Heterogeneity in the Prevalence of Risk Factors for Cardiovascular Disease and Type 2 Diabetes Mellitus in Obese Individuals

Effect of Differences in Insulin Sensitivity

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Background: The possibility that substantial heterogeneity in metabolic abnormalities exists in moderately obese individuals has not been emphasized in studies of the effect of obesity on morbidity and mortality. We tested the hypothesis that risk factors for type 2 diabetes mellitus and cardiovascular disease vary dramatically in moderately obese individuals as a function of differences in a specific measure of insulin sensitivity.

Methods: Participants included 211 apparently healthy, obese (body mass index [calculated as weight in kilograms divided by height in meters squared], 30.0-34.9) volunteers for weight loss studies. Main outcome measures included insulin-mediated glucose uptake as quantified by the insulin suppression test and metabolic variables known to increase the risk for type 2 diabetes and cardiovascular disease.

Results: Insulin sensitivity varied 6-fold. When compared with the most insulin-sensitive third, the most insulin-resistant third of the population had significantly higher (P<.001) systolic and diastolic blood pressure (139±20 vs 123±18 mm Hg, and 83±3 vs 75±10 mm Hg, respectively), higher fasting and 2-hour oral glucose load concentrations (103±11 vs 95±11 mg/dL [5.7±0.6 vs 5.3±0.6 mmol/L], and 139±30 vs 104±19 mg/dL [7.7±1.7 vs 5.8±1.1 mmol/L], respectively), higher plasma triglyceride concentrations (198±105 vs 114±51 mg/dL [2.2±1.2 vs 1.3±0.6 mmol/L]), lower plasma high-density lipoprotein cholesterol concentrations (41±9 vs 50±13 mg/dL [1.1±0.2 vs 1.3±0.3 mmol/L]), and more prevalent impaired glucose tolerance (47% vs 2%).

Conclusions: The magnitude of risk factors for type 2 diabetes and cardiovascular disease varies markedly in moderately obese individuals as a function of differences in degree of insulin sensitivity. Because not all moderately obese individuals are at similar risk for developing type 2 diabetes and cardiovascular disease, intensive therapeutic interventions should be addressed to the insulin-resistant subset of this population.

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More recently, a meta-analysis of 250 153 subjects with established CVD, enrolled in 40 studies, found that neither total nor CVD mortality was increased in moderately obese (BMI, ≥30.0-34.9) compared with normal-weight individuals. The results did not change significantly when adjusted for a number of other potentially confounding variables, leading the authors to conclude that “rather than prove that obesity is harmless, our data suggest that alternative methods might be needed to better characterize individuals who truly have an excess of body fat, compared with those in whom BMI is raised because of preserved muscle mass.”

There is no reason to doubt that improved medical treatment has decreased the adverse clinical impact of obesity, and we do not suggest that obesity is harmless. However, we submit that the relationship between obesity and morbidity and mortality is more complicated than depicted in these reports. Specifically, we suggest that insulin resistance and the concomitant presence of associated metabolic abnormalities vary among obese individuals, and insulin resistance and/or hyper-insulinemia is an independent predictor of DM2, essential hypertension, and CVD. Thus, it can be argued that the risk of developing these clinical syndromes will be accentuated in those obese individuals who are also more insulin resistant.

Based on these considerations, we thought it would be useful to confirm, in a much larger population, our previous findings in small numbers of moderately obese individuals, stratified into insulin-resistant and insulin-sensitive subgroups, that metabolic risk factors for DM2 and CVD were confined to insulin-resistant individuals. Consequently, we quantified insulin-mediated glucose uptake and risk factors for the development of DM2 and CVD in 211 consecutive individuals who volunteered for weight loss studies at Stanford University, Stanford, Calif.

**METHODS**

The study was conducted in a cross-sectional manner. We compiled data from all individuals with a BMI of 30.0 to 34.9 who volunteered for various weight loss studies conducted consecutively by our laboratory. All volunteers were respondents to advertisements requesting “healthy, moderately overweight volunteers for weight loss study,” which were posted in the major newspapers serving the San Francisco Bay area of California and Stanford University. Volunteers were required to have had a stable weight for 3 months, to not be taking corticosteroids or other medications known to alter glucose metabolism, to be free of major medical diseases with the exception of hypertension, to have a fasting plasma glucose concentration of less than 126 mg/dL (<7.0 mmol/L), and to have discontinued medication therapy to lower lipid levels for at least 4 weeks before testing insulin resistance and lipid and lipoprotein values. Subjects taking antihypertensive drugs were required to have had a stable weight for 3 months, to not be taking corticosteroids or other medications known to alter glucose metabolism, to be free of major medical diseases with the exception of hypertension, to have a fasting plasma glucose concentration of less than 126 mg/dL (<7.0 mmol/L), and to have discontinued medication therapy to lower lipid levels for at least 4 weeks before testing insulin resistance and lipid and lipoprotein values. Subjects taking antihypertensive drugs were allowed to continue to receive their usual medications.

Included in this analysis were 211 individuals who met these eligibility requirements and who completed a history and physical examination, an oral glucose tolerance test, and a quantitative test for insulin-mediated glucose uptake. An additional 25 subjects who completed only the oral glucose tolerance test were not included in the analysis. Of the 211 subjects, 147 began 1 of 3 weight loss studies, and 111 completed their assigned study. These results are reported separately. All studies were approved by the Stanford Human Subjects Committee, and all subjects gave written, informed consent.

On the initial visit, after a 12-hour overnight fast, height and weight in light clothing were obtained, and the BMI was calculated. Blood was drawn for measurement of plasma glucose level, after which a 75-g glucose beverage was administered. Blood was redrawn 2 hours later for a second measurement of glucose concentration.

On a separate visit, typically within 2 weeks, after a 12-hour overnight fast, blood was drawn for the measurement of lipid and lipoprotein concentrations, after which insulin-mediated glucose uptake was quantified by a modification of the insulin suppression test as originally described and validated. Briefly, subjects underwent infusion for 180 minutes with octreotide acetate (0.27 µg/m² per minute), insulin human (25 mU/m² per minute), and glucose (240 mg/m² per minute). Blood was drawn at 10-minute intervals from 150 to 180 minutes of the infusion to measure plasma glucose and insulin concentrations, and the mean of these 4 values was used as the steady-state plasma insulin and steady-state plasma glucose (SSPG) concentrations for each individual. Because steady-state plasma insulin concentrations are similar in all subjects during these tests (approximately 60 µIU/mL [416.7 mmol/L]), the SSPG concentration provides a load: higher SSPG concentrations indicate that the individual is more insulin resistant. To explore the variability of risk markers as a function of insulin resistance, individuals were divided into tertiles on the basis of their SSPG concentration. It should be emphasized that the mean SSPG concentrations and the range of the values in the 3 tertiles thus formed were almost identical to the same values in a previous study from our research group of 490 apparently healthy individuals. Furthermore, in prospective studies of much smaller numbers of individuals, our group has shown that adverse clinical outcomes occurred significantly more frequently in the third of the population that was most insulin resistant.

The presence of obesity-associated clinical conditions was defined according to national guidelines. Hypertension was defined as systolic blood pressure of 140 mm Hg or greater or diastolic blood pressure of 90 mm Hg or greater per the Seventh Report of the Joint National Committee. Hypertriglyceridemia was defined as a fasting plasma triglyceride (TG) level of greater than 200 mg/dL (2.3 mmol/L) and a low high-density lipoprotein cholesterol concentration (HDL-C) of less than 40 mg/dL (1.0 mmol/L) for men or less than 50 mg/dL (1.3 mmol/L) for women as per the Adult Treatment Panel III guidelines. Impaired fasting glucose level was defined as a fasting plasma glucose level of at least 100 mg/dL (5.6 mmol/L) and impaired glucose tolerance (IGT) as a plasma glucose concentration of at least 140 mg/dL (7.8 mmol/L) and less than 200 mg/dL (11.1 mmol/L) 2 hours after a 75-g oral glucose challenge, per American Diabetes Association guidelines.

Statistical analyses were performed with SAS software (version 9.3.2; SAS Institute, Carey, NC). Unless otherwise indicated, values are presented as mean ± SD. Nonnormally distributed variables (TG concentrations) were log-transformed for statistical analyses. Comparison of continuous variables among these 3 tertiles (according to SSPG concentration) was performed with analysis of variance, with BMI, age, and sex as covariates to adjust for potential confounding. Categorical variables were compared across the 3 groups with χ² testing. The Tukey adjustment for multiple comparisons was used for these analyses. Estimation of trends across tertiles of SSPG concentration used a general linear model for continuous variables and the Cochran-Armitage test for categorical variables. For obesity-associated clinical conditions, odds ratios and 95% confi-
The experimental population divided into tertiles on the basis of their differences in insulin action are given in Table 1. By selection, SSPG concentrations in the 3 tertiles did not overlap and varied substantially, with the mean SSPG concentration in tertile 3, the most insulin-resistant group, 3-fold higher than the average of the most insulin-sensitive group (tertile 1). Despite inclusion of subjects within a relatively narrow range, there was a trend toward increased BMI values across the tertiles ($P = .04$). Otherwise, there were no significant differences among the tertiles.

Table 2 compares the blood pressure of the 3 groups and the values of metabolic variables known to increase the risk of CVD and DM2. When adjusted for differences in age, sex, and BMI, the values of every risk factor measured varied as a function of degree of insulin resistance, with the exception of total and low-density lipoprotein cholesterol; OGTT, oral glucose tolerance test; SSPG, steady-state plasma glucose; TG, triglyceride.

### RESULTS

The SSPG concentrations and demographic variables of the experimental population divided into tertiles on the...
lipoprotein cholesterol concentrations. A comparison of individual tertiles showed all variables to differ in tertiles 3 vs 1, and most of the values in tertile 3 were also significantly different from those in tertile 2. Perhaps of greatest clinical relevance was the dramatic difference in IGT between tertile 1 (2%) and tertile 3 (47%).

Table 3 gives the odds ratio, unadjusted and adjusted for differences in age, sex, and BMI, of individuals in tertile 3 compared with tertile 1, of belonging to a diagnostic category at increased risk of developing CVD or DM2 as defined by the Seventh Report of the Joint National Committee. Adult Treatment Panel III, or American Diabetes Association. Similar to the results in Table 2, there was a trend toward greater risk as the SSPG concentration increased. Thus, subjects in tertile 2 had significantly greater risk of being hypertriglyceridemic and of having IGT than did those in tertile 1, whereas all 5 risk factors were significantly greater when those in tertile 3 were compared with individuals in tertile 1 (ranging from adjusted odds ratios of 3.0-54.8). The results of the univariate correlations between the experimental variables, shown in Table 4, indicate that every marker, with the exception of low-density lipoprotein cholesterol level, BMI, and fasting glucose level, remained statistically significant after adjustment for all other markers (partial correlation coefficients are given in Table 4).

COMMENT

Our cross-sectional analysis of 211 apparently healthy individuals with BMIs ranging from 30.0 to 34.9 demonstrates that a large degree of variability in both insulin resistance and related metabolic risk factors existed in the study population, despite the fact that every participant was obese. For example, SSPG concentrations varied 6-fold (from 55 to 329 mg/dL [3.1 to 12.8 mmol/L]), as did plasma TG concentrations (from 47 to 319 mg/dL [0.5 to 3.6 mmol/L]). Furthermore, as emphasized in Table 4, with the exception of the low-density cholesterol level, there was a significant correlation between SSPG concentrations and all of the CVD risk factors, even after adjustment for associated metabolic risk factors. Although insulin resistance (SSPG concentration) and obesity (BMI) were modestly related (r = 0.17), the only metabolic risk factor correlated with BMI was the fasting glucose concentration. Thus, at the simplest level, it is quite clear that there are considerable differ-

Table 3. Rates of Adverse Clinical Outcomes Associated With Insulin Resistance in Tertiles 2 and 3 of SSPG Concentration Compared With Tertile 1

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Tertile 1 (n = 70)</th>
<th>Tertile 2 (n = 70)</th>
<th>P Value</th>
<th>Tertile 3* (n = 71)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension, No. (%) of participants†</td>
<td>11 (16)</td>
<td>20 (29)</td>
<td>.40</td>
<td>34 (48)</td>
<td>.001</td>
</tr>
<tr>
<td>Unadjusted OR (95% CI)‡</td>
<td>1.2 (0.9-1.7)</td>
<td>2.0 (0.9-4.7)</td>
<td>.09</td>
<td>4.7 (2.1-10.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adjusted OR (95% CI)‡</td>
<td>1.2 (0.9-1.7)</td>
<td>2.0 (0.9-4.6)</td>
<td>.12</td>
<td>4.2 (1.9-9.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertriglyceridemia (≥150 mg/dL), No. (%) of participants</td>
<td>12 (18)</td>
<td>35 (51)</td>
<td>.001</td>
<td>42 (69)</td>
<td>.001</td>
</tr>
<tr>
<td>Unadjusted OR (95% CI)</td>
<td>1.1 (0.7-1.6)</td>
<td>4.6 (2.1-10.1)</td>
<td>&lt;.001</td>
<td>7.0 (3.2-15.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adjusted OR (95% CI)‡</td>
<td>1.1 (0.7-1.6)</td>
<td>4.3 (2.0-9.5)</td>
<td>&lt;.001</td>
<td>6.5 (2.9-14.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Low HDL-C level, No. (%) of participants</td>
<td>29 (45)</td>
<td>36 (52)</td>
<td>.38</td>
<td>47 (68)</td>
<td>.007</td>
</tr>
<tr>
<td>Men, &lt;40 mg/dL</td>
<td>9 (20)</td>
<td>14 (42)</td>
<td>.34</td>
<td>24 (71)</td>
<td>.004</td>
</tr>
<tr>
<td>Women, &lt;50 mg/dL</td>
<td>20 (45)</td>
<td>22 (61)</td>
<td>.34</td>
<td>23 (66)</td>
<td>.004</td>
</tr>
<tr>
<td>Unadjusted OR (95% CI)</td>
<td>1.1 (0.7-1.7)</td>
<td>1.4 (0.7-2.7)</td>
<td>.38</td>
<td>2.7 (1.3-5.4)</td>
<td>.007</td>
</tr>
<tr>
<td>Adjusted OR (95% CI)‡</td>
<td>1.1 (0.7-1.7)</td>
<td>1.4 (0.7-2.8)</td>
<td>.34</td>
<td>3.0 (1.4-6.3)</td>
<td>.004</td>
</tr>
<tr>
<td>IFG level (≥100 mg/dL), No. (%) of participants</td>
<td>19 (29)</td>
<td>30 (45)</td>
<td>.001</td>
<td>43 (67)</td>
<td>.001</td>
</tr>
<tr>
<td>Unadjusted OR (95% CI)</td>
<td>1.1 (0.7-1.7)</td>
<td>2.0 (1.0-4.0)</td>
<td>.07</td>
<td>5.0 (2.4-10.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adjusted OR (95% CI)‡</td>
<td>1.1 (0.7-1.7)</td>
<td>1.8 (0.8-3.9)</td>
<td>.13</td>
<td>4.0 (1.8-9.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>IGT (2-h level ≥140 mg/dL), No. (%) of participants</td>
<td>1 (2)</td>
<td>18 (28)</td>
<td>.003</td>
<td>28 (47)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Unadjusted OR (95% CI)</td>
<td>1.1 (0.7-1.7)</td>
<td>21.9 (2.8-170.0)</td>
<td>.003</td>
<td>49.0 (6.4-377.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adjusted OR (95% CI)‡</td>
<td>1.1 (0.7-1.7)</td>
<td>27.2 (3.4-220.0)</td>
<td>.002</td>
<td>54.8 (7.0-442.5)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OR, odds ratio; SSPG, steady-state plasma glucose.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; glucose to millimoles per liter, multiply by 0.0555; triglyceride to millimoles per liter, multiply by 0.0113.

*Percentages are adjusted for missing data.
†Hypertension was defined as systolic blood pressure of 140 mm Hg or higher or diastolic blood pressure of 90 mm Hg or higher.
‡Logistic regression model to determine independent effect of being in tertile 2 or tertile 3 as compared with tertile 1, adjusted for body mass index, age, and sex.
§Defined as 2-hour glucose level of 140 mg/dL or higher during the 75-g oral glucose tolerance test.
Inability of Flegal et al. and Romero-Corral and colleagues to document a powerful adverse effect of moderate obesity cannot be entirely explained by better health care and/or the inability of BMI to identify individuals at risk for DM2 and CVD. Furthermore, because the insulin-resistant subgroup of moderately obese individuals benefits significantly more from weight loss, given the difficulty of achieving weight loss in overweight/obese individuals, it seems mandatory to identify those obese individuals who are at greatest risk for DM2 and CVD. In that context, we have presented evidence that the plasma concentration ratio of TG/high-density lipoprotein cholesterol is a good surrogate marker of insulin resistance, and a ratio of 3.0 or higher can help to identify moderately obese individuals who demonstrate both insulin resistance and the dyslipidemia characteristic of this defect in insulin action. Although this approach may not be useful in all races—and it and all surrogate markers of insulin resistance should be validated in minority groups—it is an example of a means by which obese individuals at high risk may be targeted for intensive efforts for risk reduction to prevent DM2 and CVD. Furthermore, because the insulin-resistant subgroup of moderately obese individuals benefits significantly more from weight loss than does the insulin-sensitive subgroup or the subgroup of non–insulin-resistant but equally obese individuals,22-26 it is an example of a means by which obese individuals at high risk may be targeted for intensive efforts for risk reduction to prevent DM2 and CVD. Furthermore, because the insulin-resistant subgroup of moderately obese individuals benefits significantly more from weight loss than does the insulin-sensitive subgroup or the subgroup of non–insulin-resistant but equally obese individuals,22-26 identification of this high-risk subgroup takes on even more clinical relevance. It has been debated whether obesity might represent a useful addition to the Framingham Risk score. The results of our study suggest that perhaps a marker of insulin resistance, rather than obesity, might be a more appropriate addition to this tool for identifying high-risk individuals.

Our conclusions must be tempered by the following caveats. First, because our subjects were largely white and because we studied only moderately obese individuals, our results may not apply to individuals who are nonwhite or who are overweight (BMI, ≥25.0 and <29.9) or severely obese (BMI, ≥35.0). Furthermore, our population consisted of volunteers who responded to advertisements for weight loss studies, and may thus not reflect the general population of obese individuals. In addition, we excluded individuals with known disease; therefore, our findings may not apply to less healthy obese individuals appearing to be at increased risk for DM2 and CVD must be viewed in the context of realizing that it is only this subset that benefits significantly from weight loss.22-26 Given the difficulty of achieving weight loss in overweight/obese individuals, it seems mandatory to identify those obese individuals who are at greatest risk for DM2 and CVD.36,37 In that context, we have presented evidence37 that the plasma concentration ratio of TG/high-density lipoprotein cholesterol is a good surrogate marker of insulin resistance, and a ratio of 3.0 or higher can help to identify moderately obese individuals who demonstrate both insulin resistance and the dyslipidemia characteristic of this defect in insulin action. Although this approach may not be useful in all races—and it and all surrogate markers of insulin resistance should be validated in minority groups—it is an example of a means by which obese individuals at high risk may be targeted for intensive efforts for risk reduction to prevent DM2 and CVD. Furthermore, because the insulin-resistant subgroup of moderately obese individuals benefits significantly more from weight loss than does the insulin-sensitive subgroup or the subgroup of non–insulin-resistant but equally obese individuals,22-26 identification of this high-risk subgroup takes on even more clinical relevance. It has been debated whether obesity might represent a useful addition to the Framingham Risk score.39 The results of our study suggest that perhaps a marker of insulin resistance, rather than obesity, might be a more appropriate addition to this tool for identifying high-risk individuals.

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individuals. Perhaps of even greater importance is that this was a cross-sectional study, with risk factors for CVD and DM2, rather than disease, as the outcomes. Thus, despite the fact that IGT was present in only 2% of the most insulin-sensitive third of the population compared with 42% in the most insulin-resistant third, it does not necessarily mean that the rate of developing DM2 would differ in these 2 groups. Obviously, the answers to all of these issues depend on the results of future prospective studies performed in different ethnic groups that include appropriate phenotyping at baseline.

CONCLUSIONS

We have demonstrated that there is considerable disparity in insulin resistance and associated metabolic risk factors for CVD and DM2 in moderately obese, otherwise healthy individuals (BMI, 30.0-34.9). The fact that not all obese individuals are at equal risk of developing DM2 and CVD may contribute to recent findings of an adverse effect on morbidity and mortality that was less than expected in moderately obese individuals.12,14 To a large extent, the effects of obesity on the increasing risk of DM2 and CVD are primarily because being overweight/obese makes it more likely that a given individual will be insulin resistant. In light of the obesity epidemic, it is essential that we optimally stratify (according to risk) individuals in whom aggressive early intervention may prevent DM2 and CVD. Rather than limit our risk evaluation to the identification of obesity alone, we should focus our efforts on identifying high-risk, insulin-resistant, obese individuals.

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REFERENCES


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**Correction**

In the Original Investigation by Wang et al titled “Outpatient Hypertension Treatment, Treatment Intensification, and Control in Western Europe and the United States,” published in the January 22 issue of the *ARCHIVES* (2007; 167:141-147), an error occurred in Figure 1 on page 144. In that figure, the order of countries in the key, to coordinate with the shading of the bars from darkest to lightest, should have appeared as follows: France (n=3009), Germany (n=3178), Italy (n=3316), Spain (n=3704), United Kingdom (n=2809), and United States (n=3750). The corrected figure is reproduced here with its legend.

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Cross-national differences in the use of 7 antihypertensive drug classes and combination drug therapy among treated hypertensive patients. ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; and CCB, calcium channel blocker.