Upper-Body Fat Distribution: A Hyperinsulinemia-Independent Predictor of Coronary Heart Disease Mortality

The Paris Prospective Study

Philippe Casassus, Annick Fontbonne, Nadine Thibult, Pierre Ducimetière, Jacques L. Richard, Jean-Roger Claude, Jean-Michel Warnet, Gabriel Rosselin, and Eveline Eschwege

The Paris Prospective Study is a long-term investigation of the factors predicting coronary heart disease in a large population of middle-aged men. The first follow-up examination involved 7,152 subjects, who were natives of metropolitan France and were free of any cardiovascular history. At that time, the usual cardiovascular risk factors and plasma insulin levels were recorded. An index of body fat distribution, the iliac-to-thigh ratio, was entered into the list of predictive variables, despite the fact that it had been measured 1 year before the first follow-up examination. After 11 years of mean follow-up, 129 of the men had died of coronary heart disease. Univariate analysis showed that the iliac-to-thigh ratio (p<0.0001) and plasma insulin level (both fasting [p<0.003] and 2-hour postload [p<0.02]), as well as the four major risk factors of coronary heart disease (age, smoking, blood pressure, and plasma cholesterol level) were significantly higher in subjects who died of coronary heart disease compared with those who had died of another cause or were alive at the end of follow-up. In multivariate stepwise logistic regression, the iliac-to-thigh ratio appeared as an independent predictor of coronary heart disease death, thereby causing the removal of fasting insulin level from the list of significant independent predictors. Nevertheless, in a model that entered 2-hour postload insulin in two classes (high or low), both the insulin level and iliac-to-thigh ratio were found as significant independent predictors. These results suggest that much of the already demonstrated predictive power of plasma insulin levels could be mediated through their association with upper-body fat distribution. However, 2-hour postload insulin concentration appears to improve the prediction and may denote the existence of metabolic abnormalities that are not entirely summarized by the type of fat distribution. (Arteriosclerosis and Thrombosis 1992;12:1387-1392)

KEY WORDS • epidemiology • Paris Prospective Study • risk factors • coronary heart disease mortality • body-fat distribution • plasma insulin level • alcohol • cigarette smoking

The fact that hyperinsulinemia is an independent predictor for coronary heart disease (CHD) mortality has been ascertained by three large prospective studies1-3 in the last 10 years. This result remained unchanged in the Paris Prospective Study over a longer follow-up period.4 This epidemiological finding is consistent with the hypothesis of cardiovascular risk attached to "syndrome X" as defined by Reaven,5 i.e., that hyperinsulinemia is linked to insulin resistance and potentially atherogenic abnormalities (high very low density lipoprotein triglyceride level, low high density lipoprotein cholesterol level, elevated blood pressure, and glucose intolerance). Stout6 also proposed some physiological hypotheses that could give credibility to a causal role of hyperinsulinemia per se.

In parallel during the last decade, upper-body fat distribution has emerged as another "new" independent risk factor for CHD and as a correlate of angiographically documented coronary atherosclerosis.7-10 This prospectively confirmed Jean Vague's observations, published in 1956,11 that women with cardiovascular complications or non-insulin-dependent diabetes tended to have android (upper-body) rather than gynoid obesity. Some epidemiological results suggest that android fat distribution is closely linked to hyperinsulinemia,12,13 and there are physiological hypotheses to explain this relation,14-16 mostly those involving free fatty acid metabolism.

Thus, it seemed interesting to compare the respective roles of hyperinsulinemia and upper-body fat distribution as predictors of CHD mortality. The Paris Prospective Study provided the means of performing this comparison, since baseline variables included measurements of both anthropometric indices and plasma insulin concentrations.
Methods

The present analysis was performed on data from the Paris Prospective Study, of which the general aims, detailed methodology, and population characteristics have been previously described. Only relevant data are summarized here. The inclusion session took place between 1967 and 1972.

The first of four consecutive annual follow-up examinations, performed during the period 1968–1973, involved 7,152 male employees of the Paris police, aged 43–54 years, who were included after having given consent to participate and who were assessed with respect to the following conditions: place of birth in metropolitan France (i.e., excluding Caribbean natives) and freedom from any cardiovascular history.

Among this population, the iliac and the thigh circumferences had been measured 1 year before, i.e., at the initial entry examination, in 7,141 subjects. Anthropometric indices were measured by three specially trained technicians, with the subjects in a standing position (the arms at rest along the body) and in apnea fixed at the midrespiratory phase. Iliac (at the iliac crest level) and left thigh (middle distance between the trochanter and external condylus) circumferences to the nearest millimeter were obtained with a flexible measuring tape. The ratio of these two circumferences, or the iliac-to-thigh ratio (ITR), was used as an estimate of fat distribution. The first annual examination included a 0–2-hour 75-g oral glucose tolerance test, with measurement of glucose levels in 7,003 men; of fasting plasma insulin level in (FPI) in 6,937 men; and of postload insulin (PI) levels in 6,889. The major CHD mortality risk factors were recorded: blood pressure, smoking habits, body mass index (BMI, weight/height², in kilograms per square meter), and plasma cholesterol and triglyceride levels. Diabetes prevalence was estimated by grouping subjects with newly diagnosed diabetes (2-hour plasma glucose equal to or above 11.1 mmol/l) and subjects with known diabetes. Also, because alcohol is supposed to increase intra-abdominal fat deposits, erythrocyte mean corpuscular volume (MCV), a marker of alcohol consumption, was calculated (MCV=hematocrit/red blood cell count, fl).

All deaths up to January 1, 1983 were counted (mean follow-up, 11 years), and the present analysis was performed at this point, where the predictive power of insulin concentrations was shown to be the strongest. Nevertheless, the major results were checked at the next reckoning point, January 1, 1987 (mean follow-up, 15 years). Deaths were systematically reported by the different administrative departments of the Paris Police Service. Complementary inquiries to families, health practitioners, and hospitals were organized to obtain information regarding the circumstances and causes of death. The underlying cause of death was ascertained and coded by a panel of physicians. Coding was performed according to the International Classification of Diseases (8th revision); in the present analysis, only deaths caused by CHD to a large extent (codes 410.0–414.9, myocardial infarction; 795.0, sudden death; 782.0–782.9, 427.0, 427.1, and 519.1, heart failure) were considered.

For statistical analyses, subjects of the baseline cohort with missing values for one or more variables used in the test were excluded. All testing methods were the usual parametric ones. Multivariate analyses of the predictive power of baseline variables toward CHD death used the stepwise logistic-regression model. In the case of a nonlinear relation between a variable and CHD mortality, the variable was either logarithmically transformed or categorized to ensure a better fit to statistical modeling. Four interaction variables were created by calculating the product of ITR with FPI and 2-hour postload insulinemia (2hPI), either continuously or in two classes, and were expressed in standard deviation units. Because of the narrow age range of the population, no adjustment for age was made for univariate analyses. However, age was systematically included in multivariate analyses. All statistical analyses were done using the SAS statistical package.

Results

At 11-year follow-up, 129 men of the initial cohort had died of CHD. They differed significantly on all

<table>
<thead>
<tr>
<th>Variable</th>
<th>CHD death (n=129)</th>
<th>Other (n=7,023)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.9±2.1</td>
<td>48.4±2.0</td>
<td>0.006</td>
</tr>
<tr>
<td>Cigarettes (No/day)</td>
<td>13±10</td>
<td>9±10</td>
<td>&lt;0.0001</td>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>157±30</td>
<td>144±21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.8±3.3</td>
<td>26.0±3.3</td>
<td>0.008</td>
</tr>
<tr>
<td>Iliac-to-thigh ratio</td>
<td>1.8±0.15</td>
<td>1.77±0.15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cholesterol level (mmol/l)</td>
<td>6.0±1.0</td>
<td>5.6±1.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglyceride level (mmol/l)*</td>
<td>1.79±0.02</td>
<td>1.24±0.02</td>
<td>&lt;0.0004</td>
</tr>
<tr>
<td>Fasting glucose level (mmol/l)</td>
<td>5.9±1.0</td>
<td>5.7±0.8</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>2-Hour glucose level (mmol/l)</td>
<td>6.4±3.0</td>
<td>5.8±2.2</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>Diabetes prevalence (%)</td>
<td>7.87</td>
<td>3.96</td>
<td>0.004</td>
</tr>
<tr>
<td>Fasting insulin level (pmol/l)*</td>
<td>85±14</td>
<td>71±14</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>2-Hour insulin level (pmol/l)*</td>
<td>277±17</td>
<td>233±16</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Mean corpuscular volume (fl)</td>
<td>98.6±6.0</td>
<td>96.7±5.3</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CHD, coronary heart disease.

*These values were computed in log values and then transformed into the original units.
Fat Distribution, Hyperinsulinemia, and Coronary Risk

3.55

FIGURE 1. Bar graph of 11-year coronary heart disease (CHD) mortality rates according to classes of iliac-to-thigh ratio (ITR) below or above the median of 1.77 and of fasting plasma insulin (FPI) below or above the lower limit of the fifth quintile of 108 pmol/l. Number of deaths, from left to right, are 40/3,122, 38/2,174, 6/632, and 39/998.

baseline variables listed in Table 1 from those who were alive or who had died of another cause. CHD mortality was significantly associated with older age; higher cigarette use; and higher levels of blood pressure, BMI, plasma cholesterol, triglyceride, fasting and postload blood glucose, and PI. Moreover, subjects who died of CHD had a significantly higher ITR (p<0.0001) and a more elevated MCV (p<0.0001). All of these variables were interrelated to some extent. Specifically, ITR was correlated with FPI (r=0.22, p<0.0001) and 2hPI (r=0.18, p<0.0001).

To study the interrelation of fat distribution and insulin concentration to CHD risk, two classes were created for each variable: for ITR, classes were above and below 1.77, which was the median of the distribution, and for FPI and 2hPI levels, the classes were the last quintile versus first four quintiles, in accordance with previous reports.4,9 The “high-ITR” group had approximately twice the annual CHD mortality rate of the “low-ITR” group: 2.22% versus 1.15% (p<0.0002). Figures 1 and 2 illustrate CHD mortality in relation to ITR classes and FPI and 2hPI levels. Each factor, when isolated, either had little influence on CHD death rates or was inoperative (e.g., FPI). However, when a high ITR was observed concurrently with a high PI level, CHD mortality was 4.1 times higher (for FPI) and 2.4 times higher (for 2hPI) than in the respective low-ITR group. In Figure 2, CHD mortality rate appeared more or less equal in the high-ITR-low-2hPI group and the low-ITR-high-2hPI group; this result indicates the possibility that both variables are independent CHD risk factors.

The results of several multivariate analyses are given in Table 2. The four major risk factors of CHD were added as explanatory variables to ITR and PI levels with four modalities (FPI taken continuously, FPI in two classes as defined above, 2hPI taken continuously, and 2hPI in two classes as defined above). In all four models, ITR appeared as an independent predictor of CHD death. FPI level, whether continuous or dichotomized, did not reach statistical significance as an independent predictor of CHD death when ITR was taken into account. However, the dichotomized (but not the continuous) 2hPI level retained a significant predictive power together with ITR. BMI, plasma glucose, and triglyceride levels never reached a significant probability value in any of the models. The results were similar at 15-year follow-up.

FIGURE 2. Bar graph of 11-year coronary heart disease (CHD) mortality rates according to classes of iliac-to-thigh ratio (ITR) below or above the median of 1.77 and of 2-hour postload plasma insulin (2h PI) below or above the lower limit of the fifth quintile of 452 pmol/l. Number of deaths, from left to right, are 38/3,226, 42/2,329, 9/512, and 35/811.
To complete this analysis, a multivariate stepwise logistic regression was performed with an interaction variable between insulin (in the four previously described modalities) and ITR. In no model was the interaction variable entered, and it never affected the coefficient for ITR and insulin.

To find some explanation for the independent predictive roles of 2hPI level and fat distribution, we estimated by the ITR is greater enhanced the predictive power.

Discussion

The present analysis confirms a previous analysis of the Paris Prospective Study that showed an association of 2hPI level with CHD mortality risk. However, upper-body fat distribution estimated by the ITR is shown here to be another powerful independent predictor of CHD mortality. It even replaces FPI, which predicted CHD death in a model that did not control for body-fat distribution. This result is in accordance with those of other prospective studies, which demonstrated a link between various measures of upper-body fat and cardiovascular outcomes. Moreover, the data set of the Paris Prospective Study allowed us to separate the predictive power of upper-body fat distribution and of PI levels, a question that had been raised because of the physiological relations between these two parameters.

The ratio of waist-to-hip circumferences is more frequently used than the ITR as an estimate of fat distribution. In the Paris Prospective Study, waist and hip circumferences were not initially measured in contrast to those of the iliac and thigh. Nevertheless, ITR can be considered a good marker of upper-body obesity. This ratio is clearly related to BMI (Table 4) and to skinfold thicknesses. Within this male population the iliac circumference must be influenced more by differences in fat deposition rather than by different skeletal characteristics. Moreover, if differential muscle mass in the thigh can also be suspected to contribute to CHD prediction with this index, we found that iliac circumference alone was strongly predictive of CHD death (p<0.0001), whereas the thigh circumference was not (p=0.30). Using the ratio of the two circumferences greatly enhanced the predictive power.

The correlation of hyperinsulinemia and upper-body (or male-type) fat distribution is well established and was also confirmed in the present study. In contrast to what had been found previously, FPI did not reach a significant probability value as a predictor of CHD in multivariate analyses after ITR was entered in the model. Because it has been hypothesized that hyperinsulinemia...
Tabu: 4. Mean Values (±SD) of Baseline Variables According to Quintiles of Iliac-to-Thigh Ratio at Entry to Follow-up and Univariate Correlation Coefficients Between These Variables and Iliac-to-Thigh Ratio

<table>
<thead>
<tr>
<th>Quintiles of iliac-to-thigh ratio</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.7±2</td>
<td>48.8±2</td>
<td>48.9±2</td>
<td>48.9±2</td>
<td>48.9±2</td>
<td>0.02</td>
<td>NS</td>
</tr>
<tr>
<td>Cig (No./day)</td>
<td>7.8±10</td>
<td>9±10</td>
<td>9±10</td>
<td>10.2±10</td>
<td>10.8±11</td>
<td>0.08</td>
<td>0.0001</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>137±18</td>
<td>140±20</td>
<td>145±22</td>
<td>147±22</td>
<td>154±26</td>
<td>0.22</td>
<td>0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.3±3</td>
<td>25.3±3</td>
<td>26.2±3</td>
<td>27.0±3</td>
<td>28.0±4</td>
<td>0.33</td>
<td>0.0001</td>
</tr>
<tr>
<td>Chol (mmol/l)</td>
<td>5.29±0.93</td>
<td>5.52±1.06</td>
<td>5.58±1.06</td>
<td>5.68±1.08</td>
<td>5.73±1.08</td>
<td>0.12</td>
<td>0.0001</td>
</tr>
<tr>
<td>FPI (pmol/l)</td>
<td>65.9±50</td>
<td>78.2±57</td>
<td>91.1±65</td>
<td>103.2±100</td>
<td>119.7±86</td>
<td>0.22</td>
<td>0.0001</td>
</tr>
<tr>
<td>2-Hour postload insulin (pmol/l)</td>
<td>229.4±179</td>
<td>279.6±251</td>
<td>329.8±294</td>
<td>372.8±323</td>
<td>415.9±387</td>
<td>0.18</td>
<td>0.0001</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>96.5±5</td>
<td>96.8±5</td>
<td>96.8±5</td>
<td>97.2±6</td>
<td>97.4±6</td>
<td>0.05</td>
<td>0.0007</td>
</tr>
<tr>
<td>Diabetes prevalence (%)</td>
<td>0.99</td>
<td>1.9</td>
<td>3.38</td>
<td>5.68</td>
<td>8.89</td>
<td>0.12</td>
<td>0.0001</td>
</tr>
<tr>
<td>CHD mortality (%)</td>
<td>0.67</td>
<td>1.35</td>
<td>2.07</td>
<td>1.98</td>
<td>3.91</td>
<td>0.06</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Cig: cigarette smoking; SBP, systolic blood pressure; BMI, body mass index; ITR, iliac-to-thigh ratio; Chol, plasma cholesterol level; FPI, fasting plasma insulin level; MCV, mean corpuscular volume; CHD, coronary heart disease.

Hyperinsulinemia is a feature of syndrome X as described initially by Reaven and that this syndrome could be the explanation of the epidemiological finding of the relation between insulin levels and CHD, then it is probably correct to think, as was suggested by Zimmet, that upper-body fat distribution should be added to the metabolic syndrome. This latter variable, as another specific metabolic effect, such as a possible insulin resistance, is a feature of syndrome X as described initially by Reaven, and that this syndrome could be the explanation of the epidemiological finding of the relation between insulin levels and CHD.

However, a second important finding of this analysis is the independent predictive power of dichotomized 2hPI level even when a marker of fat distribution and the four major coronary risk factors (blood pressure, smoking, age, and plasma cholesterol level) are controlled for in the model. This latter result could be consistent with a direct effect of the highest PI levels on hepatic insulin resistance first and hyperinsulinemia second. Our results support the idea of a greater predictive power for ITR, which may involve alcohol consumption and cigarette use, because they increase with increasing ITR, whereas they decrease with increasing PI level.

Thus, our analysis confirms that hyperinsulinemia and male-type fat distribution are two interrelated predictors of CHD mortality. This may be explained in part because both factors are markers of a metabolic syndrome associated with insulin resistance. However, some part of their predictive power seems to be independent. Pathophysiological explanations are still needed to account for this fact.

References
17. Roselin GE, Assan R, Yalow RS, Berson SA: Separation of antibody bound and unbound peptide hormone labelled with
iodine 131 by talcum powder and precipitates silica. Nature 1966;
212:355–357
P Casassus, A Fontbonne, N Thibult, P Ducimetière, J L Richard, J R Claude, J M Warnet, G Rosselin and E Eschwège

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