Resting Electrocardiographic Abnormalities Suggestive of Asymptomatic Ischemic Heart Disease Associated With Non–Insulin-Dependent Diabetes Mellitus in a Defined Population

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The prevalence of ischemic heart disease (IHD) in older adults by glucose tolerance status was evaluated in 2,223 white men and women, aged 50–89 years, in the Rancho Bernardo cohort who were studied between 1984 and 1987. Impaired glucose tolerance (IGT) and non–insulin-dependent diabetes mellitus (NIDDM) were classified according to World Health Organization criteria. End points of ischemic heart disease were defined by Rose Questionnaire and resting electrocardiogram (ECG) according to the Minnesota Code. IHD by electrocardiographic changes was classified as asymptomatic (without history of chest pain or overt IHD) or symptomatic (with history). IHD by all criteria combined was significantly more common in men and women with NIDDM, and in women with IGT, than in those with normal glucose tolerance. The prevalence of myocardial infarction, defined by major Q wave, Rose Questionnaire chest pain criteria, or personal history, was higher in persons with NIDDM than in persons without; the difference was highly significant in women (odds ratio, 2.08 [1.22, 3.56]; p=0.009). Angina pectoris was not significantly related to NIDDM or IGT in either sex. Electrocardiographic evidence of asymptomatic IHD was significantly more prevalent in both men and women with NIDDM as compared with those with normal glucose tolerance (odds ratios, 1.75 [1.10, 2.81] for men and 1.80 [1.07, 3.01] for women; p<0.05). This significant association persisted after excluding persons on digitalis or diuretic therapy and, in women, was also independent of the effect of major known IHD risk factors. These population-based data are consistent with clinical reports suggesting an association of diabetes with silent myocardial infarction or ischemia. The presence of ischemic resting electrocardiographic abnormalities in the asymptomatic diabetic patient is likely to have prognostic and therapeutic implications. (Circulation 1990;81:899–906)

Over the past 25 years, an excess risk of ischemic heart disease (IHD) morbidity and mortality has been observed consistently in diabetics of Western societies despite variable study designs and changing diagnostic criteria.1,2 Very few population-based studies have considered both standardized criteria for nonfatal IHD end points and current criteria for non–insulin-dependent diabetes mellitus (NIDDM) and impaired glucose tolerance (IGT).3–5 Data are particularly scarce regarding the association of diabetes with painless (silent) myocardial infarction or ischemia although clinical studies have drawn attention to this coincidence.6–8 We report, here, the prevalence of...
symptomatic and asymptomatic (by resting electrocardiogram [ECG]) IHD in nondiabetics and in persons with NIDDM or IGT from the Rancho Bernardo community of older adults, and the independent association of asymptomatic IHD as suggested by ECG with diabetic status after controlling for other IHD risk factors in this population.

**Methods**

**Population**

The Rancho Bernardo Heart and Chronic Disease Study was initiated as part of a Lipid Research Clinics prevalence study between 1972 and 1974. The original study cohort comprised 82% of a geographically defined, upper-middle class white adult community. This report is based on an evaluation of surviving cohort members who were 40 years old or older at baseline, and who were invited to a repeat survey between 1984 and 1987; 84.5% of men and 78.4% of women participated. A total of 11.2% (138 men and 236 women) had moved out of state, and data collection in these cases was accomplished in cooperation with local hospitals or clinics but did not include an oral glucose tolerance test or resting ECG. Thus, these participants were excluded for the purpose of the present analysis. Of the remaining 2,480, we excluded participants who fasted less than 12 hours (n=13), who were currently using insulin (n=13), or who were unclassifiable because of incomplete ECG records (n=46) or plasma glucose measurements (n=84). We further excluded 101 persons who exceeded the age range of 50–89 years, yielding a study population of 2,223 older adults, that is, 1,236 women and 987 men.

**Data Collection**

All 2,223 persons were seen at the La Jolla Lipid Research Clinic by trained nurses and technicians between 7:00 and 11:00 AM after a requested 12-hour fast. Fasting venous blood was drawn for measurements of fasting plasma glucose (FPG), lipids, and lipoproteins. Two hours after a standardized 75-g oral glucose load, a second blood specimen was taken for postchallenge plasma glucose levels. Determination of plasma glucose was performed in a research laboratory using a glucose oxidase method. Information on age, cigarette smoking, history of diabetes mellitus, and current use of insulin or oral antidiabetic drugs, was obtained by standardized interview. Reported current use of any medication was verified by the original prescription or container brought to the clinic for this purpose.

Cardiovascular parameters were assessed by specifically trained personnel, different from the interviewer who obtained the medical history. Blood pressure was measured using a standard mercury sphygmomanometer after the participant had been seated for at least 5 minutes, according to the Hypertension Detection and Follow-up Program protocol. The mean value of two measurements taken at least 1 minute apart was used in the data analysis. A history of heart attack or chest pain was obtained using the Rose cardiovascular questionnaire. A standard 12-lead resting ECG was performed before the glucose load by trained personnel according to the 1982 Minnesota protocol; readings were sent to the Minnesota Coding Center for standardized interpretation according to the Minnesota Code criteria.

Coding was blind to glucose tolerance test results or history of diabetes.

**Diagnostic Criteria**

NIDDM and IGT were defined by current World Health Organization criteria, based on National Diabetes Data Group (NDDG) recommendations for epidemiologic studies, and were as follows: 1) NIDDM: FPG ≥140 mg/dl (7.8 mmol/l) or 2-hr plasma glucose ≥200 mg/dl (11.1 mmol/l), or history of physician-diagnosed diabetes; and 2) IGT: FPG <140 mg/dl (7.8 mmol/l) and 2-hr plasma glucose 140–199 mg/dl (7.8–11.1 mmol/l).

A history of physician-diagnosed diabetes, with or without current use of hypoglycemic agents, differentiated newly diagnosed and previously known NIDDM. All those who did not meet the above criteria for either NIDDM or IGT were classified as having normal glucose tolerance.

End points of IHD were determined by standard epidemiological methods and consisted of angina pectoris (grade 1 and 2, according to Rose criteria), possible myocardial infarction (major Q wave [Minnesota Code, 1.1] or history of myocardial infarction or severe chest pain for more than 1/2 hour), and ischemic resting electrocardiographic abnormalities (Minnesota Code criteria). Electrocardiographic changes were subcategorized into “ECG coronary probable” (major Q or QS wave [Minnesota Code 1.1, 1.2] and complete left bundle branch block [Minnesota Code 7.1.1]), and “ECG coronary possible” (small Q or QS wave [Minnesota Code 1.3], ST depression [Minnesota Code 4.1–4.3], and T wave items [Minnesota Code 5.1–5.3]). This algorithm is based on Whitehall criteria as applied in the WHO Multinational Study of Diabetes and Vascular Disease. Overall Ischemic Heart Disease was a summary category composed of all individual IHD end points, counting individuals contributing to several end points only once.

The diagnosis of asymptomatic IHD was made if an individual had one or more of the above electrocardiographic changes but no history of myocardial infarction, angina pectoris, or chest pain (i.e., discomfort, pressure, or pain) not meeting the Rose algorithm. Ischemic electrocardiographic changes accompanied by any history of myocardial infarction, angina, or chest pain were defined as symptomatic IHD. A history of myocardial infarction had previously been validated in 85% of a subset for whom hospital records had been obtained.
Data Analyses and Statistical Procedures

The statistical package for the social sciences (SPSSX) and biomedical data programming (BMDP) were used for data analysis. All prevalence rates were age-adjusted across four 10-year age groups, the total study population serving as the standard. Sex-specific, age-adjusted prevalence rates of IHD by different end points were assessed for each category of glucose tolerance. Age-adjusted IHD prevalence rates were compared, by end point, between persons with IGT or NIDDM and those with normal glucose tolerance, using the Mantel-Haenszal χ² procedure. Sex- and age-specific odds ratios were calculated by 10-year age strata, and tests for homogeneity were used to identify interaction between diabetes and age. Where appropriate, Mantel-Haenszal summary (age-adjusted) odds ratios were assessed and approximate 95% confidence intervals were calculated according to Miettinen. Because of the importance of age as a potential confounder, age adjustment was repeated using multiple logistic regression, which included testing for interaction between age and glucose tolerance. Results were similar and only the results obtained by the logistic models are shown.

Using multiple logistic regression, we tested the independent association of asymptomatic IHD (ischemic electrocardiographic abnormalities in the absence of symptoms) with diabetic status and major IHD risk factors. Because collinearity between independent variables is likely to reduce statistical precision of the results, the association of asymptomatic IHD with fasting and postchallenge plasma glucose was examined in separate analyses. The individual model was fitted by the method of maximum likelihood, accommodating the dichotomized dependent variable (asymptomatic IHD, yes or no), as well as categorical and continuous independent variables. For each independent variable, adjusted odds ratios and 95% confidence intervals were calculated as a measure of independent association with asymptomatic IHD. In the case of continuous variables, the reported odds ratios and confidence intervals were weighted by 1 SD. All models were repeated for men and women separately, and after exclusion of all persons using diuretic antihypertensives or digitalis preparations.

All p values presented are based on two-tailed tests; a probability level of less than 0.05 was considered statistically significant. Adjustment for multiple testing was not done because we were testing a single a priori hypothesis using previously established heart disease risk factors as covariates. We have included exact p values to assist readers who wish to make such calculations.

Results

Prevalence of Abnormal Glucose Tolerance

The classification of the study population by glucose tolerance is summarized in Table 1. Similar to a comparison of crude rates, a comparison of age-adjusted rates showed that NIDDM (overall and known) was significantly more prevalent in men than in women (age-adjusted rates, 16.0% vs. 12.9%, p = 0.04; and 5.5% vs. 3.2%, p = 0.007; respectively). In contrast, IGT was significantly less prevalent in men than in women (age-adjusted rates, 23.9% vs. 28.2%, p = 0.02). In the 94 persons with known NIDDM (i.e., diagnosed as diabetic by a physician before the survey), the diagnosis was confirmed by glucose tolerance test or record review in 96%; only 44% were currently taking hypoglycemic agents.

Prevalence of Ischemic Heart Disease End Points by Category of Glucose Tolerance

The age-adjusted prevalence of overall IHD and individual IHD end points (i.e., possible myocardial infarction, angina pectoris, and ischemic electrocardiographic changes) is presented by category of glucose tolerance for men and women in Tables 2 and 3. As compared with persons with normal glucose tolerance, overall IHD was significantly more common in men and women with NIDDM, and in women with IGT. Overall ischemic electrocardiographic changes and minor ischemic (coronary possible) electrocardiographic changes were also significantly associated with NIDDM in both sexes. A possible myocardial infarction was strongly related to NIDDM only among women. Angina pectoris was not significantly associated with NIDDM or IGT in either sex.

Relation of Electrocardiographic Changes With and Without Symptoms to Abnormal Glucose Tolerance

The age-adjusted prevalence of ischemic resting electrocardiographic changes with and without symptoms by glucose tolerance category is shown in Table 4. The odds ratios (based on the comparison to persons with normal glucose tolerance) reflect a consistent positive association of abnormal glucose tolerance with both end points. In both sexes, however, the association with NIDDM was more pronounced for asymptomatic than for symptomatic electrocardiographic abnormalities.

Although persons with NIDDM were more likely than persons with normal glucose tolerance to use digitalis preparations or diuretic antihypertensives, drug use did not explain these observations. Exclud-
TABLE 2. Age-Adjusted Prevalence of Ischemic Heart Disease End Points by Normal and Impaired Glucose Tolerance and Non-Insulin-Dependent Diabetes Mellitus Among Men Aged 50–89 Years

| IHD end point | Normal | | | | | | | | | | | | | NIDDM | | | | | | | | | | | | | | | | |
|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                | % | n | % | n | Odds ratio* (95% CL)* | p | % | n | Odds ratio* (95% CL)* | p |
| Possible MI    | 13.2 | 73 | 18.4 | 48 | 1.56 (1.04, 2.36) | 0.035 | 17.1 | 29 | 1.35 (0.83, 2.18) | 0.235 |
| Angina pectoris | 9.1 | 51 | 11.2 | 30 | 1.32 (0.81, 2.15) | 0.275 | 9.0 | 17 | 1.05 (0.58, 1.90) | 0.871 |
| Ischemic ECG   | 22.3 | 125 | 28.2 | 74 | 1.39 (0.98, 1.98) | 0.064 | 34.7 | 57 | 1.70 (1.16, 2.53) | 0.008 |
| Probable       | 5.9 | 34 | 9.2 | 24 | 1.64 (0.94, 2.87) | 0.086 | 6.1 | 9 | 0.87 (0.40, 1.87) | 0.713 |
| Possible       | 16.4 | 91 | 19.0 | 50 | 1.20 (0.81, 1.78) | 0.373 | 28.6 | 48 | 1.96 (1.29, 2.97) | 0.002 |
| Overall IHD    | 32.0 | 180 | 38.5 | 99 | 1.37 (0.99, 1.89) | 0.057 | 43.1 | 73 | 1.59 (1.10, 2.30) | 0.014 |

Values are from study at Rancho Bernardo, California, 1984–87.

*Odds ratios and 95% confidence intervals calculated with logistic regression according to maximum likelihood method.

IGT, impaired glucose tolerance; NIDDM, non–insulin-dependent diabetes mellitus; IHD, ischemic heart disease; CL, confidence limit; MI, myocardial infarction; ECG, electrocardiogram.

The men (n=225) and women (n=329) taking digitalis or diuretic preparations or both did not materially change the age-adjusted odds ratios between the odds of asymptomatic ischemic electrocardiographic changes among persons with NIDDM and the odds of asymptomatic ischemic electrocardiographic changes among those with normal glucose tolerance (odds ratio, 1.95 [1.09, 3.49]; p=0.031 in men and odds ratio, 1.87 [0.98, 3.57]; p=0.068 in women).

Similar associations of asymptomatic and symptomatic electrocardiographic abnormalities with NIDDM were observed when newly diagnosed and previously known diabetics were separately compared with persons with normal glucose tolerance (data not shown).

Independent Association of Asymptomatic Ischemic Electrocardiographic Abnormalities With Abnormal Glucose Tolerance and Major Ischemic Heart Disease Risk Factors

The independent association of diabetic status and major IHD risk factors with asymptomatic electrocardiographic changes among men and women combined is presented in Table 5. When adjusted for the effect of established risk factors of IHD in the multivariate model, NIDDM, as compared with normal glucose tolerance, was significantly and independently associated with asymptomatic electrocardiographic changes, as was postchallenge plasma glucose in a separate model. Male sex, age, and systolic blood pressure were also strongly associated with asymptomatic electrocardiographic changes in each model.

When men and women were analyzed separately, as shown in Tables 6 and 7, the positive association of an abnormal resting ECG in the absence of symptoms with NIDDM was statistically significant only in women (adjusted odds ratio in men, 1.26 [0.76, 2.09]; adjusted odds ratio in women, 1.79 [1.05, 3.04]). These results were not materially changed after exclusion of all persons on digitalis, diuretics, or both (adjusted odds ratio in men, 1.51 [0.81, 2.81]; p=0.199 and adjusted odds ratio in women, 1.86 [0.95, 3.65]; p=0.079).

The independent association of NIDDM with asymptomatic electrocardiographic abnormalities remained unchanged on additional adjustment for body mass index in men and women (adjusted odds ratio in men, 1.26 [0.76, 2.09]; p=0.380 and adjusted odds ratio in women, 1.78 [1.04, 3.04]; p=0.038). First-order interaction terms between NIDDM and systolic blood pressure or any of the other IHD risk factors included in the models were not statistically significant.

TABLE 3. Age-Adjusted Prevalence of Ischemic Heart Disease End Points by Normal and Impaired Glucose Tolerance and Non-Insulin-Dependent Diabetes Mellitus Among Women Aged 50–89 Years

| IHD end point | Normal | | | | | | | | | | | | | NIDDM | | | | | | | | | | | | | | | | |
|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                | % | n | % | n | Odds ratio* (95% CL)* | p | % | n | Odds ratio* (95% CL)* | p |
| Possible MI    | 7.2 | 53 | 9.5 | 33 | 1.31 (0.82, 2.08) | 0.261 | 13.7 | 24 | 2.08 (1.22, 3.56) | 0.009 |
| Angina pectoris | 7.9 | 54 | 10.2 | 37 | 1.38 (0.88, 2.16) | 0.162 | 10.7 | 22 | ... | ... |
| Ischemic ECG   | 19.6 | 129 | 23.3 | 84 | 1.25 (0.91, 1.73) | 0.170 | 30.0 | 55 | 1.91 (1.29, 2.83) | 0.002 |
| Probable       | 2.3 | 15 | 1.6 | 6 | 0.66 (0.25, 1.76) | 0.399 | 4.0 | 8 | 1.79 (0.73, 4.41) | 0.219 |
| Possible       | 17.3 | 114 | 21.7 | 78 | 1.34 (0.96, 1.86) | 0.085 | 26.0 | 47 | 1.79 (1.19, 2.70) | 0.006 |
| Overall IHD    | 28.5 | 195 | 34.3 | 123 | 1.33 (1.01, 1.77) | 0.045 | 41.9 | 74 | 1.99 (1.38, 2.86) | 0.001 |

Values are from study at Rancho Bernardo, California, 1984–87.

IGT, impaired glucose tolerance; NIDDM, non–insulin-dependent diabetes mellitus; IHD, ischemic heart disease; CL, confidence limit; MI, myocardial infarction; ECG, electrocardiogram.

*Odds ratios and 95% confidence intervals calculated with logistic regression according to maximum likelihood method.

†The age-adjusted odds ratio did not appropriately reflect association because of small case number in younger age groups; age-specific odds ratios (95% confidence interval) by 10-year age groups were 0, 0.54 (0.05, 5.61), 2.18 (1.25, 3.79), and 2.00 (0.78, 5.11).
TABLE 4. Age-Adjusted Prevalence of Ischemic Resting Electrocardiographic Abnormalities With and Without Symptoms by Normal and Impaired Glucose Tolerance and Non–Insulin-Dependent Diabetes Mellitus Among Men and Women Aged 50–89 Years

<table>
<thead>
<tr>
<th>Sex and ischemic ECG</th>
<th>Normal</th>
<th>IGT</th>
<th>NIDDM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>n</td>
<td>Odds ratio* (95% CL)*</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With symptoms</td>
<td>10.3</td>
<td>57</td>
<td>15.2</td>
</tr>
<tr>
<td>Without symptoms</td>
<td>12.0</td>
<td>68</td>
<td>13.0</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With symptoms</td>
<td>10.8</td>
<td>71</td>
<td>11.3</td>
</tr>
<tr>
<td>Without symptoms</td>
<td>8.8</td>
<td>58</td>
<td>12.0</td>
</tr>
</tbody>
</table>

Values are from study at Rancho Bernardo, California, 1984–87.
IGT, impaired glucose tolerance; NIDDM, non–insulin-dependent diabetes mellitus; ECG, electrocardiogram; CL, confidence limit.
*Calculated with logistic regression according to maximum likelihood method.

Discussion

Often in research, the more demanding, invasive, and sophisticated the diagnostic procedure, the smaller the number of subjects, and the greater the potential for the study of atypical patients or volunteers. In the present study of a large population-based cohort, a diagnosis of new diabetes or impaired glucose tolerance was based on a single oral glucose tolerance test and asymptomatic IHD, on a single resting ECG. The limitation of these methods compared with repeated testing of glucose tolerance and the more specific and more sensitive clinical diagnosis of silent episodes of IHD by radionuclide studies or Holter monitoring are recognized.26–30 As a result, although we applied current standard criteria for epidemiological studies of diabetes and IHD, misclassification for both probably occurred. Such random misclassification, however, tends to obscure, not create, associations.31 Thus, the association of NIDDM with asymptomatic IHD reported here is conservatively biased, and the true magnitude of the risk of asymptomatic IHD, given NIDDM, is likely to be greater than estimated by the odds ratios shown here. The advantage of the population-based study is that it is less subject to Berkson’s fallacy, that is, the increased odds that a person with two diseases (i.e., diabetes and heart disease) is more likely than a

TABLE 5. Odds Ratios Between the Odds of Asymptomatic Resting Electrocardiographic Abnormalities Among Persons With Non–Insulin-Dependent Diabetes Mellitus and the Odds of Asymptomatic Resting Electrocardiographic Abnormalities Among Persons With Normal Glucose Tolerance Adjusted for the Effect of Established Risk Factors of Ischemic Heart Disease

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Adjusted odds ratio*</th>
<th>95% Confidence interval</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIDDM (yes vs. no)</td>
<td>1.50</td>
<td>(1.04, 2.16)</td>
<td>0.032</td>
</tr>
<tr>
<td>Sex (men vs. women)</td>
<td>1.47</td>
<td>(1.04, 2.08)</td>
<td>0.028</td>
</tr>
<tr>
<td>Age (per 9.32 yr)</td>
<td>1.23</td>
<td>(1.02, 1.48)</td>
<td>0.030</td>
</tr>
<tr>
<td>Systolic BP (per 21.46 mm Hg)</td>
<td>1.63</td>
<td>(1.38, 1.92) &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>HDL (per 18.97 mg/dl)</td>
<td>0.94</td>
<td>(0.79, 1.12)</td>
<td>0.952</td>
</tr>
<tr>
<td>LDL (per 36.64 mg/dl)</td>
<td>1.00</td>
<td>(0.85, 1.18)</td>
<td>0.964</td>
</tr>
<tr>
<td>Smoking (yes vs. no)</td>
<td>1.25</td>
<td>(0.76, 2.05)</td>
<td>0.385</td>
</tr>
<tr>
<td>2-hour plasma glucose† (per 57.84 mg/dl)</td>
<td>1.17</td>
<td>(1.04, 1.32) 0.011</td>
<td></td>
</tr>
<tr>
<td>Fasting plasma glucose† (per 20.24 mg/dl)</td>
<td>1.08</td>
<td>(0.97, 1.25) 0.197</td>
<td></td>
</tr>
</tbody>
</table>

Values are from study at Rancho Bernardo, California, 1984–87.
NIDDM, non–insulin-dependent diabetes mellitus; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
*Odds ratios are adjusted for effects of all other factors in model; odds ratios for continuous variables are presented per standard deviation as for men and women combined.
†Association with 2-hour postchallenge and fasting plasma glucose was examined in two separate models that included all variables except NIDDM.

TABLE 6. Odds Ratios Between the Odds of Asymptomatic Resting Electrocardiographic Abnormalities Among Men With Non–Insulin-Dependent Diabetes Mellitus and the Odds of Asymptomatic Resting Electrocardiographic Abnormalities Among Men With Normal Glucose Tolerance Adjusted for the Effect of Established Risk Factors of Ischemic Heart Disease

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Adjusted odds ratio*</th>
<th>95% Confidence interval</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIDDM (yes vs. no)</td>
<td>1.26</td>
<td>(0.76, 2.09)</td>
<td>0.379</td>
</tr>
<tr>
<td>Age (per 9.32 yr)</td>
<td>1.15</td>
<td>(0.90, 1.47)</td>
<td>0.273</td>
</tr>
<tr>
<td>Systolic BP (per 21.46 mm Hg)</td>
<td>1.67</td>
<td>(1.31, 2.11) &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>HDL (per 18.97 mg/dl)</td>
<td>0.90</td>
<td>(0.68, 1.18)</td>
<td>0.434</td>
</tr>
<tr>
<td>LDL (per 36.64 mg/dl)</td>
<td>0.89</td>
<td>(0.70, 1.13)</td>
<td>0.343</td>
</tr>
<tr>
<td>Smoking (yes vs. no)</td>
<td>1.42</td>
<td>(0.70, 2.89)</td>
<td>0.343</td>
</tr>
<tr>
<td>2-hour plasma glucose† (per 57.84 mg/dl)</td>
<td>1.16</td>
<td>(0.99, 1.37) 0.072</td>
<td></td>
</tr>
<tr>
<td>Fasting plasma glucose† (per 20.24 mg/dl)</td>
<td>1.12</td>
<td>(0.96, 1.31) 0.169</td>
<td></td>
</tr>
</tbody>
</table>

Values are from study at Rancho Bernardo, California, 1984–87.
NIDDM, non–insulin-dependent diabetes mellitus; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
*Odds ratios are adjusted for the effects of all other factors in model; odds ratios for continuous variables are presented per standard deviation as for men and women combined.
†Association with 2-hour, postchallenge and fasting plasma glucose was examined in two separate models that included all variables except NIDDM.

Men missing certain anthropometric variables (i.e., systolic BP, n=2; HDL and LDL, n=8; 2-hour glucose, n=9) were excluded from analyses involving these variables.
TABLE 7. Odds Ratios Between the Odds of Asymptomatic Resting Electrocardiographic Abnormalities Among Women With Non-Insulin-Dependent Diabetes Mellitus and the Odds of Asymptomatic Resting Electrocardiographic Abnormalities Among Women With Normal Glucose Tolerance Adjusted for the Effect of Established Risk Factors of Ischemic Heart Disease

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Adjusted odds ratio*</th>
<th>95% Confidence interval</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIDDM (yes vs. no)</td>
<td>1.79</td>
<td>(1.05, 3.04)</td>
<td>0.037</td>
</tr>
<tr>
<td>Age (per 9.32 yr)</td>
<td>1.34</td>
<td>(1.00, 1.79)</td>
<td>0.048</td>
</tr>
<tr>
<td>Systolic BP (per 21.46 mm Hg)</td>
<td>1.61</td>
<td>(1.28, 2.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL (per 18.97 mg/dl)</td>
<td>1.12</td>
<td>(0.88, 1.41)</td>
<td>0.372</td>
</tr>
<tr>
<td>LDL (per 36.64 mg/dl)</td>
<td>1.10</td>
<td>(0.88, 1.38)</td>
<td>0.418</td>
</tr>
<tr>
<td>Smoking (yes vs. no)</td>
<td>1.08</td>
<td>(0.54, 2.17)</td>
<td>0.834</td>
</tr>
<tr>
<td>2-hr plasma glucose† (per 57.84 mg/dl)</td>
<td>1.18</td>
<td>(0.98, 1.41)</td>
<td>0.089</td>
</tr>
<tr>
<td>Fasting plasma glucose† (per 20.24 mg/dl)</td>
<td>1.03</td>
<td>(0.85, 1.24)</td>
<td>0.800</td>
</tr>
</tbody>
</table>

Values are from study at Rancho Bernardo, California, 1984–87. NIDDM, non-insulin-dependent diabetes mellitus; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*Odds ratios are adjusted for effects of all other factors in model; odds ratios for continuous variables are presented per standard deviation as for men and women combined.

†Association with 2-hour, postchallenge and fasting plasma glucose was examined in two separate models that included all variables except NIDDM.

Women missing certain anthropometric variables (i.e., systolic BP, n=1; HDL and LDL, n=4; 2-hour glucose, n=7) were excluded from analyses involving these variables.

A person with a single disease to be seen in a clinic or hospital study group.92

The prevalence of known and newly diagnosed NIDDM in the Rancho Bernardo population was similar to that reported from a representative US sample studied in the National Health and Nutrition Examination Survey (NHANES II), using the same World Health Organization criteria for diagnosis.33 We observed an excess of prevalent IHD among men and women with NIDDM, similar to that reported in other population-based studies applying current epidemiological criteria.3–5 In this study, prevalence rates for most IHD end points increased in both sexes in a stepwise manner, from normal to IGT to NIDDM, although the differences between persons with normal and persons with IGT were not statistically significant, except in women for all IHD end points combined. Some persons with IGT probably would have normal glucose tolerance on retesting; such misclassification could have obscured an IGT-IHD association. The clinical significance of an association of nonfatal IHD with IGT is supported by recent population studies describing excess IHD mortality in persons with IGT, particularly women.34,35

We examined several possible explanations for our observation that asymptomatic but not symptomatic electrocardiographic abnormalities or angina pectoris were significantly associated with diabetes in this study.

Misclassification for NIDDM might have weakened the positive association with symptomatic IHD in the present study but would not explain the significant association between asymptomatic IHD and NIDDM. Besides, similar associations were observed among diabetics newly diagnosed at the survey and among those with a previous clinical diagnosis of NIDDM.

Other prevalence studies that have found a significant association between NIDDM and symptomatic IHD end points have considered the possibility that diagnostic detection bias inflated the association between clinically diagnosed diabetes and symptomatic IHD because persons with diabetes might be more likely to report chest pain, and diabetes would be more often detected in persons presenting with angina.3,5 Diagnostic detection bias is very unlikely to play a role in the present study because two thirds of diabetics were newly diagnosed at the survey.

We considered the possibility that persons with symptomatic heart disease might have been less likely to visit the clinic than others. We compared the age-adjusted prevalence rates of angina pectoris between the studied population and the 374 nonlocal participants who were interviewed by phone, and found no evidence of selection bias (data not shown). We also compared the age-adjusted rates of angina pectoris, and symptomatic and asymptomatic electrocardiographic changes between the study population and persons who were not classifiable for diabetic status; these analyses also did not suggest selection bias. Because we were not able to systematically profile nonparticipants for diabetic status and IHD, however, we cannot entirely exclude selection bias; lower participation rates among diabetics with symptomatic IHD might have diluted the association between NIDDM and symptomatic IHD. We also cannot exclude a higher mortality among diabetics with symptomatic heart disease because the long-term prognosis of silent as compared with symptomatic ischemia or infarction is uncertain. Evidence of ischemic activity in completely asymptomatic persons seems to carry an adverse prognosis in the presence of other IHD risk factors.36–39

Increased use of digitalis and diuretics was observed in persons with NIDDM here and elsewhere, and could have systematically biased our results by affecting electrocardiographic tracings as well as glucose tolerance.34,40 Use of these drugs alone, however, is unlikely to explain the association between asymptomatic resting electrocardiographic abnormalities and NIDDM because it persisted even after exclusion of all persons taking digitalis or diuretic preparations. It is also unlikely that postchallenge hyperglycemia caused spuriously abnormal electrocardiographic tracings because all ECGs in this study were performed in fasting subjects before the oral glucose tolerance test.41

Evidence from clinical and autopsy studies supports the observation that silent manifestations of IHD are more prevalent in persons with than without
NIDDM. Three prospective population-based studies have found a higher incidence of unrecognized myocardial infarction (defined by major Q waves on resting ECG) in persons with diabetes as compared with those without diabetes although the differences were not statistically significant.

The mechanisms underlying painless manifestations of IHD remain unclear. In diabetics, decreased cardiac pain perception (as a result of autonomic neuropathy) has been suggested by others and would be compatible with the absence of a significant increase in angina pectoris and resting electrocardiographic abnormalities accompanied by symptoms among persons with NIDDM in this population. Part of the excess of electrocardiographic abnormalities in the absence of symptoms could reflect diabetic cardiomyopathy, the nature of which (atherosclerotic or nonatherosclerotic) remains controversial. Recent clinical studies have characterized pathophysiological differences between silent and painful episodes of myocardial ischemia and raised the question whether silent ischemia indicates a functional component of atherosclerotic heart disease, apart from just morphological stenosis of the coronary arteries. In this regard, it is interesting that systolic blood pressure but not lipoproteins showed a consistent independent relation with resting electrocardiographic abnormalities suggestive of asymptomatic IHD in this study, as with unrecognized myocardial infarction in previous reports. Several previous studies have observed a strong positive association between blood pressure and diabetes mellitus or asymptomatic hyperglycemia but the pathophysiological basis of this coincidence is not completely understood. There is evidence that cardiac mortality in diabetics increases in the presence of hypertension. Whether this might, in part, be because of a synergistic effect of blood pressure and diabetic status on the development of silent IHD remains to be further investigation. Obesity did not confound the association between electrocardiographic changes not accompanied by symptoms and NIDDM or systolic blood pressure in the present study. The lack of the expected association between current smoking and asymptomatic electrocardiographic changes in this study might be a function of smoking intervention or increased health consciousness among this upper-middle class Californian population.

In accord with our observations here, a greater relative impact of diabetes on IHD morbidity and mortality among women than men has been consistently reported over the past decade but the reasons for a sex differential remain to be elucidated.

With the increasing recognition that the clinical significance of inapparent or silent IHD has been widely underestimated in the past, identification of high-risk groups and putative risk factors is an initial but important step toward a more complete understanding of the clinical picture of IHD. These population-based results support the clinical impression of a coincidence between diabetes mellitus and silent manifestations of IHD. Based on these results, we caution that IHD is likely to be present at the time of diabetes diagnosis and might not reliably present with classical symptoms. In view of the previously observed excess of IHD mortality among persons with newly diagnosed NIDDM and IGT, it seems prudent to use widely available noninvasive diagnostic tests for monitoring glucose tolerance and ischemic electrocardiographic changes among older patients, particularly in the presence of other IHD risk factors. Given the cross-sectional design of this study, further insight into the prognostic significance of an abnormal resting ECG in the asymptomatic diabetic population could be gained from prospective studies correlating electrocardiographic evidence of IHD (silent or symptomatic) with subsequent IHD mortality.

References


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