Ethnic Differences in the Relationship between Adiponectin and Insulin Sensitivity in South Asian and Caucasian Women


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Received for publication 10 September 2007 and accepted in revised form 4 January 2008.
ABSTRACT

Objective: To assess whether lower adiponectin concentrations in South Asian (SA) Indians may be responsible for their greater degree of insulin resistance.

Research Design and Methods: Insulin-mediated glucose uptake and plasma total and HMW adiponectin concentrations were quantified in 52 women of SA and Caucasian (CAU) ancestry and compared.

Results: Mean (± SD) total (2965 ± 1278 vs. 4235 ± 160) and HMW (1001 ± 352 vs. 1591 ± 854) adiponectin (ng/mL) were lower (p<0.005) in SA. CAU-IR had lower (p<0.01) total (2665 ± 1040 vs. 5133 ± 1086) and HMW (987±479 vs.1935 ±838) adiponectin than CAU-IS, but there were no significant differences between IR and IS SA. HMW adiponectin did not differ between SA-IR and CAU-IR, but SA-IS had significantly lower adiponectin concentrations than CAU-IS.

Conclusions: Insulin resistance status is not associated with significantly lower levels of adiponectin in these SA women, in contrast to the CAU women.
Insulin sensitivity (1-3) and circulating adiponectin (3, 4) concentrations have been reported to be reduced in individuals of South Asian (SA) ancestry, leading to the theory that lower adiponectin values may explain the increased prevalence of insulin resistance in SA. However, previous cross-sectional studies have not controlled for differences in insulin resistance within and between ethnic groups, nor have prior comparisons of adiponectin between SA and Caucasians (CAU) included measurement of circulating high molecular weight (HMW) adiponectin, possibly the multimer most closely related to insulin sensitivity (5).

The current analysis was initiated to address both of these unresolved issues, and involved comparing total plasma and HMW adiponectin concentrations and related metabolic variables, in volunteers of CAU and SA ancestry, stratified into insulin resistant (IR) and sensitive (IS) subgroups.

RESEARCH DESIGN AND METHODS

The study population consisted of 52 women volunteers of SA (n=30) and CAU (n=22) ancestry. Participants were 30-65 years of age, nondiabetic, healthy, and not taking medication known to affect carbohydrate or lipid metabolism. After obtaining informed consent they were admitted to the General Clinical Research Center, and plasma glucose and lipid concentrations were determined after an overnight fast, as described previously (6). Steady state plasma glucose (SSPG) concentrations were determined by a modified version (7) of the insulin suppression test (IST, 8, 9). The results of the IST were used to stratify volunteers into IR and IS subgroups based on the results of a previous study (10) - subjects whose SSPG concentrations were in the upper 40% were classified as IR, and those in the lowest 40% as IS.

Plasma total and high molecular weight adiponectin levels were measured with an enzyme-linked immunosorbent assay (ELISA) established by Alpco Diagnostics (Salem, NH) (effective range of 0.075 to 4.8 ng/mL, samples were diluted appropriately), and a coefficient of variation < 15%.

Data are expressed as mean ± SD, and statistical significance (p<0.05) of comparisons were made by appropriate independent t-tests and chi square tests. All statistical analyses, including multivariate modeling, were performed using SPSS Version 13.0.

RESULTS

Table 1 compares variables in SA vs. CAU, as well as variables stratified into IR and IS subgroups. SA and CAU were not different in terms of age, body mass index (BMI), waist circumference (WC: only available on 77% of the SA and 95% of the CAU group and data not shown), or in most other variables measured, including SSPG, except for smoking and total cholesterol. Both total and HMW adiponectin concentrations were significantly lower in the SA group, despite having similar BMI and SSPG values.

Within subgroup comparisons show SSPG concentration (by selection) was higher in SA-IR than in SA-IS individuals, associated with higher TG and lower high density lipoprotein cholesterol (HDL-C) concentrations. There were no differences between the IR and IS subgroups of SA women in any other variables. Despite the difference in SSPG concentrations, total adiponectin, HMW adiponectin concentrations and
HMW/total adiponectin ratio (data not shown) were not significantly lower in SA-IR as compared to SA-IS individuals.

The relationship between SSPG and adiponectin concentrations was quite different in CAU individuals. Higher SSPG concentrations in the CAU-IR group were associated with significantly lower total and HMW adiponectin concentrations than in the CAU-IS group. Post hoc power analysis in the SA group suggests that this study had 99% power to detect an adiponectin difference of similar magnitude (2468 ng/ml), and 80% power to detect half the difference (1285 ng/ml) between SA-IR and SA-IS individuals that we observed between CAU-IR and CAU-IS individuals. We had limited power (36%) in the SA group to detect a quarter (702 ng/mL) of the observed difference in the IR versus IS Caucasian groups.

As BMI varied between the two CAU groups, total and HMW adiponectin concentrations were compared in the 8 CAU-IS individuals with the highest BMI values to 8 CAU-IR subjects with the lowest BMI values. When this was done, the BMI values in these subgroups were no longer significantly different (31.6 ± 4.7 vs. 29.0 ± 0.95 kg/m²), but the IR group still had significantly lower values for total (2665 ± 1040 vs. 5104 ± 1402 ng/mL, p=0.014) and HMW adiponectin (987±479 vs. 2017 ± 1012 ng/mL, p=0.02) concentrations. Comparable results were present when subjects were matched on WC instead of BMI.

These results suggest that total and HMW adiponectin concentrations vary as a function of SSPG concentrations in individuals of CAU ancestry, but not in SA women. Total and HMW adiponectin were not significantly different when comparing IR women in the two ethnic groups (p=0.85), whereas IS women of SA ancestry had significantly lower (p <0.001) total and HMW adiponectin concentrations when compared to CAU-IS individuals. In multivariate modeling, even after fully adjusting for age, BMI, WC, HDL-C, smoking status, ethnicity and insulin resistance status, the interaction term for insulin resistance status and ethnicity was a significant independent predictor (p = 0.04) of adiponectin levels. Similar results for these data were seen when insulin resistance was used as a continuous measure.

**DISCUSSION**

The data presented are consistent with previous studies demonstrating that adiponectin concentrations are lower in SA individuals (3, 4), and shows for the first time that this is also true for HMW adiponectin. However, these finding do not necessarily mean that lower total or HMW adiponectin concentration accounts for the increased prevalence of insulin resistance in SA individuals. The difference between the SA and CAU groups occurs because, in contrast to the presence of higher values in IS as compared to IR CAU women, total and HMW adiponectin concentrations were not higher in IS as compared to IR individuals of SA ancestry. This lack of a difference between the two SA groups occurred despite the fact that the SSPG concentrations were three-fold lower in the IS individuals. Thus, the ethnic difference in adiponectin concentrations is due to the fact that adiponectin concentrations remain low in SA, irrespective of the degree of insulin sensitivity; a finding that does not appear to support the idea that lower adiponectin concentrations are responsible for greater insulin resistance in SA. Finally, the lack of a relationship between insulin sensitivity and circulating adiponectin concentrations...
concentrations in SA women is not unique, and is similar to the disassociation between measures of insulin sensitivity and plasma adiponectin concentrations previously noted to occur in smokers (11), and following moderate amounts of weight loss (12), exercise training (13), and the administration of cis-retinoic acid (14).

These data indicate that both total and HMW adiponectin concentrations are lower in IR as compared to IS women of CAU ethnicity. Since these values are lower in SA women, irrespective of their degree of insulin sensitivity, it appears that the relationship between insulin resistance and total and HMW adiponectin concentrations is different in SA as compared to CAU women. The strength of our findings is the use of a specific accurate method (rather than an estimate based on surrogate markers) to quantify insulin action, and measurement of both total and HMW adiponectin.

An obvious weakness is the relatively few subjects enrolled in the study. As noted above, we had limited power (36%) to detect the 702 ng/mL that was actually observed between the SA IR and IS groups. However, it should be noted that this difference in adiponectin levels (702 ng/mL) between the SA IR and IS (16 vs.14 subjects) groups was considerably smaller than the statistically significant difference observed in adiponectin in the CA IR (n=8) and IS (n=14) groups (2468 ng/mL). Despite the greater number of subjects in the SA group, it is possible that our study was not sufficiently powered to assess the smaller difference noted in this group. However, the results of our multivariate modeling did reveal a significant interaction between ethnicity and insulin resistance status in predicting adiponectin levels, providing additional evidence suggesting that the relationship between insulin resistance and adiponectin varies by ethnicity.

Subject selection may also be considered a limitation. We chose to contrast the extremes of insulin resistance in each ethnic group, and thus compared subjects in the highest 40% and lowest 40% of the insulin resistance distribution. The decision to compare the most insulin resistant and insulin sensitive in each ethnicity allows us to more closely examine the interaction of insulin resistance and ethnicity on adiponectin levels. For this purpose, the most important contrast is between the IR and IS in each ethnic group, as it is already well known that SA generally have lower adiponectin levels than CAU (3, 4). Despite these potential limitations, these data suggest that the increased prevalence of insulin resistance in SA is not explained by lower total and HMW adiponectin concentrations, and emphasize that comparisons of adiponectin concentrations between different ethnic groups must be made between individuals of comparable degrees of insulin sensitivity.

ACKNOWLEDGEMENTS
This research was supported by the General Clinical Research Center at Stanford University (RR000070). Dr. Palaniappan received support from a National Institute of Child Health and Human Development K12 Award (5K12HD043452-02)
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13. Marcell TJ, McAuley KA, Traustadottir T and Reaven PD: Exercise training is not associated with improved levels of C-reactive protein or adiponectin. *Metabolism* 54:533-41, 2005
**TABLE 1.** Comparison of demographic and metabolic variables in South Asian and Caucasian women and insulin resistant and insulin sensitive subgroups of these races

<table>
<thead>
<tr>
<th></th>
<th>South Asians</th>
<th>Caucasians</th>
<th>p-value</th>
<th>South Asians</th>
<th>Caucasians</th>
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<th>Caucasians</th>
<th>p-value</th>
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<tr>
<td></td>
<td>(n=30)</td>
<td>(n=22)</td>
<td></td>
<td>IR (n=14)</td>
<td>IS (n=16)</td>
<td></td>
<td>IR (n=8)</td>
<td>IS (n=14)</td>
<td></td>
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<tr>
<td>Age (years)</td>
<td>45 ± 9</td>
<td>47 ± 8</td>
<td>0.3</td>
<td>44 ± 8</td>
<td>45 ± 11</td>
<td>0.7</td>
<td>47 ± 5</td>
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<td>BMI (kg/m²)</td>
<td>28.6 ± 2.6</td>
<td>28.5 ± 4.4</td>
<td>1.0</td>
<td>28.9 ± 2.1</td>
<td>28.3 ± 3</td>
<td>0.5</td>
<td>31.6 ± 4.7</td>
<td>26.8 ± 3.2</td>
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<td>Cigarette use (%)</td>
<td>0 (0)</td>
<td>8 (36)</td>
<td>&lt;0.001</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>--</td>
<td>2 (25)</td>
<td>6 (43)</td>
<td>0.4</td>
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<td>SBP (mm Hg)</td>
<td>117 ± 19</td>
<td>119.2 ± 14.7</td>
<td>0.603</td>
<td>114 ± 20</td>
<td>119 ± 19</td>
<td>0.4</td>
<td>123 ± 16</td>
<td>117 ± 15</td>
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<tr>
<td>DBP (mm Hg)</td>
<td>70 ± 10</td>
<td>71 ± 9</td>
<td>0.7</td>
<td>68.9 ± 10</td>
<td>70.7 ± 10.6</td>
<td>0.7</td>
<td>73 ± 9</td>
<td>70 ± 9</td>
<td>0.4</td>
</tr>
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<td>SSPG (mg/dl)</td>
<td>157 ± 7</td>
<td>138 ± 56</td>
<td>0.3</td>
<td>225 ± 54</td>
<td>98 ± 21</td>
<td>&lt;.0001</td>
<td>204 ± 24</td>
<td>100 ± 21</td>
<td>&lt;.001</td>
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<tr>
<td>FPG (mg/dl)</td>
<td>93 ± 10</td>
<td>93 ± 9</td>
<td>0.9</td>
<td>95 ± 11</td>
<td>91 ± 9</td>
<td>0.3</td>
<td>97 ± 9</td>
<td>91 ± 9</td>
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<tr>
<td>TC (mg/dl)</td>
<td>176 ± 3</td>
<td>198 ± 39</td>
<td>0.027</td>
<td>181 ± 38</td>
<td>172 ± 24</td>
<td>0.5</td>
<td>188 ± 30</td>
<td>204 ± 44</td>
<td>0.4</td>
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<tr>
<td>HDL-C (mg/dl)</td>
<td>108 ± 22</td>
<td>120 ± 32</td>
<td>0.094</td>
<td>43 ± 9</td>
<td>54 ± 11</td>
<td>0.009</td>
<td>50 ± 10</td>
<td>56 ± 11</td>
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<tr>
<td>LDL-C (mg/dl)</td>
<td>49 ± 11</td>
<td>54 ± 11</td>
<td>0.099</td>
<td>108 ± 29</td>
<td>107 ± 15</td>
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<td>110 ± 24</td>
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<tr>
<td>TG (mg/dl)</td>
<td>123 ± 72</td>
<td>123 ± 70</td>
<td>0.992</td>
<td>158 ± 82</td>
<td>93 ± 46</td>
<td>0.01</td>
<td>142 ± 64</td>
<td>113 ± 74</td>
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<td>Adiponectin (ng/ml)</td>
<td>2965 ± 1278</td>
<td>4235 ± 160</td>
<td>0.003</td>
<td>2589 ± 821</td>
<td>3293 ± 1525</td>
<td>0.1</td>
<td>2665 ± 1040</td>
<td>5133 ± 1086</td>
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<td>HMW Adiponectin (ng/ml)</td>
<td>1001 ± 352</td>
<td>1591 ± 854</td>
<td>0.001</td>
<td>908 ± 256</td>
<td>1083 ± 410</td>
<td>0.2</td>
<td>987 ± 479</td>
<td>1935 ± 838</td>
<td>0.009</td>
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</table>

BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic; SSPG=steady-state plasma glucose concentration; FPG=fasting plasma glucose; TC=total cholesterol; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; TG=triglyceride; HMW=high molecular weight