IS WAIST CIRCUMFERENCE AN ESSENTIAL COMPONENT OF THE METABOLIC SYNDROME?

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Short/Running Title: Obesity and metabolic syndrome

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The role of obesity for the metabolic syndrome definition is controversial (1,2) even though obesity is strongly related to insulin resistance (fasting insulin levels) (3), chronic inflammation (high-sensitive C-reactive protein [hsCRP] levels) (4), and coronary heart disease (CHD) (5). Obesity is considered an essential criterion by the International Diabetes Federation (IDF) (1) definition. However, the National Cholesterol Education Program-Adult Treatment Panel III (NCEP) definition accepts any three of five criteria (2). If obesity were essential, significant insulin and hsCRP levels and CHD risk would not be present in lean subjects. We examined this hypothesis in populations from Mexico City and Spain because of their distinct risk factor profile (more type 2 diabetes, low HDL cholesterol, and hypertriglyceridemia in Mexico City; more hypertension and hypercholesterolemia in Spain) (6).

RESEARCH METHODS AND PROCEDURES
The Mexico City Diabetes Study from Mexico City (7,8) and the Spanish Insulin Resistance Study (6) and Segovia Study (9) from Spain were designed as population-based studies. The two studies from Spain were fused in a single dataset, because protocols and one of the principal investigators (M.S-R.) were the same for both studies.

Nondiabetic subjects were considered eligible for analysis (in Spain, n = 1311; in Mexico City, n = 1918) due to the absence of a reliable surrogate of insulin resistance for diabetic subjects. Framingham risk equations were used to estimate CHD risk (10) for two reasons: absence of prospective data in Spain and small number of both CVD events and lean subjects with multiple metabolic disorders in Mexico City. Specific insulin was measured by radioimmunoassay in Mexico City (interassay coefficient of variation [CV], 3 - 7%) (Linco Research, St. Louis, MO) (7) and immunoassay in Spain (interassay CV, 9.1 - 11.4%) (Linco Research, St. Louis, MO); hsCRP, by immunoassay in Mexico City (interassay CV, 8.9%) (Calbiochem, Darmstadt, Germany) (8) and Spain (interassay CV, 3.3%) (Beckman Coulter, Fullerton, CA).

Components of the metabolic syndrome were defined according to the IDF criteria (1): hypertriglyceridemia (≥1.7 mmol/l), low HDL cholesterol level (<1.0 mmol/l in men, <1.3 mmol/l in women), high blood pressure (systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, or pharmacological treatment), and fasting hyperglycemia (≥5.6 mmol/l), and elevated waist circumference (≥94 cm in men, ≥80 cm in women).

We used one-way analysis of covariance to analyze insulin and hsCRP levels and Framingham risk estimates in order to account for the effect of age and sex. We performed analyses on the log-transformed values of insulin, and hsCRP levels and on the logit transformation of Framingham risk estimates to correct for skewness and kurtosis. These variables were then back-transformed to their natural units for presentation.

RESULTS
In Spain, 26.3% of subjects had ≥3 metabolic disorders; in Mexico City, 55.2% of subjects. Normal waist circumference was present in 5.2% of Spanish subjects with ≥3 metabolic disorders and 4.8% of Mexican counterparts.

Among subjects with one or more metabolic disorders, elevated waist circumference was directly related to the number of disorders (Table). Insulin and hsCRP levels and CHD risk estimates were not increased in subjects with elevated waist circumference after adjusting for number of
metabolic components except for insulin levels in Mexico City.

Among subjects with ≥3 metabolic disorders, age- and sex-adjusted estimates of CHD risk were not increased in subjects with elevated waist circumference (yes vs. no) (in Spain 14.5% [13.8 – 15.3] vs. 14.9% [11.6 – 19.1], p = 0.836; in Mexico City, 7.4% [7.1 – 7.6] vs. 9.7% [8.4 – 11.2], p <0.001), and neither were hsCRP levels (mg/l) (in Spain, 1.86 ± 0.11 vs. 1.72 ± 0.47, p = 0.734; in Mexico City, 1.73 ± 0.05 vs. 1.60 ± 0.22, p = 0.546). Insulin levels (µIU/ml) were not increased in subjects with elevated waist circumference (yes vs. no) in Spain (13.5 ± 0.4 vs. 11.1 ± 1.5, p = 0.171), but were increased in Mexico City (15.3 ± 0.3 vs. 12.5 ± 0.9, p = 0.004).

CONCLUSIONS
In the US population, 4.6% of men and 6.2% of women with normal weight have ≥3 metabolic disorders (11). Normal weight individuals may have insulin resistance. Insulin resistant, normal weight individuals have more CVD risk factors (12,13), greater CHD and diabetic risks (14-16), and more total and intra-abdominal fat than insulin sensitive, normal weight individuals (14). Similarly, absence of central obesity, as assessed by waist circumference, cannot rule out the presence of multiple metabolic disorders (17). Our results indicate that significant insulin and hsCRP levels and CHD risk estimates may be present in subjects with metabolic disorders other than obesity.

There is much support in the literature for the concept that waist circumference is not an independent predictor of CVD and that risk increases with number of components (18,19). The component most strongly associated with insulin resistance is obesity, but clustering of metabolic disorders greatly exceeds chance association in both obese and lean individuals (3). The cross-sectional design of this study limits our ability to reach conclusions. Nevertheless, our results suggest that the metabolic syndrome is not found exclusively in obese individuals.
REFERENCES


Table: Number of metabolic disorders, insulin and hsCRP levels, and CHD risk estimates stratified by waist circumference category in nondiabetic subjects with one or more metabolic disorders.

<table>
<thead>
<tr>
<th></th>
<th>Elevated waist circumference</th>
<th>Normal waist circumference</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
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<tr>
<td></td>
<td></td>
<td>956</td>
<td>187</td>
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<tr>
<td>Number of metabolic disorders *</td>
<td>2.21 ± 0.03</td>
<td>1.42 ± 0.07</td>
<td>&lt;0.001</td>
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<tr>
<td>Fasting insulin level (µIU/ml) *</td>
<td>11.2 ± 0.2</td>
<td>9.5 ± 0.5</td>
<td>0.001</td>
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<td>Fasting insulin level (µIU/ml) †</td>
<td>11.0 ± 0.2</td>
<td>10.5 ± 0.5</td>
<td>0.335</td>
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<tr>
<td>hsCRP level (mg/l) *</td>
<td>1.60 ± 0.05</td>
<td>1.46 ± 0.12</td>
<td>0.324</td>
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<tr>
<td>hsCRP level (mg/l) †</td>
<td>1.57 ± 0.05</td>
<td>1.58 ± 0.13</td>
<td>0.923</td>
</tr>
<tr>
<td>CHD risk estimate over 10 years (%) *</td>
<td>10.5 (10.2 – 10.9)</td>
<td>10.2 (9.3 – 11.1)</td>
<td>0.425</td>
</tr>
<tr>
<td>CHD risk estimate over 10 years (%) †</td>
<td>10.2 (9.8 – 10.5)</td>
<td>12.5 (11.5 – 13.2)</td>
<td>&lt;0.001</td>
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<tr>
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<th>Elevated waist circumference</th>
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<td></td>
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<td>1455</td>
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<td>Number of metabolic disorders *</td>
<td>2.83 ± 0.02</td>
<td>1.56 ± 0.06</td>
<td>&lt;0.001</td>
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<td>Fasting insulin level (µIU/ml) *</td>
<td>14.3 ± 0.1</td>
<td>9.4 ± 0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting insulin level (µIU/ml) †</td>
<td>13.5 ± 0.1</td>
<td>11.4 ± 0.3</td>
<td>&lt;0.001</td>
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<td>hsCRP level (mg/l) *</td>
<td>1.62 ± 0.05</td>
<td>1.35 ± 0.07</td>
<td>0.006</td>
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<td>hsCRP level (mg/l) †</td>
<td>1.57 ± 0.05</td>
<td>1.46 ± 0.09</td>
<td>0.349</td>
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<tr>
<td>CHD risk estimate over 10 years (%) *</td>
<td>6.1 (5.8 – 6.3)</td>
<td>5.6 (5.3 – 5.9)</td>
<td>0.027</td>
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<tr>
<td>CHD risk estimate over 10 years (%) †</td>
<td>5.5 (5.4 – 5.6)</td>
<td>7.8 (7.4 – 8.2)</td>
<td>&lt;0.001</td>
</tr>
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* Results adjusted for age and sex; † Results adjusted for age, sex, and number of components of the metabolic syndrome