Hyberinsulinemia, Sex, and Risk of Atherosclerotic Cardiovascular Disease

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Background. The possibility that hyperinsulinemia may be involved in the etiology of atherosclerotic cardiovascular disease (CVD) was first suggested 20 years ago. During the last decade, this possibility has received support from three large prospective studies.

Methods and Results. In the present study, the association between CVD, glucose intolerance, obesity, and hypertension (the GOH conditions) and hyperinsulinemia was examined cross-sectionally in a representative sample (n=1,263) of the adult Jewish population aged 40–70 years in Israel. Previously known diabetics were excluded. CVD comprising clinical or ECG evidence of ischemic heart disease, as well as clinical evidence of cerebrovascular or peripheral vascular disease, was identified in 97 men and 39 women. A significant (p<0.01) hyperinsulinemia-sex interaction was found for CVD rate, with the adjusted risk ratios (followed by 95% confidence limits), relative to the rate in 298 normoinsulinemic women, being 1.15 (0.68–1.95) in 328 normoinsulinemic men, 0.85 (0.48–1.49) in 277 hyperinsulinemic women, and 2.27 (1.33–3.08) in 360 hyperinsulinemic men. Age-adjusted CVD rates in men versus women were: a) similar and low among all normoinsulinemic normotensives and hyperinsulinemics free of any of the GOH conditions (all rates ≤6.5%); b) similar and high among normoinsulinemic hypertensives (13.4% versus 10.4%); c) significantly higher in men among hyperinsulinemic normotensives with glucose intolerance and/or obesity (15.2% versus 3.3%; p=0.02) and all hyperinsulinemic hypertensives (21.5% versus 12.8%; p=0.04). These trends remained significant after adjusting for age, ethnic group, and blood lipids.

Conclusions. Therefore, hyperinsulinemia was associated with excess CVD risk in men but not in women, and all excess CVD risk in men was confined to hyperinsulinemic individuals in the presence of glucose intolerance, obesity, or hypertension. (Circulation 1991;84:1165–1175)

The possibility that hyperinsulinemia may be involved in the etiology of atherosclerotic cardiovascular disease (CVD) was first suggested 20 years ago. It received support in the last decade from three large-scale prospective studies, which indicated that increased insulin levels in men free of ischemic heart disease, independently predicted future development of this disease. Moreover, we and others have shown that each of the four main established risk factors for CVD (hypertension, obesity, and glucose intolerance [the GOH conditions], as well as dyslipoproteinemia) is associated with hyperinsulinemia even in the absence of the other three factors. Another prominent constitutional risk factor for CVD is male sex. In this report we demonstrate that the excess CVD risk associated with hyperinsulinemia was evident only in men, confirming the results of the only prospective study that included women. Moreover, we show that in normoinsulinemic men CVD risk resembled that in women and excess CVD risk in hyperinsulinemic men appeared only in the presence of at least one of the GOH conditions.

Methods

Participants and Clinical Procedures

The Israel Study of Glucose Intolerance, Obesity, and Hypertension (the Israel GOH Study) is an ongoing nationwide longitudinal study of risk factors for CVD in a representative adult population sample.
The 681 individuals in whom lipoproteins were measured showed the same similarity to the phase I sample.\textsuperscript{12,21}

**Laboratory Procedures**

Plasma glucose was determined by routine automated Technicon Autoanalyzer II method (Technicon Instruments Corp., Tarrytown, N.Y.), using potassium ferricyanide reduction. Plasma insulin (mIU/l) was determined in duplicate by Phadebas Radioimmunoassay kit (Pharmacia Diagnostics Inc., Piscataway, N.J.), the within assay coefficient of variation being 4\% and between assay 8\%. Analysis and quality control of lipid and lipoprotein levels conformed to the Lipid Research Clinics Program.\textsuperscript{24}

**Definitions of Variables**

The interrelations between CVD, sex, hyperinsulinemia, and the GOH conditions were analyzed using both continuous and categorical forms of the variables as previously described.\textsuperscript{11} I. GOH conditions. a) Relative weight: continuous form—body mass index (BMI) (wt/ht\textsuperscript{2}, kg/m\textsuperscript{2}); categorical form—obesity (defined as BMI$\geq$27). b) Blood pressure: continuous form—mean of the four home measurements of systolic blood pressure (mm Hg) (diastolic pressure was not included since preliminary analysis indicated that the systolic pressure accounted for all its effect); categorical form—hypertension (defined by use of antihypertensive medications [including diuretics] or by at least two of the measurements being either systolic $>$145 mm Hg or diastolic $>$93 mm Hg [mostly mild hypertension, diastolic $\geq$100 mm Hg found in only 6\% of the untreated cases]). This definition of untreated hypertension, which has been used in our previous reports,\textsuperscript{11,12} was selected to include mild hypertensives and was found in preliminary analyses of our data to give better discrimination of associations with other risk factors and with CVD than the mean of the measurements. c) Glucose tolerance: continuous form—sum glucose, namely sum of 1 and 2 hours after load plasma glucose levels, representing the area under the glucose response curve. Categorical form—glucose intolerance, the combined group of nondiagnostic and impaired glucose tolerance, and diabetes, defined according to the National Diabetes Data Group criteria.\textsuperscript{22}

II. Insulin response. Continuous form—sum of the 1 and 2 hours after load levels (sum insulin) as a measure of the area under the insulin response curve. Categorical form—defining hyperinsulinemia as sum insulin greater than 137.3 mIU/l. This cutoff point, used in our previous studies,\textsuperscript{11,12} is the 75th percentile of the distribution of sum insulin in 282 participants of the current study group with normal glucose tolerance, BMI less than 25, and normal blood pressure in both phase I and phase II of the study. CVD rates were also compared between normoinsulinemic individuals with insulin levels less than the
50th percentile and those with levels in the 50–75th percentile range (low and intermediate response).

III. Prevalent CVD. This was determined by a detailed standardized medical history questionnaire including review of body systems during the home interview that covered the period from the phase I to the phase II interview. In addition, thorough review of complete hospital records (without knowledge of clinical or laboratory data of the patient) was done by one of the study physicians (I.O.) in those cases reporting hospital admissions for any reason. Completeness of reporting of hospital admissions was assessed by a telephone survey of 50 randomly selected cases among those who had not reported any hospital admission, all of whom reconfirmed the negative history. Individual diagnoses were classified by the 9th International Classification of Diseases (ICD-9) codes and grouped into three categories: 1) no CVD; 2) overt CVD, hospital diagnosis (in 77.1%) or history consistent with ischemic heart disease, cerebrovascular, or peripheral vascular disease (ICD-9 codes included were 410-414, 428, 430-438, 440, and 443); and 3) asymptomatic CVD: no overt CVD, with ECG findings consistent with myocardial ischemia, (in the absence of complete left bundle branch block, or the Wolff-Parkinson-White syndrome), determined by the following electrocardiographic criteria (based on the revised Minnesota Code for resting ECG22): a) abnormal Q and QS patterns (Code 1), b) abnormal T waves (Codes 5-1, 5-2), c) abnormal ST junction and segment depression (Code 4-1), and d) ST-segment elevation (Code 9-2). Categories c and d were classified as ischemia only in the absence of right bundle branch or intraventricular block. ICD-9 coding and ECG evaluation were done in a blinded fashion; that is, without knowledge of the results of the OGTT, blood pressure, BMI, lipoprotein levels, or insulin response.

Statistical Analysis

Age-adjusted analysis of the effect of each of the GOH conditions and of sex on rate of CVD, as well as comparisons of CVD rates between the various subgroups by insulin response category, sex, and combinations of the GOH conditions, was done by computing prevalence rates of CVD, adjusted for age by the direct method. Age categories were less than 60 years and 60 years or more after preliminary analysis indicated that further breakdown yielded practically the same results. The age distribution in the total study group was used as the standard population. A value of 0.5 for CVD cases was assigned to cells in which there were no such cases. Statistical comparison of CVD rates accounting for age was done by the Mantel-Haenszel test.

Multivariate analysis testing the effect of the various risk factors on the rate of CVD as the dependent variable was done using a step down logistic regression procedure (Biomedical Computer Programs, University of California 1980 [BMDP] program LR), which removes variables from the model if the probability values associated with their effects are larger than or equal to 0.15. The following set of four analyses was done: a) analysis of the total study group with sex, ethnic group (comprising the four main groups in Israeli Jews, those of Yemenite, North African, Mid-Eastern, and European origin), hyperinsulinemia, and the GOH conditions, as well as total triglycerides (assigning a value of 400 mg/dl to 11 cases with extreme values), total cholesterol, and age in their continuous form as the independent variables, including a sex-hyperinsulinemia interaction; b and c) separate analyses of hyperinsulinemic and normoinsulinemic individuals with the same independent variables. In each of these three analyses (a–c), glucose intolerance, obesity, and hypertension were entered into the model once as three separate variables and again as a combined single variable, dividing the study group into three mutually exclusive risk categories: I) individuals with none of the GOH conditions; II) normotensives who were glucose intolerant, obese, or both; and III) all hypertensives. d) Separate analysis of the group of all hypertensives with the same independent variables, including the hyperinsulinemia-sex interaction, and entering glucose intolerance and obesity once as separate variables and once as a single combined variable (i.e., obese and/or glucose intolerant).

In all analyses (a–d) the reported risk ratios pertaining to the GOH conditions, followed by 95% confidence limits in brackets, apply only to the combined variables, because the results using each of the GOH conditions as a separate variable were similar.

This set of analyses was repeated on the subgroup of 681 individuals on whom lipoprotein measurements were available, entering VLDL, TG, LDL, and HDL in their continuous form as independent variables into the model.

A complementary analysis, using all variables in their continuous form, was analysis of covariance (BMDP program 2V) with log transformed sum insulin as the dependent variable. This was done in the 681 individuals whose lipoproteins were measured, with sex and CVD as grouping factors and with age, BMI, mean systolic blood pressure, sum blood glucose, LDL, VLDL, HDL, and total cholesterol to HDL ratio as covariates. Internal comparisons were done using the error mean square. The adjusted logarithmic means of sum insulin are reported in their antilog form. This analysis was repeated three times: once on all 681 individuals, once excluding those on antihypertensive medications, and again in nonsmokers.

Results

Sex and CVD

The study group comprised 688 men and 575 women, their mean±SD ages being 53.1±8.1 years and 51.6±7.5 years, respectively. Altogether there were 136 CVD cases, 97 men and 39 women, yielding rates of prevalent CVD of 14.1% and 6.8%, respec-
tively ($p<0.001$). Of the CVD cases among men, 43.3% had asymptomatic myocardial ischemia (by ECG), overt CVD comprised 30.9% symptomatic ischemic heart disease, and 25.8% had cerebrovascular or peripheral vascular disease; the respective rates in women were 28.2%, 30.8%, and 41.0%. The differences in the distribution of CVD subcategories between men and women were not significant.

**Sex, CVD, and the GOH Conditions**

The male sex was associated with a significant and over twofold excess in age-adjusted CVD rates both in the presence or absence of each of the GOH conditions (Table 1). A trend for higher prevalence of CVD was associated with each of the GOH conditions, but the age-adjusted effect was significant only for hypertension in both sexes ($p<0.001$) and for obesity in men ($p=0.03$).

**Sex, CVD, and Hyperinsulinemia**

The association of CVD rates with hyperinsulinemia in both sexes was similar for all CVD subcategories (see Appendix Table). Therefore, all further analysis related to CVD as a single category. Comparison of the age-adjusted rates of CVD in normoinsulinemic individuals (Figure 1) indicated that there was no significant difference between those with low or intermediate insulin response, and that the rates for the total normoinsulinemic group were similar in men and women (8.5% versus 7.5%, $p>0.60$). In hyperinsulinemic men, age-adjusted rates of CVD doubled as compared with normoinsulinemic men (17.7% versus 8.5%, $p<0.001$). In women, no effect of hyperinsulinemia on this rate was noted (7.5% versus 7.3%, $p>0.90$). These trends persisted after exclusion of 89 newly found diabetic cases and were similar in all ethnic groups (data not shown).

These associations of CVD with hyperinsulinemia and sex were examined in the study group by logistic regression analysis adjusting for age, ethnic group, glucose intolerance, obesity, hypertension, total cholesterol, and triglycerides. In this analysis the sex-insulin response interaction was highly significant ($p<0.01$), confirming the divergent association of hyperinsulinemia with CVD in men and women. The adjusted risk ratios, relative to the rate of CVD in normoinsulinemic women, were 1.15 (0.68–1.95) in normoinsulinemic men, 0.85 (0.48–1.49) in hyperinsulinemic women, and 2.27 (1.33–3.08) in hyperinsulinemic men. Essentially similar results were obtained in the subgroup with complete lipoprotein profile, entering VLDLTG, LDLC, and HDLC into the model.

**Table 1. Crude and Age-Adjusted Prevalence of CVD by GOH Conditions and Sex**

<table>
<thead>
<tr>
<th></th>
<th>Men ($n=688$)</th>
<th></th>
<th>Women ($n=575$)</th>
<th></th>
<th>$p^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total no.</td>
<td>CVD No.</td>
<td>%</td>
<td>Total no.</td>
<td>CVD No.</td>
</tr>
<tr>
<td>Glucose intolerance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>431</td>
<td>49</td>
<td>11.4 (11.8)</td>
<td>433</td>
<td>27</td>
</tr>
<tr>
<td>Present</td>
<td>257</td>
<td>48</td>
<td>18.7 (16.0)</td>
<td>142</td>
<td>12</td>
</tr>
<tr>
<td>$p^+$</td>
<td></td>
<td></td>
<td>0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>465</td>
<td>55</td>
<td>11.9 (11.2)</td>
<td>360</td>
<td>21</td>
</tr>
<tr>
<td>Present</td>
<td>225</td>
<td>42</td>
<td>18.7 (17.7)</td>
<td>215</td>
<td>18</td>
</tr>
<tr>
<td>$p^+$</td>
<td></td>
<td></td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>332</td>
<td>24</td>
<td>7.2 (7.9)</td>
<td>333</td>
<td>10</td>
</tr>
<tr>
<td>Present</td>
<td>356</td>
<td>73</td>
<td>20.5 (17.4)</td>
<td>242</td>
<td>29</td>
</tr>
<tr>
<td>$p^+$</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CVD, cardiovascular disease; GOH, glucose intolerance, obesity, and hypertension.

$^*$Men vs. women.

$^+$Presence vs. absence of the GOH condition.

All $p$ values are adjusted for age by Mantel-Haenszel test.

Values in parentheses are age adjusted.

**Figure 1. Bar graph showing age-adjusted prevalence (%) of cardiovascular disease (CVD) by sex and insulin response level. L, I, and H indicate low, intermediate, and high insulin response, respectively. Numbers within bars indicate number of cases. Numbers above bars are % CVD.**
**TABLE 2. Age-Adjusted Prevalence (%) of CVD by Presence of Hyperinsulinemia and Combinations of the GOH Conditions by Sex**

<table>
<thead>
<tr>
<th>Risk category</th>
<th>GOH conditions</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normoinsulinemic</td>
<td>Hyperinsulinemic</td>
<td>Normoinsulinemic</td>
</tr>
<tr>
<td>I</td>
<td>GOH conditions absent</td>
<td>5.3</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>(135)</td>
<td>(59)</td>
<td>(139)</td>
</tr>
<tr>
<td>II</td>
<td>Obese and/or glucose intolerant normotensives</td>
<td>3.1</td>
<td>15.2*</td>
</tr>
<tr>
<td></td>
<td>(52)</td>
<td>(86)</td>
<td>(55)</td>
</tr>
<tr>
<td>III</td>
<td>Hypertensives</td>
<td>13.4‡</td>
<td>21.5‡</td>
</tr>
<tr>
<td></td>
<td>(141)</td>
<td>(215)</td>
<td>(104)</td>
</tr>
</tbody>
</table>

GOH, glucose intolerance, obesity, and hypertension.

I. Individuals with none of the GOH conditions; II, normotensives who were glucose intolerant, obese, or both; III, all hypertensives.

* *p* < 0.04 vs. normoinsulinemic men and *p* < 0.02 vs. hyperinsulinemic women in risk category II.

† *p* < 0.01 vs. normoinsulinemic normotensive men.

‡ *p* = 0.03 vs. normoinsulinemic men and *p* = 0.03 vs. hyperinsulinemic women in risk category III.

§ *p* < 0.01 vs. all normotensive women.

All *p* values are adjusted for age by Mantel-Haenszel test.

See Appendix Table for detailed distributions and crude rates.

Values in parentheses indicate number of cases.

**Sex, CVD, Hyperinsulinemia, and GOH Conditions**

Stratification by all possible combinations of the GOH conditions revealed complex inter-relations between the GOH conditions, hyperinsulinemia, and sex, with respect to their effect on CVD rate (Table 2 and Appendix Table). This analysis delineated three risk categories: I) This category comprised individuals with none of the GOH conditions. In it, age-adjusted rates of CVD in men compared with women, as well as in normoinsulinemic compared with hyperinsulinemic individuals in each sex, were not significantly different and were all low, 6.5% or less. II) This category comprised all normotensives who were not part of risk category I, and therefore included three subgroups—those with glucose intolerance alone, obesity alone, or both. These subgroups were pooled in the table because of the similarity of CVD rates when stratified by hyperinsulinemia and sex (see Appendix Table for detailed data on each subgroup). In this pooled category, age-adjusted rates of CVD in normoinsulinemic men and women and in hyperinsulinemic women were similar, were also low, (6% or less), and did not differ significantly from the respective rates in risk category I. However, in hyperinsulinemic men in this category, CVD rate was significantly increased more than twofold (15.2%; *p* = 0.04 versus normoinsulinemic men and *p* = 0.015 versus hyperinsulinemic women in the same risk category). III) This category comprised all hypertensives. These were pooled here since CVD rates were not affected by the presence or absence of glucose intolerance or obesity (see Appendix Table for detailed data). Here, the normoinsulinemic individuals manifested age-adjusted CVD rates, which were significantly increased more than twofold relative to the normoinsulinemic in risk categories I and II (i.e., normoinsulinemic normotensives), in both men (13.4%) and women (10.4%). In men, this difference was significant (*p* < 0.01). In women, the difference reached significance (*p* < 0.01) only when compared with all normotensive women. The increased rate in normoinsulinemic hypertensives did not differ significantly in men and women. In hyperinsulinemic men, the rate of CVD increased almost twofold relative to those who were normoinsulinemic (21.5% versus 13.4%, *p* = 0.03) as well as relative to hyperinsulinemic women (21.5% versus 10.4%, *p* = 0.03) in the same risk category. In women, however, no significant effect of hyperinsulinemia was noted (12.8% versus 10.4%).

To summarize, this analysis revealed a subgroup that constitutes 35.8% of men and 44.9% of women in our study group (comprising all normoinsulinemic normotensives and hyperinsulinemic individuals free of the GOH conditions) in whom the age-adjusted CVD rate was low (<5%) and similar in both sexes. An additional subgroup manifesting similar rates in both sexes was the normoinsulinemic hypertensives (constituting 20.5% of men and 18.1% of women), but here the age-adjusted CVD rates were more than twofold higher as compared with the first subgroup. Therefore, all excess CVD risk associated with the male sex was confined to hyperinsulinemic individuals with at least one of the GOH conditions. Based on the data from the 681 individuals on whom complete lipoprotein data were available, there was no indication that disturbed lipoprotein profile accounted for these observations because the same trends were observed among men in whom all lipoprotein fractions were completely normal (as defined in our previous study); thus, CVD rates among these men were 18.8% in 16 hyperinsulinemic normotensives with glucose intolerance and/or obesity and 20.6% in 34 hyperinsulinemic hypertensives. It is, however, noteworthy in hyperinsulinemic hypertensives who presented a combination of high VLDL, high LDL, and low HDL as defined in our previous study, CVD rates were very high and similar in 48 men and...
TABLE 3. Risk Ratios Associated With Hyperinsulinemia, Sex, and Combinations of GOH Conditions, Adjusted for Age, Ethnic Group, Total Cholesterol, and Total Triglycerides

<table>
<thead>
<tr>
<th>Hyperinsulinemia and sex*</th>
<th>Total study group</th>
<th>All normoinsulinemics</th>
<th>All hyperinsulinemics</th>
<th>All hypertensives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoinsulinemic women</td>
<td>1.00 (baseline)</td>
<td>1.00</td>
<td>...</td>
<td>1.00</td>
</tr>
<tr>
<td>Normoinsulinemic men</td>
<td>1.15 (0.68–1.95)</td>
<td>1.11 (0.65–1.91)</td>
<td>...</td>
<td>1.34 (0.45–3.97)</td>
</tr>
<tr>
<td>Hyperinsulinemic women</td>
<td>0.85 (0.48–1.49)</td>
<td>...</td>
<td>1.00</td>
<td>1.26 (0.36–4.41)</td>
</tr>
<tr>
<td>Hyperinsulinemic men</td>
<td>2.27 (1.33–3.08)</td>
<td>...</td>
<td>2.74 (1.74–4.32)</td>
<td>2.50 (1.19–5.22)</td>
</tr>
</tbody>
</table>

GOH combinations

<table>
<thead>
<tr>
<th>GOH conditions absent</th>
<th>1.00 (baseline)</th>
<th>1.00</th>
<th>1.00</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese and/or glucose intolerant†</td>
<td>1.36 (0.74–2.50)</td>
<td>0.54 (0.18–1.62)</td>
<td>3.20 (1.09–9.38)</td>
<td>1.18 (0.66–2.17)</td>
</tr>
<tr>
<td>All hypertensives</td>
<td>2.98 (1.82–4.90)</td>
<td>2.52 (1.45–4.43)</td>
<td>6.59 (2.42–17.97)</td>
<td>...</td>
</tr>
<tr>
<td>Hyperinsulinemia–sex interaction</td>
<td>2.74 (1.74–4.32)</td>
<td>2.74 (1.74–4.32)</td>
<td>2.74 (1.74–4.32)</td>
<td>...</td>
</tr>
</tbody>
</table>

GOH, glucose intolerance, obesity, and hypertension.

*Risk ratios in the total study group and in hypertensives were computed relative to normoinsulinemic women and not separately for overall effects of hyperinsulinemia and sex because of significant interactions.

†In the total study group, and in groups of all normoinsulinemics and all hyperinsulinemics, risk ratios relate only to normotensive obese and/or glucose intolerant individuals (risk category II), as compared with normotensives in whom these conditions are absent (risk category I). In the group of all hypertensives (risk category III), risk ratio is of obese and/or glucose intolerant individuals within this group as compared with those in whom these conditions are absent.

14 women, 31.3% and 28.6%, respectively. This combination was observed, however, only in 15.1% of hyperinsulinemic hypertensive women; therefore, this combination had little effect on the overall CVD rate in this group. In normoinsulinemic hypertensives and in risk categories I and II, this disturbed lipoprotein profile did not appear to confer any additional CVD risk in either of the sexes.

The trends demonstrated in Table 2 were corroborated by logistic regression analyses, adjusting for age, ethnic group, and blood lipids (Table 3). In normoinsulinemic individuals, hypertension had an independent highly significant effect on CVD rate ($p<0.001$) with a risk ratio of 2.52 (1.43–4.43); sex, as well as glucose intolerance and obesity, alone or in combination, had no significant effect. In hyperinsulinemic individuals each of the factors had a highly significant independent effect: The adjusted risk ratio associated with the male sex was 2.74 (1.74–4.32), and those associated with risk categories II and III compared with category I were 3.20 (1.09–9.38) and 6.59 (2.42–17.97), respectively. Within risk category III, there was a significant ($p=0.03$) hyperinsulinemia-sex interaction, but glucose intolerance and obesity alone, or in combination, had no significant effect.

Sex, CVD, and Insulin Response

Finally, mean insulin response, adjusted for all other variables in their continuous form (age, BMI, systolic blood pressure, sum blood glucose, LDL, VLDL/LTG, HDL, and total cholesterol to HDL ratio), was compared in individuals with and without CVD in both sexes (Figure 2). Insulin response was similar in men free of CVD and in women with or without CVD (133.9, 125.8, and 133.8, respectively). However, it was significantly increased in men with CVD (adjusted mean 162.3, $p<0.001$). The adjusted means of insulin response by CVD and sex remained practically the same when individuals on antihypertensive medications and smokers were excluded (Table 4), indicating that these factors had no appreciable effect on insulin levels or on their association with CVD.

**Discussion**

Excess CVD risk in men compared with women is an unequivocally inherent characteristic of this disease. The only exception is diabetes, in which equally high rates have been reported by some but not all investigators. In our representative sample of a population in the age range of 40–70, the overall prevalence of CVD morbidity in men was double that in women. However, stratification by hyperinsulinemia and the GOH conditions revealed a sizeable category, constituting about 40% of our sample, in whom CVD rate in men was equally low to that in

![Figure 2. Bar graph illustrating mean insulin response, adjusted for age, body mass index (BMI), sum glucose, systolic blood pressure, very low density lipoprotein triglycerides (VLDL-LTG), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), and total cholesterol/high density lipoprotein cholesterol ratio by sex and cardiovascular disease (CVD).](http://circ.ahajournals.org/)

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women. These were the normoinsulinemic normotensives as well as the hyperinsulinemic individuals free of the GOH conditions. Moreover, all excess risk of CVD in men was confined to hyperinsulinemic individuals, in whom at least one of the GOH conditions was present.

Three large-scale community-based prospective studies generated the main evidence associating elevated insulin levels with increased risk of ischemic heart disease (IHD) morbidity and mortality, as well as with overall CVD mortality. These studies showed that elevated insulin levels predict this risk after accounting for the effects of age, the GOH conditions, and blood lipid levels. The only one of these studies that included women showed that elevated insulin levels were predictive of CVD only in men and is, therefore, consistent with our data. However, in that study CVD rates were not compared in the normoinsulinemic men and women.

It is noteworthy that in our data glucose intolerance or obesity conveyed independent excess CVD risk only in hyperinsulinemic men. There was no indication for a different trend in the newly found diabetes cases, but their number was too small for definite conclusions. Hypertension was the only GOH condition independently associated with excess CVD in normoinsulinemic individuals of both sexes as well as in hyperinsulinemic women, but in men the risk was further enhanced in the presence of hyperinsulinemia. Central adiposity was not measured in our study. Because central adiposity is more prevalent in men and positively and independently correlated with hyperinsulinemia/insulin resistance, hypertension, glucose intolerance, and CVD, it could play a role in our findings. It seems, however, unlikely that it would be the only factor, because this type of adiposity should have been present in the majority of our obese women whose BMI was equal to or more than 27 and most of whom were postmenopausal.

Of the three prospective studies, only the Paris Prospective Study of ischemic heart disease mortality risk in men directly analyzed the effects of the interaction of hyperinsulinemia with the GOH conditions on this risk. The pattern found was strikingly similar to ours in that significant excess mortality among hyperinsulinemic individuals appeared only in the presence of at least one of the GOH conditions. Also, within their group of normoinsulinemic individuals IHD mortality was increased in hypertensives but not in individuals who were glucose intolerant or obese. Mortality in hyperinsulinemic hypertensives was highest.

Finally, we did not find any clinical pattern of CVD as specifically characterizing hyperinsulinemic men. Asymptomatic electrocardiographic evidence of myocardial ischemia, which constituted 40% of our CVD cases, was associated with hyperinsulinemia in much the same way as overt ischemic heart disease. This association has not been previously reported and is consistent with studies showing that both hyperinsulinemia and asymptomatic myocardial ischemia preceded overt CVD. Cerebrovascular and peripheral vascular diseases were also increased in the presence of hyperinsulinemia in our men. In the Australian prospective study, hyperinsulinemia in men was predictive of total CVD mortality but separate analysis of subcategories was done only for ischemic heart disease. Increased incidence of claudication in hyperinsulinemic individuals, mainly with noninsulin-dependent diabetes, has recently been reported in a small prospective study.

The main limitation of our data is that they are cross sectional, but this does not negate the major findings. It is unlikely that the similarly low prevalence of CVD in men and women among normoinsulinemic normotensives and hyperinsulinemic individuals free of the GOH conditions was due to selective mortality. This would imply that men in this risk category had higher mortality than the hyperinsulinemic men with the GOH conditions, contradicting the results of the Paris Prospective Study. The potential confounding effect of smoking and use of antihypertensive medications was negated by the similarity of results in the absence of these two factors. The possibility that hyperinsulinemia developed subsequent to the onset of CVD could at most offer only a partial explanation for our results, as evidenced by the results of the prospective studies.

The data from the three prospective studies as well as cross-sectional epidemiological and clinical studies showing independent correlation of elevated insulin levels and insulin resistance with the GOH conditions and dyslipoproteinemia (elevated VLDL and LDL as well as reduced HDL), have been interpreted as supporting the putative role of hyperinsulinemia and/or insulin resistance in the atherogenic process. However, the data from our study, the Australian Study, and the Paris Prospec-
tive Study\textsuperscript{2} indicate that hyperinsulinemia was not associated with CVD in all women or in men free of the GOH conditions. This suggests that hyperinsulinemia in itself is not atherogenic.

The increased propensity of men to develop CVD is yet to be explained. The inclination has been to ascribe it to the androgenic sex hormone profile.\textsuperscript{41,42} In contrast with the consistent association of CVD with hyperinsulinemia in men, the evidence for its association with androgenic hormone profile is equivocal. Decreased sex hormone binding globulin (SHBG), which reflects higher levels of free testosterone and other androgens,\textsuperscript{42,43} has been associated in men as well as in pre- and postmenopausal women with an atherogenic plasma lipoprotein profile.\textsuperscript{42,44-46} The association of decreased SHBG with obesity and hyperinsulinemia\textsuperscript{42-44} seemed to link the putative roles of sex hormones and of hyperinsulinemia/insulin resistance in CVD risk. However, case-control studies in men attempting to correlate CVD with androgenic hormone profile have yielded contradictory results, and two large-scale prospective studies in men failed to show that sex steroid hormone levels or SHBG were predictive of CVD.\textsuperscript{41,44,47,48} No such studies have been conducted in women. The absence of excess CVD risk in our hyperinsulinemic obese women, in whom SHBG levels are expected to be lower,\textsuperscript{42,43} are not compatible with the suggested role for androgenic hormone profile in CVD risk in them.

An alternative explanation for the association of excess CVD in men with hyperinsulinemia and at least one GOH condition would be the changes in lipoprotein profile and metabolism characterizing hyperinsulinemia/insulin resistance.\textsuperscript{12,36-40,49} Our previously reported finding that the adverse lipoprotein profile that characterizes the GOH conditions was confined to hyperinsulinemic individuals\textsuperscript{12} seems to support this notion. A protective effect of the considerably higher HDL levels in women at all ages\textsuperscript{10,28,50} even in the presence of hyperinsulinemia,\textsuperscript{12} could in this case offer an explanation for the lack of effect of hyperinsulinemia or CVD in women. However, in our hyperinsulinemic men with at least one GOH condition, the high CVD risk was not accounted for by lipoprotein profile because the risk remained high even when all lipoprotein fractions were normal. We have previously also demonstrated\textsuperscript{12} that lipoprotein profile was disturbed to the same extent in hyperinsulinemic individuals in the presence and absence of the GOH conditions. Therefore, our current findings of low CVD rates in hyperinsulinemic men free of the GOH conditions cannot be ascribed to a better lipoprotein profile.

Clearly then, the mechanisms responsible for our findings must be complex and involve additional presently unidentified factors. This notion seems to be supported by the fact that insulin levels were high in our men with CVD, even after adjusting for levels of glucose response, blood pressure, BMI, lipoproteins, and age, suggesting a role for additional factors in this association. Other factors known to be associated with hyperinsulinemia/insulin resistance, as well as with atherosclerosis, could participate in this mechanism. These are vascular smooth muscle proliferation,\textsuperscript{51-53} increased blood coagulability,\textsuperscript{54-57} reduced tissue lipoprotein lipase activity,\textsuperscript{48,58,59} and altered activity of the autonomic nervous system.\textsuperscript{50-62} With the exception of reduced lipoprotein lipase activity in men,\textsuperscript{63} sex-related differences in these factors have not been reported. However, even if such differences were found, the low CVD rates in all hyperinsulinemic women and in hyperinsulinemic men free of the GOH conditions indicate that such a relation would not be straightforward.

Notwithstanding, the excess CVD risk in men is obviously related in some way to the insulin-resistant state. In this context, it is of interest that significantly lower glucose levels at similar insulin levels have been reported in women compared with men.\textsuperscript{64} Similar findings were observed in our study group after adjustment for age and BMI. In addition, during the OGTT about 40% of our women compared with only about 20% of the men reattained fasting levels within 1 hour (M. Modan et al, unpublished data). Also, as others\textsuperscript{29} have found, both insulin and glucose responses to oral glucose load were lower in our women. These findings may reflect greater insulin sensitivity in women, which could account for the lack of association of hyperinsulinemia with CVD in them.

The strong association between all classical pathophysiological risk factors for CVD with each other and with hyperinsulinemia and its attendant insulin resistance has been interpreted to reflect the existence of a syndrome rather than a series of independent factors.\textsuperscript{16,37} We found a wide range of CVD risk associated with the various combinations of the GOH conditions, hyperinsulinemia, and sex. This seems to indicate that rather than a single syndrome, there appear to be a number of entities with differential CVD risk and divergent etiology. In this context it is of interest to mention the recently identified syndrome of familial dyslipidemic hypertension that is characterized by hyperinsulinemia\textsuperscript{65} and our finding in the current report, albeit based on small numbers, of excessively high CVD rate in hyperinsulinemic hypertensives with overall disturbed lipoprotein profile of both sexes.

The possible involvement of hyperinsulinemia/insulin resistance in the pathogenesis of CVD has potential implications regarding prevention of this pandemic of industrialized society. Major environmental CVD risk factors are associated with diminished insulin sensitivity. The main evidence relates to excessive total caloric intake\textsuperscript{2,3,31,37,66} and sedentary life-style.\textsuperscript{21,60,66-68} Moreover, the Finnish prospective study\textsuperscript{3} demonstrated negative correlations of physical activity and physical fitness with IHD morbidity and mortality as well as with insulin levels. Therefore, the currently recommended health-promoting lifestyle\textsuperscript{10,66,69} may exert its preventive effect on CVD and its risk factors, at least in part, by improving insulin sensitivity.\textsuperscript{11,37}
Appendix

**APPENDIX TABLE.** Crude Prevalence of CVD by Presence of Hyperinsulinemia, Combinations of the GOH Conditions, and Sex

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Hypertension</th>
<th>Glucose intolerance</th>
<th>Obesity</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total no.</td>
<td>No.</td>
<td>%</td>
<td>Total no.</td>
<td>No.</td>
</tr>
<tr>
<td>I</td>
<td>135</td>
<td>6</td>
<td>4.4</td>
<td>59</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>25</td>
<td>1</td>
<td>3.8</td>
<td>33</td>
<td>6</td>
</tr>
<tr>
<td>III</td>
<td>68</td>
<td>10</td>
<td>14.9</td>
<td>50</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>7</td>
<td>18.5</td>
<td>65</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>3</td>
<td>13.0</td>
<td>46</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>1</td>
<td>9.1</td>
<td>65</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>328</td>
<td>29</td>
<td>8.8</td>
<td>368</td>
<td>60</td>
</tr>
<tr>
<td>Overt ischemic heart disease</td>
<td>9</td>
<td>2.7</td>
<td>21.5</td>
<td>6</td>
<td>2.0</td>
</tr>
<tr>
<td>Cerebrovascular and peripheral vascular disease</td>
<td>7</td>
<td>2.1</td>
<td>18.5</td>
<td>7</td>
<td>2.4</td>
</tr>
<tr>
<td>ECG ischemic changes</td>
<td>13</td>
<td>4.0</td>
<td>29.8</td>
<td>6</td>
<td>2.0</td>
</tr>
</tbody>
</table>

GOH, glucose intolerance, obesity, and hypertension; CVD, cardiovascular disease; I, individuals with none of the GOH conditions; II, normotensives and Cerebrovascular Risk; III, other risk factors who were glucose intolerant, obese, or both; III, all hypertensives; ECG, electrocardiogram.

**References**


**KEY WORDS**  
- glucose intolerance  
- obesity  
- hypertension  
- lipoproteins
Hyperinsulinemia, sex, and risk of atherosclerotic cardiovascular disease.
M Modan, J Or, A Karasik, Y Drory, Z Fuchs, A Lusky, A Chetrit and H Halkin

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