Abdominal Obesity, Impaired Nonesterified Fatty Acid Suppression, and Insulin-Mediated Glucose Disposal Are Early Metabolic Abnormalities in Families With Premature Myocardial Infarction

Jaspal S. Kooner, Ragavendra R. Baliga, John Wilding, David Crook, Christopher J. Packard, Linda M. Banks, Stanley Peart, Timothy J. Aitman, James Scott

Abstract—British Indian Asian men aged <40 years have a twofold to threefold increased risk of death from coronary heart disease (CHD) compared with British whites. Epidemiological studies have suggested an association between glucose intolerance and hyperinsulinemia with premature CHD in Indian Asians. We tested the association of insulin action with myocardial infarction (MI) by using the hyperinsulinemic-euglycemic clamp in 17 MI patients: 8 Punjabi Sikhs (PSMI), 9 British whites (BMW), and 17 control subjects (9 PSCs and 8 BWCs). Metabolic factors associated with insulin resistance were investigated in 51 MI patients (24 PSMIs and 27 BMWIs) and 53 control subjects (28 PSCs and 25 BWCs). Familial aggregation of defective insulin action was examined by studying five pedigrees of Sikh survivors of MI. Sikh survivors of premature MI demonstrated impaired insulin-mediated glucose uptake (P<.001) by use of the clamp technique and nonesterified fatty acid (NEFA) suppression (P<.05) by using both clamp techniques and the oral glucose tolerance test, as compared with Sikh control subjects. White patients had impaired insulin-mediated glucose uptake but normal NEFA suppression. Metabolic factors usually associated with insulin resistance, including increased 2-hour post–oral glucose tolerance test triglycerides, smaller low density lipoprotein particle size, and increased plasminogen activator inhibitor-1, were present in white (all P<.05) but surprisingly absent in Sikh (all P>.05) MI patients compared with respective ethnic control subjects. Fasting glucose and total cholesterol levels did not differ between patients and control subjects. Abdominal obesity, impaired NEFA suppression after oral glucose, and fasting hyperinsulinemia were present in Sikh MI patients and their nondiabetic first-degree relatives compared with Sikh control subjects. PS survivors of premature MI demonstrated impaired insulin-mediated glucose disposal and NEFA suppression compared with ethnic control subjects. BWMIs showed abnormalities of carbohydrate, but not of NEFA, metabolism compared with white control subjects. Defects of insulin action manifested as abdominal obesity, impaired NEFA suppression, and fasting hyperinsulinemia are present in Sikh MI patients and their asymptomatic, nondiabetic, first-degree relatives. We suggest that these defects may be early metabolic markers that predict risk of premature MI among PSs. (Arterioscler Thromb Vasc Biol. 1998;18:1021-1026.)

Key Words: myocardial infarction ■ abdominal obesity ■ nonesterified fatty acids ■ insulin resistance


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Premature CHD mortality is higher in British Indian Asians than in British whites.1 Increased mortality in Indian Asians is particularly marked in men aged 30 to 39 years, in whom the relative risk of death from CHD is 2, and in men aged 20 to 29, for whom the relative risk is 3, compared with age-matched whites.1 Conventional risk factors, including smoking, hypercholesterolemia, or hypertension, do not account for the higher cardiovascular mortality in this population group.2 In fact, the prevalence of these risk factors is generally reduced in Indian Asians compared with whites.2 Insulin resistance and its metabolic consequences are increasingly recognized as risk factors for CHD.3−11 However, the association of insulin action with MI has not been formally examined in Indian Asians or in British whites. We studied Punjabi Sikh (Indian Asian [PS]) survivors of premature MI for defects of insulin action. A comparable group of white MI survivors (BMW) was also studied. Familial aggregation of defective insulin action was examined by investigating first-degree relatives of Sikh MI patients to search for early markers of MI.

Methods

Subjects Seventeen male MI patients (8 PSMIs and 9 BMWIs) and 17 control subjects (9 PSCs and 8 BWCs) underwent the hyperinsulinemic-euglycemic clamp study to test the association of insulin action with MI. Fifty-one male MI patients (24 PSMIs and 27 BMWIs) and 53 control subjects (28 PSCs and 25 BWCs) were studied to examine familial aggregation of insulin resistance.
matched male control subjects (28 PSCs and 25 BWCs) were investigated after an oral glucose load for metabolic disturbances associated with insulin resistance. Factors showing significant differences between Sikh MI patients and Sikh control subjects were assessed in 37 first-degree relatives of 5 Sikh MI patients.

Diagnosis of MI and angiographic coronary disease was made before the age of 50 years, patients were not studied within 3 months of an MI or coronary intervention. Patients with fasting blood glucose values greater than 6.7 mmol/L, previous history of non-insulin-dependent diabetes mellitus (NIDDM), insulin-dependent diabetes mellitus (IDDM), hypertension, dyslipidemia (cholesterol levels greater than 8.0 mmol/L and triglycerides greater than 4 mmol/L), abnormal liver or thyroid function tests, and a BMI greater than 30.0 kg/m\(^2\) were excluded. Treatment with \(\beta\)-blockers (6 PSMIs and 5 BWMIs) and angiotensin-converting enzyme inhibitors (3 PSMIs and 4 BWMIs) was stopped 2 weeks before the study. The remaining subjects were not taking \(\beta\)-blockers, thiazide diuretics, or other drugs affecting lipid or carbohydrate metabolism. Specific dietary counseling or coronary rehabilitation was not undertaken after the acute event or prior to the study in MI patients. Control subjects were healthy male volunteers randomly selected from three general practitioners’ lists and had no previous history of cardiovascular disease or diabetes. All had a normal resting electrocardiogram and a normal exercise electrocardiogram at high work load. Control subjects were matched as a group to patients with MI with respect to ethnic origin, age, weight, and BMI. None were taking any medication. The Sikhs were residents of the United Kingdom for a mean of 22 years (range, 8 to 34).

Thirty-seven first-degree relatives of five PSMIs (20 men and 17 women; mean±SD age, 36±13 years) were also studied to investigate familial aggregation of defective insulin action. Relatives with a previous history of CHD, NIDDM, IDDM, hypertension, major organ disease, or a BMI greater than 30.0 kg/m\(^2\) were excluded. All subjects gave informed consent before participating in the study.

Medical history and physical activity (leisure time) were assessed by interview. The physical activity score, based on the frequency, duration, and intensity of exercise undertaken in the 4 weeks prior to the study, was calculated for each individual (as the best approximate available), and energy expenditure was calculated according to published data. Blood pressure was measured with a random-zero sphygmomanometer (Hawksley and Sons) after a 10-minute rest and with the subject in the sitting position. Systolic and diastolic blood pressures were measured at the time of the first and fifth Korotkoff sounds, respectively. Waist and hip girths were measured in the standing position with a fiberglass tape. Waist was measured as the smallest horizontal girth between the costal margin and the iliac crests and the hip as the circumference at the level of the greater trochanters. The study protocol was approved by the hospital ethics committee.

**Experimental Protocol**

The association of insulin action with MI was tested in 17 MI patients (8 PSMIs and 9 BWMIs) and 17 control subjects (9 PSCs and 8 BWCs) by using the hyperinsulinemic-euglycemic clamp technique in 17 MI patients (8 PSMIs and 9 BWMIs) and 17 control subjects (9 PSCs and 8 BWCs). Two polyethylene cannulas were inserted, one into an antecubital vein (for infusion of 20% glucose) and the second retrogradely into the contralateral wrist vein, which was placed in a heated (65°C) box for sampling of arterial blood. After baseline blood samples were taken, a constant infusion of short-acting human insulin (Actrapid, Novo Industry) was administered at a rate of 0.05 U · kg\(^{-1}\) · h\(^{-1}\). Plasma glucose concentration was determined at 5-minute intervals by using a Yellow Springs glucose analyzer, and the infusion of 20% glucose was adjusted to maintain a constant plasma glucose concentration of 4.0 mmol/L for 210 minutes. Plasma insulin rates corrected for the steady-state glucose concentration are expressed in micromoles per kilogram per minute per milliliter per liter.

**OGTT**

Fifty-one MI patients (24 PSMIs and 27 BWMIs), 53 matched, male control subjects (28 PSCs and 25 BWCs), and 37 first-degree relatives of 5 PSMI patients were given a 75-g oral glucose load. Venous blood was taken in the fasting state and at 60 and 120 minutes during the OGTT for determination of glucose, insulin, lipids, and NEFA levels. Samples were stored on ice. Plasma was separated within 10 minutes and stored at −70°C until analysis.

**Dual-Energy X-Ray Absorptiometry (DXA)**

Body composition was measured by DXA scan (Lunar DPX-L scanner, Lunar Radiation Corp.). This method has very high precision and accuracy for measurement of total body and regional fat. Abdominal fat mass, measured between the costal margins and iliac crest, was assessed as a percentage of total fat mass.

**Biochemical and Hemostatic Assays**

Blood glucose was measured by the glucose oxidase method on a Yellow Springs glucose analyzer. Plasma insulin was measured by an immunoradiometric assay. The interassay coefficient of variation was 10%. Serum NEFAs were measured by enzymatic assay (NEFA C, Wako Chemicals GmbH). Serum cholesterol and triglycerides were analyzed by automated enzymatic methods (C-System, Boehringer Mannheim). Lipoprotein(a) was measured by an ELISA (Biopool AB). PAI-1 was measured as described previously. Small-LDL particle size (LDL-III) was measured on fresh plasma by density gradient ultracentrifugation by the method of Griffin et al. In brief, fresh plasma (with EDTA, 1 g/L) was subfractionated by discontinuous, nonequilibrium density gradient centrifugation in an SW-40 swing-out rotor (Beckman) using a six-step salt gradient. After 24 hours of centrifugation (40 000 rpm, 23°C) the LDL subfractions were eluted from the centrifuge tube by upward displacement through a spectrophotometer and continuously monitored at 280 nm. LDL subfractions were calculated by proportioning the total mass (lipid and protein) of sequentially isolated LDL (d=1.019 to 1.063 g/mL) on the basis of the areas beneath the elution profile after correction for differences in extinction coefficients at 280 nm. The reproducibility of this fractionation procedure was assessed by replicates analysis of plasma from a single individual. The within-run coefficient of variation (n=6×1 rotor) was 4.2% for LDL-III isolated by this procedure was <5.4%. The between-batch variation (n=6×2 rotors) for the same subfractions was <6.5%.

**Statistical Analysis**

Statistical analysis was performed with the SPSS program (SPSS Inc.). The logarithms of variables were used in the statistical analysis to normalize the distributions. Comparisons were performed separately between PSMI patients and PSCs and between BWMI patients and BWCs by ANOVA. The study was not designed to compare differences between the two ethnic groups. Sheffe’s test was used when the overall F statistic was significant. All data are expressed as mean and SEM. P<.05 was considered statistically significant.
**Results**

**Hyperinsulinemic-Euglycemic Clamp Study**

Insulin-mediated glucose uptake during the last 30 minutes of the clamp was markedly lower in PSMI patients than in PSCs (5.8±0.5 versus 7.7±0.6 μmol·kg⁻¹·min⁻¹·mmol⁻¹·L⁻¹, P<.05). BWMI patients had reduced insulin-mediated glucose uptake compared with BWCs (8.2±0.8 versus 10.6±0.7 μmol·kg⁻¹·min⁻¹·mmol⁻¹·L⁻¹, P<.05). Steady-state insulin-mediated glucose uptake in 1 of the 8 PSMI patients with diabetes was 3.18 μmol·kg⁻¹·min⁻¹·mmol⁻¹·L⁻¹ and in 1 of the 9 PSCs with diabetes was 4.27 μmol·kg⁻¹·min⁻¹·mmol⁻¹·L⁻¹. Removal of data for these two subjects did not affect the significant differences in insulin-mediated glucose uptake between the PSMI patients and PSCs (6.2±0.4 versus 8.1±0.6 μmol·kg⁻¹·min⁻¹·mmol⁻¹·L⁻¹, P<.05). Steady-state insulin levels were similar among patients and their respective control subjects (PSMI, 73±6; PSC, 73±8; BWMI, 77±4; and BWC, 65±5 mU/L). The study design did not enable comparisons between the two ethnic groups (Figure 1).

Insulin-mediated suppression of NEFAs was impaired in PSMI patients compared with PSCs (for PSMIs at 0 to 30 minutes, 0.63±0.04 to 0.15±0.03 mEq/L versus PSCs at 0 to 30 minutes, 0.45±0.07 to 0.07±0.02 mEq/L, P<.05). There were no differences in insulin-mediated suppression of NEFAs in BWMI patients compared with BWCs (for BWMIs at 0 to 30 minutes, 0.43±0.03 to 0.08±0.05 mEq/L versus BWCs at 0 to 30 minutes, 0.54±0.07 to 0.12±0.02 mEq/L, P=NS). Abdominal fat as a percentage of total body fat was greater in MI patients compared with their respective ethnic control subjects (for PS, 38.7±1.8% versus 30.4±1.6%; and for BW, 35.0±2.5% versus 28.9±1.8%, both P<.05).

Among patients undergoing the hyperinsulinemic-euglycemic clamp study, fasting cholesterol, HDL cholesterol and its subfractions, triglyceride, LDL mass, and lipoprotein(a) were similar in MI patients and control subjects. However, apolipoprotein B, small dense LDL (as a percentage of total LDL mass), and PAI-1 were higher in BWMI patients than in BWCs (101±8 versus 81±4 mg/dL, 41±9% versus 22±6%, and 14.3±3.0 versus 8.3±1.2 IU/mL, respectively, all P<.05). There were no differences in insulin-mediated suppression of NEFAs but not in PSCs compared with BWMI patients (88±5 versus 79±2 mg/dL, 19±6% versus 44±11%, and 8.9±1.7 versus 8.0±1.6 IU/mL, respectively).

**OGTT**

Fasting blood glucose was <6.7 mmol/L in all subjects. Fasting plasma insulin was higher in MI patients from both ethnic groups than in their respective control subjects. Among PSSs, 5 of the 24 MI patients had impaired glucose tolerance (2-hour glucose levels of 11.0, 11.1, 10.0, 11.3, and 11.7 mmol/L), 3 of the 24 MI patients had diabetes (2-hours glucose levels of 12.5, 12.1, and 12.8 mmol/L), and 1 of the 25 control subjects had diabetes (2-hour glucose level of 11.9 mmol/L). Among BWs, all MI patients had normal glucose tolerance, but 1 of the 25 control subjects had impaired glucose tolerance (2-hour glucose level of 10.9 mmol/L) (Tables 1 and 2).

Basal serum NEFAs were similar among MI patients and control subjects. Two hours after an oral glucose load, NEFAs were suppressed normally and completely in PSCs but not in PSMI patients. The two-hour post-OGTT NEFA level was higher in PSMI patients than in PSCs (P<.05). Serum NEFA was suppressed normally after the glucose load in BWCs and BWMI patients (Table 3).

Fasting cholesterol and triglycerides were similar among MI patients and control subjects. Two-hour post-OGTT triglyceride values were similar in PSCs but in BWMI patients than in BWCs (P<.05). Fasting insulin was significantly related to fasting triglycerides in whites (MI patients, r=-.53, P<.006; control subjects, r=.41, P=.049) but not in Sikhs (MI patients, r=.25, P=.21; control subjects, r=.12, P=.51). As a group, fasting insulin was inversely related to HDL cholesterol in whites (r=-.29, P=.045) but not in Sikhs (r=-.16, P=.26).

Waist-to-hip girth ratio was higher in PSMI patients than in PSCs (P<.05) but similar among white patients and control

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**TABLE 1. Physical Characteristics of the Study Subjects**

<table>
<thead>
<tr>
<th></th>
<th>PSMI (n=24)</th>
<th>PSC (n=28)</th>
<th>BWMI (n=27)</th>
<th>BWC (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>48.1±1.9</td>
<td>44.3±2.3</td>
<td>50.3±2.2</td>
<td>48.1±3.3</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>75.9±1.6</td>
<td>72.3±1.8</td>
<td>77.4±1.8</td>
<td>76.1±1.9</td>
</tr>
<tr>
<td>Body-mass index, kg/m²</td>
<td>26.1±0.4</td>
<td>25.1±0.5</td>
<td>26.4±0.4</td>
<td>25.3±0.5</td>
</tr>
<tr>
<td>Waist to hip ratio</td>
<td>0.96±0.01*</td>
<td>0.91±0.02</td>
<td>0.95±0.01</td>
<td>0.95±0.01</td>
</tr>
<tr>
<td>Leisure-time activity, MJ/wk</td>
<td>4.0±0.2</td>
<td>4.3±0.1</td>
<td>3.9±0.1</td>
<td>3.8±0.2</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>117±4.0</td>
<td>127±5.0</td>
<td>124±3.0</td>
<td>124±3.0</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>73±3.0</td>
<td>79±3.0</td>
<td>78±2.0</td>
<td>78.0±2.0</td>
</tr>
</tbody>
</table>

*P<.05 compared with respective ethnic control subjects.
Insulin Resistance in Premature Myocardial Infarction

TABLE 2. Metabolic Characteristics of All Subjects Undergoing the OGTT

<table>
<thead>
<tr>
<th></th>
<th>PSMI (n=24)</th>
<th>PSC (n=28)</th>
<th>BWMI (n=27)</th>
<th>BWC (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose, mmol/L</td>
<td>5.9±0.2</td>
<td>5.3±0.1</td>
<td>5.3±0.2</td>
<td>5.3±0.1</td>
</tr>
<tr>
<td>Post-OGTT plasma glucose, mmol/L</td>
<td>8.7±0.7*</td>
<td>5.9±0.3</td>
<td>5.8±0.4</td>
<td>5.7±0.3</td>
</tr>
<tr>
<td>Fasting plasma insulin, mU/L</td>
<td>13.1±1.9*</td>
<td>5.9±0.7</td>
<td>11.7±2.6*</td>
<td>4.6±0.5</td>
</tr>
<tr>
<td>Post-OGTT plasma insulin, mU/L</td>
<td>76±8*</td>
<td>32±3</td>
<td>35±6</td>
<td>24±3</td>
</tr>
<tr>
<td>Fasting NEFAs, mEq/L</td>
<td>0.64±0.05</td>
<td>0.72±0.08</td>
<td>0.50±0.04</td>
<td>0.60±0.05</td>
</tr>
<tr>
<td>Post-OGTT NEFAs, mEq/L</td>
<td>0.26±0.02*</td>
<td>0.16±0.02</td>
<td>0.14±0.02</td>
<td>0.18±0.03</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.6±0.2</td>
<td>6.0±0.3</td>
<td>5.9±0.2</td>
<td>6.0±0.2</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.12±0.06*</td>
<td>1.34±0.07</td>
<td>1.03±0.06</td>
<td>1.18±0.06</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.51±0.17</td>
<td>3.48±0.25</td>
<td>3.29±0.39</td>
<td>3.36±0.36</td>
</tr>
<tr>
<td>Fasting triglycerides, mmol/L</td>
<td>2.0±0.2</td>
<td>2.14±0.62</td>
<td>2.54±0.45</td>
<td>1.71±0.20</td>
</tr>
<tr>
<td>Post-OGTT triglycerides, mmol/L</td>
<td>2.2±0.3</td>
<td>2.0±0.3</td>
<td>2.75±0.4*</td>
<td>1.65±0.20</td>
</tr>
</tbody>
</table>

Values are mean ± SEM of untransformed data.
*P<.05 compared with respective ethnic control subjects.

Family Studies

Fasting plasma insulin, post-OGTT NEFA, and waist-to-hip girth ratio were similar in PSMI patients compared with their first-degree relatives. Fasting plasma insulin and waist-to-hip girth ratio were higher in relatives than in PSCs (both P<.05). Relatives of PSMI patients had a similar BMI (23±1.7 kg/m²), systolic blood pressure (123±6.2 mm Hg), leisure-time activity (3.2±0.9 MJ/wk), fasting glucose (5.6±0.5 mmol/L), 2-hour post-OGTT glucose (7.5±1.2 mmol/L), HDL cholesterol (1.21±0.1 mmol/L), fasting triglycerides (1.83±0.23 mmol/L) and fasting NEFAs (0.58±0.7 mEq/L), and lower total cholesterol (5.2±0.4 mmol/L, P<.05) compared with PSCs (Figure 2).

Discussion

Results of this study show that PS survivors of premature MI have impaired insulin-mediated glucose disposal and NEFA suppression, indicating the presence of insulin resistance, compared with PSCs. BWMI patients were studied for comparison and showed similar defects of carbohydrate, but not of NEFA, metabolism compared with BWCs. Despite similar body weight and BMI, body fat distribution showed increased total abdominal fat in PS and BWMI patients compared with their respective ethnic control subjects.

Increased abdominal fat is associated with insulin resistance. 10,19–21 Although the mechanisms linking the two have

TABLE 3. Characteristics of the Subjects Undergoing the Hyperinsulinemic-Euglycemic Clamp Study

<table>
<thead>
<tr>
<th></th>
<th>PSMI (n=8)</th>
<th>PSC (n=9)</th>
<th>BWMI (n=9)</th>
<th>BWC (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fat, %</td>
<td>32.6±1.7*</td>
<td>25.1±1.7</td>
<td>30.6±2.2*</td>
<td>25.8±1.6</td>
</tr>
<tr>
<td>Abdominal fat, % of total fat</td>
<td>38.7±1.8*</td>
<td>30.4±1.6</td>
<td>35.0±2.5*</td>
<td>28.9±1.8</td>
</tr>
<tr>
<td>Fasting NEFAs, mEq/L</td>
<td>0.63±0.04*</td>
<td>0.45±0.07</td>
<td>0.43±0.03</td>
<td>0.54±0.07</td>
</tr>
<tr>
<td>30-Minute clamp NEFAs, mEq/L</td>
<td>0.15±0.03*</td>
<td>0.07±0.02</td>
<td>0.08±0.05</td>
<td>0.12±0.02</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.93±0.3</td>
<td>6.49±0.5</td>
<td>6.05±0.4</td>
<td>5.76±0.4</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.29±0.10</td>
<td>1.23±0.09</td>
<td>1.07±0.10</td>
<td>1.17±0.11</td>
</tr>
<tr>
<td>HDL-III cholesterol, mmol/L</td>
<td>0.27±0.03</td>
<td>0.31±0.05</td>
<td>0.36±0.06</td>
<td>0.34±0.04</td>
</tr>
<tr>
<td>HDL-III cholesterol, mmol/L</td>
<td>0.98±0.08</td>
<td>0.87±0.06</td>
<td>0.71±0.07</td>
<td>0.83±0.09</td>
</tr>
<tr>
<td>Fasting triglycerides, mmol/L</td>
<td>1.33±0.16</td>
<td>1.73±0.30</td>
<td>2.20±0.55</td>
<td>1.50±0.16</td>
</tr>
<tr>
<td>Total LDL mass, mg/100 mL</td>
<td>250±30</td>
<td>268±26</td>
<td>292±32</td>
<td>227±35</td>
</tr>
<tr>
<td>LDL-III, %</td>
<td>19±6*</td>
<td>44±11</td>
<td>41±6*</td>
<td>22±6</td>
</tr>
<tr>
<td>Apolipoprotein A-I, mg/dL</td>
<td>130±9</td>
<td>142±15</td>
<td>132±6</td>
<td>146±10</td>
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<tr>
<td>Apolipoprotein A-II, mg/dL</td>
<td>45±4</td>
<td>46±3</td>
<td>43±2</td>
<td>43±1</td>
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<tr>
<td>Apolipoprotein B, mg/dL</td>
<td>88±5</td>
<td>79±2</td>
<td>101±8*</td>
<td>81±4</td>
</tr>
<tr>
<td>Lp(a), mg/dL</td>
<td>14.8±4.8</td>
<td>18.9±6.1</td>
<td>10.4±5.9</td>
<td>33.8±12.4</td>
</tr>
<tr>
<td>PAI-1, IU/mL</td>
<td>8.9±1.7</td>
<td>8.0±1.6</td>
<td>14.3±3.0*</td>
<td>8.3±1.2</td>
</tr>
</tbody>
</table>

Lp(a) indicates lipoprotein(a).
*P<.05 compared with respective ethnic control subjects.
not been fully elucidated, evidence from previous studies suggests that abdominal visceral fat cells are resistant to the antilipolytic effect of insulin, resulting in increased hepatic availability of NEFAs. The latter increases gluconeogenesis, reduces hepatic insulin extraction, and stimulates VLDL apolipoprotein B and triglyceride production. Increased NEFAs are also associated with reduced insulin-mediated glucose uptake through the glucose–fatty acid cycle, leading to glucose intolerance and hyperinsulinemia. In the present study, DXA did not allow quantification of visceral and subcutaneous fat in our patients. Evidence from previous studies has shown that visceral fat is the main depot associated with features of the insulin resistance syndrome. The possibility exists therefore that there are differences in the amount of visceral fat among MI patients versus control subjects, and between ethnic groups, which may contribute to the metabolic abnormalities seen in this study.

Impaired insulin-mediated and post–glucose load suppression of lipolysis has not been previously reported in MI. However, a direct role for NEFAs in CHD is suggested by the atherogenic and thrombogenic effects of fatty acids, the association of fatty acid concentrations in serum, adipose tissue, and aortic plaque, and the relationship of elevated serum NEFAs with foam cell formation. An interrelationship between defective lipolysis and glucose disposal is additionally suggested by studies showing that increased availability of NEFAs impairs insulin-mediated glucose uptake.

The contribution of diabetes to impaired insulin action was excluded in the BWMI patients, all of whom had normal glucose tolerance but were insulin resistant compared with BWCs. Sikhs have a 20% prevalence of diabetes. Five Sikh patients had abnormal glucose tolerance and five had diabetes despite normal fasting blood glucose levels (<6.7 mmol/L) at the time of study. Although abnormal glucose tolerance is likely to have contributed to impaired insulin action in these individuals, the presence of similar defects both in nondiabetic Sikh and white MI patients excludes a major role for diabetes in the development of the aforementioned metabolic abnormalities associated with defective insulin action.

Insulin resistance can be associated with hyperinsulinemia, glucose intolerance, hypertension, hypertriglyceridermia, low HDL cholesterol, small dense LDL, hyperuricemia, and elevated PAI-1. In this study, insulin was positively correlated with triglycerides and inversely with HDL cholesterol among white subjects. Furthermore, post-OGTT triglycerides, small LDL particle size, and PAI-1 were higher in BWMI patients than in BWCs, and this finding is consistent with previous studies showing a clustering of insulin resistance and metabolic risk factors in CHD. However, these patterns were notably absent in Sikhs. Our results imply that in Sikh survivors of premature MI, insulin resistance occurs as a *forme fruste*, without full expression of the "syndrome" as described by Reaven. In Sikhs, the absence of established risk factors for CHD and of the metabolic abnormalities usually associated with insulin resistance suggest that defective insulin action per se, defined herein as impaired insulin-mediated glucose uptake, impaired NEFA suppression after oral glucose, and abdominal obesity, is the primary risk factor for premature MI in this ethnic population. Although the possibility cannot be excluded by the present study that these disturbances are a primary consequence of CHD or of lifestyle changes after MI, our results are consistent with previous epidemiological studies that indicate that >70% of major Q-wave abnormalities in Indian Asians, aged 40 to 54 years, are attributable to glucose intolerance and hyperinsulinemia.

Relatives of PSMI patients were studied to investigate the familial aggregation of insulin resistance. We observed abdominal obesity, impaired NEFA suppression, and hyperinsulinemia in first-degree relatives of Sikh patients with premature MI compared with control subjects. The demonstration of defective insulin action in Sikh CHD families is consistent with family studies in other populations, which indicate that a component of insulin resistance is inherited. A role for poor nutrition in fetal life has recently been proposed by the association of low
birth weight with insulin resistance, but this does not exclude an important role for genetic factors, which may be amenable to genetic linkage analyses.

In summary, in PS survivors of premature MI, defective insulin action is characterized by impaired insulin-mediated glucose uptake, impaired insulin-mediated NEFA suppression, and abdominal obesity. In BDMI patients, the defects are impaired insulin-mediated glucose uptake and abdominal obesity. Classic coronary risk factors and metabolic features usually associated with insulin resistance, namely, increased post-OGTT triglycerides, smaller LDL particle size, and increased PAI-1, were present in white but not in Sikh MI patients. Abdominal obesity, impaired NEFA suppression, and elevated fasting insulin were also present in asymptomatic, non-diabetic, first-degree relatives of PSMI patients. Our results suggest that these defects may be early metabolic abnormalities in families with premature MI.

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