustment for smoking status, waist/hip ratio and triglyceride level, an increase in PPBG of 1.2 mmol/l or 21 mg/dl (1 standard deviation) increased the odds of an MI 1.58 times (95% CI 1.18, 2.12) in non-IGT subjects.

**DISCUSSION**

This case control study clearly shows that a high fasting or postprandial glucose level, as well as a high waist/hip ratio and history of hypertension and current smoking are independently associated with the risk of myocardial infarction in South Asians. It also shows that fasting (4.9 mmol/l or 89 mg/dl) or postprandial (6.8 mmol/l or 123 mg/dl) glucose levels lower than those associated with diabetes, IGT or even impaired fasting glucose clearly differentiate MI cases from controls and that the risk of MI increases progressively as the glucose levels increase from normal right into the diabetic range. Thus glucose elevation above a relatively low dysglycemic threshold (13) appears to be a continuous risk factor for cardiovascular disease in this population.

**Glucose levels and cardiovascular risk.** These results are consistent with data from other populations suggesting a progressive relationship between glucose levels and an increased risk of cardiovascular disease in both nondiabetic (14–17) and diabetic patients (18–21). They are also consistent with a metaregression analysis of all cohort studies of nondiabetic patients in which baseline glucose levels were related to subsequent cardiovascular events and mortality (22). The observation that the glucose-associated risk persisted even after controlling for other risk factors suggests that glucose elevation is an independent marker for atherosclerosis in South Asians.

| Table 3. Values That Best Discriminated Myocardial Infarction Cases from Controls |
|--------------------------------|----------------|----------------|
| Overall*                      | Nondiabetic Subjects |
| Cutpoint†                     | Odds Ratio (95% CI) | Cutpoint† |
| Fasting glucose (mmol/l)      | 4.9             | 3.42 (2.42, 4.83) | 5.1          | 3.12 (2.10, 4.63) |
| Postprandial glucose (mmol/l) | 6.8§            | 3.84 (2.59, 5.67) | 7.1          | 4.23 (2.72, 6.58) |
| Fasting insulin               | None‡           | N/A             | None‡       | N/A             |
| Waist/hip ratio               | 0.89            | 3.24 (2.24, 4.69) | 0.93        | 2.93 (1.96, 4.37) |

*The overall analysis was based on the matched analysis in which one case was matched to one control; the diabetic and nondiabetic analyses were done on unmatched data (because patients were not matched on the basis of diabetes status during the study). †Cutpoints are the levels which best separate cases from controls based on a receiver operating curve analysis. §No clear cutpoint was apparent from the analysis. ‡Glucose tolerance tests and insulin levels were not done in patients with known diabetes.

| Table 4. Multivariate Odds Ratios for the Independent Determinants of Myocardial Infarction |
|--------------------------------|----------------|----------------|----------------|
|                               | All Subjects Model† | Nondiabetic Subjects Model | Non-IGT Subjects Model |
| Diabetes status               | 4.89 (2.66, 9.00)  | N/A             | N/A            |
| Postprandial glucose‡         | N/A             | 2.01 (1.56, 2.59) | 1.58 (1.18, 2.12) |
| Waist/hip ratio               | 2.41 (1.75, 3.31) | 1.58 (1.19, 2.10) | 1.79 (1.29, 2.48) |
| Cholesterol/HDL ratio         | 1.36 (1.06, 1.75) | not in model    | not in model   |
| Triglyceride                  | not in model     | 0.73 (0.61, 0.88) | 0.72 (0.52, 1.00) |
| Hypertension                  | 2.52 (1.13, 11.4) | 4.91 (1.86, 12.9) | not in model   |
| Smoking                       | 6.52 (3.71, 11.4) | 7.77 (4.24, 14.2) | 5.98 (2.94, 12.2) |

*Whether or not a continuous variable was an independent predictor was determined on the basis of its continuous distribution. In this table, however, the increase in odds for every 1 standard deviation (SD) increase in the value of the independent continuous variables are reported. For the model that included all subjects, 1 SD for the waist/hip ratio = 0.06 and for the total cholesterol/HDL cholesterol ratio = 1.13; for the model that only included nondiabetic subjects, 1 SD for PPBG = 2.3 mmol/l (41 mg/dl), for waist/hip ratio = 0.06 and for triglycerides = 1.09 mmol (94 mg/dl); for the model that only included non-IGT subjects, 1 SD for PPBG = 1.2 mmol/l (21 mg/dl), waist/hip ratio = 0.06 and triglycerides = 1.11 mmol/l (96.7 mg/dl). A matched logistic regression analysis was done for all subjects, and an unmatched analysis (not matched on diabetes status but adjusted for age and sex) was done for nondiabetic and nonimpaired glucose tolerance (non-IGT) subjects. ‡Postprandial glucose was not measured in diabetic subjects.
Lipid and insulin levels and cardiovascular risk. The fact that the cholesterol/HDL ratio was an independent determinant of MI in the multivariate analysis of all subjects and the fact that triglyceride levels were not an independent determinant of MI is consistent with other epidemiologic studies (23,24). The fact that this ratio was not an independent determinant of MI in the nondiabetic subjects may have been due to the lower power to detect such a relationship in this smaller subgroup. In the univariate analysis of the nondiabetic subgroup, triglyceride levels were nonsignificantly higher in cases than in controls (data not shown). After adjustment for other risk factors, however, there was an inverse correlation in this subgroup. This may have been due to the fact that some of the MI case subjects were treated with intravenous heparin—a therapy known to lower triglyceride levels (25).

The observation that insulin levels were not independent risk factors for MI in the logistic regression suggests that the moderately higher insulin levels observed in cases may have occurred in response to the elevated glucose levels (26,27). It is also consistent with epidemiologic data from other populations suggesting that hyperinsulinemia alone may not be a strong determinant of cardiovascular disease (28). The possibility that the preinfarct hyperinsulinemia may have been minimized in post-MI cases (at the time of insulin sampling), however, cannot be ruled out.

Waist/hip ratio and cardiovascular risk. The waist/hip ratio strongly discriminated cases from controls and was a strong independent risk factor for MI in this population. Conversely, body mass index had no discriminative value. Evidence that a high waist/hip ratio reflects visceral fat accumulation, and that visceral fat is associated with abnormalities in glucose and fatty acid metabolism suggest that it is a surrogate measure for an atherogenic metabolic state (29–31). Moreover, the independence of the high waist/hip ratio in the logistic regression suggests that this ratio reflects metabolic abnormalities that are distinct from those related to the higher glucose level. The nature of these abnormalities is currently unknown.

Limitations of the case-control design. These data are limited by the case-control design. First, only one glucose tolerance test was done in cases and controls who did not have a history of diabetes. Even under ideal circumstances the postprandial (2 h) glucose result in this test is not highly reproducible (32). As this variability may be even more pronounced in patients who are within two weeks of a myocardial infarction, the classification of cases into those with diabetes and IGT according to postprandial glucose values may not be robust. Second, the postprandial glucose level is increased in people who are inactive or who are not consuming a high carbohydrate diet for several days prior to the test (33). It may also have been affected by drugs prescribed in the post-MI period. This may have magnified the elevation in postprandial glucose levels seen in nondiabetic cases (in whom glucose tolerance tests was done 9 to 10 days after admission for myocardial infarction) compared with nondiabetic controls (in whom glucose tolerance tests were done within 24 h of admission) and may have overestimated the number of cases who had (previously undiagnosed) diabetes. Despite these possibilities, the detection of clear and consistent differences in the distribution of the FBG (which are more robust than the PPBG [32,33]) as well as the PPBG among cases and controls regardless of diagnosis (i.e., in all subjects and in those without diabetes or IGT) strongly supports the inference that dysglycemia is an important and independent cardiac risk factor in this population.

Implications and conclusions. The finding of a graded risk of MI with glucose elevations within the “normal” range in South Asians strongly supports the need to explore this relationship in other ethnic groups. If these observations are confirmed, the population attributable risk of dysglycemia (i.e., the excess risk of MI in the general population attributable to glucose elevations above some low dysglycemic threshold) may be several times greater than the population attributable risk of diabetes alone. This would focus attention on the high prevalence of elevated glucose levels in the nondiabetic population and may lead to innovative ways of preventing cardiovascular disease in this group.

REFERENCES


