Insulin Resistance and the Relationship of a Dyslipidemia to Coronary Heart Disease

The Framingham Heart Study

Sander J. Robins, Asya Lyass, Justin P. Zachariah, Joseph M. Massaro, Ramachandran S. Vasan

Objective—The goal of this study was to examine the effect of insulin resistance (IR) in subjects without diabetes on the relationship of a dyslipidemia with high triglycerides and low high-density lipoprotein cholesterol (HDL-C) to the development of coronary heart disease (CHD).

Methods and Results—Lower and higher fasting plasma HDL-C and triglyceride concentrations (defined at the study population median) and presence or absence of IR (defined by upper quartile homeostatic model assessment values) were related to the development of myocardial infarction or CHD death in Framingham Heart Study participants without diabetes or a history of CHD (n = 2910) attending the 1991 to 1995 examination. During follow-up (mean, 14 years), 128 participants experienced an incident CHD event. With Kaplan-Meier plots, the incidence of CHD was significantly greater with than without IR at either the lowest HDL-C or the highest triglycerides (P < 0.001). In multivariable Cox models adjusted for major CHD risk factors, including waist circumference, only subgroups with IR had a significantly higher incidence of CHD. Compared with a reference group without IR and without higher-than-median HDL-C or lower-than-median triglycerides, the hazard ratio (HR) for incident events was significant with only IR and a lower HDL-C (HR 2.83, P < 0.001) or higher triglycerides (HR 2.50, P < 0.001). These findings were similar in men and women.

Conclusion—In this community-based sample exclusive of diabetes, incident CHD risk associated with plasma HDL-C or triglycerides was significantly increased only in the presence of IR. (Arterioscler Thromb Vasc Biol. 2011;31:00-00.)

Key Words: coronary heart disease ■ epidemiology ■ insulin resistance ■ lipids ■ risk factors

A dyslipidemia consisting of high triglycerides and low high-density lipoprotein cholesterol (HDL-C) is a widely recognized lipid pattern that is frequently associated with the development of coronary heart disease (CHD). However, in contrast to plasma low-density lipoprotein cholesterol (LDL-C), the levels of triglycerides and HDL-C that are associated with increased CHD are less sharply defined and may to a great extent depend on a number of other closely related risk factors that are frequently associated with this dyslipidemia or underlie its origins. Both high triglycerides and low HDL-C are widely known to be associated with obesity and other features that define the metabolic syndrome (MetS).1 However, it is possible that much of the cardiovascular (CV) disease that is associated with the MetS may be explained by the presence of insulin resistance (IR),1,2 and there is compelling, long-standing evidence that both high triglycerides and a low plasma HDL-C are a frequent consequence of IR.2–4

With IR, studies in humans have shown that there is increased synthesis and secretion of triglyceride-rich, very low-density lipoprotein (VLDL) particles by the liver,5 an increase in plasma triglycerides,3–5 enrichment of plasma HDL particles by triglycerides, and more active catabolism of triglyceride-rich HDL-C.6 In population studies, IR has been shown to independently predict both the development of a high-triglyceride, low-HDL-C dyslipidemia7 and new CV disease in large general populations.8–11

Reaven and colleagues have long argued that the basis for a high CHD-risk state that is frequently but not invariably associated with obesity is based on the presence of IR, and they have demonstrated in well-defined, relatively small subgroups that an increase in plasma triglycerides or the ratio of plasma triglycerides to HDL-C is strongly predictive of IR.12,13 In this present analysis, we have sought to broaden the scope of these observations by assessing the effect of IR in the population-wide Framing-
ham Heart Study (FHS) on the prevalence of dyslipidemia and the extent to which both low and high levels of triglycerides and HDL-C might predict the development of CHD events in the presence of IR but the absence of diabetes. In this study, we especially sought to determine the effect of IR-related dyslipidemia on the development of CHD independent of other conventional CHD risk factors and, most particularly, independent of abdominal obesity that characterizes the MetS.

Methods

Study Design and Population Characteristics

The design of the Framingham Offspring Study has been previously described in detail. Briefly, 5124 children of the original FHS and spouses of those children are screened for CV disease and related risk factors by periodic questionnaires, review of relevant health records, and regular examinations every 4 to 5 years. Data obtained from the Offspring examination 5 (undertaken from January 1991 to June 1995) were used for this analysis. Of the 3799 participants attending examination, 5377 were excluded for prevalent CV disease, 211 for the presence of diabetes, 137 for missing clinical or laboratory variables, and an additional 164 for treatment with a lipid-modifying drug. Exclusion of diabetes was made to avoid a disproportionate contribution of glucose to the homeostasis model assessment (HOMA) measurement of IR (see below). The final sample for this study included 2910 participants (1289 men, 1621 women). This study was approved by the Boston University Medical Center Institutional Review Board, and written consent was obtained from each participant.

Laboratory Measurements

Venous blood was drawn after a 12-hour fast. Plasma cholesterol and triglyceride concentrations were measured by enzymatic methods. HDL-C after precipitation of apolipoprotein B-containing lipoproteins with dextran-sulfate magnesium, glucose using hexokinase reagent, and insulin by radioimmunoassay as total immunoreactive insulin (Coat-A-Count Insulin, Diagnostic Products, Los Angeles, CA). A measure of IR, the HOMA-IR, was calculated as described by Matthews et al.14 and IR was defined by the upper quartile of HOMA-IR in sex-pooled participants without diabetes.

Outcome Events, Covariate Definitions, and Follow-up

Incident CHD events consisted of the first occurrence of nonfatal or fatal myocardial infarction (MI) or CHD death. Incident events were those that occurred from the time of a Participant’s 5th FHS Offspring examination to 12/2009 or for a period that averaged 13.5 years for men, 14.3 years for women, and 14.0 years for the entire group.

To obtain comparable-sized groups with lower and higher values of HDL-C and triglycerides, low HDL-C and high triglycerides were defined at the baseline examination to be below and above the median value of each lipid class. Median values for HDL-C in the entire population, men, and women were 49, 42, and 56 mg/dL, respectively, and for triglycerides, the values were 112, 121, and 108 mg/dL, respectively. The covariate of non-HDL-C was calculated as the difference between total cholesterol and HDL-C. The covariate of nontriglyceride-associated cholesterol was calculated by subtracting from the total cholesterol an average amount of cholesterol approximated by the Friedewald formula15 to be associated with fasting triglyceride-rich lipoproteins (ie, VLDL), where cholesterol is approximated to be 20% of the fasting concentration of triglycerides. Other covariates included binary variables for the presence of cigarette smoking, as defined by an average of 1 or more cigarettes per day; alcohol consumption, as defined by the number of drinks/week; drug therapy for hypertension; hormone replacement therapy; waist circumference; and the continuous covariates of age in years and systolic blood pressure in mm Hg.

Table 1. Population Characteristics at Baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men (n=1289)</th>
<th>Women (n=1621)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>53.8 (9.8)</td>
<td>54.1 (9.8)</td>
<td>0.39</td>
</tr>
<tr>
<td>Body mass index, mean (SD), kg/m²</td>
<td>28.0 (4.1)</td>
<td>26.2 (5.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist, mean (SD), cm</td>
<td>98.6 (10.8)</td>
<td>85.6 (13.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood pressure, mean (SD), mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>77.1 (9.7)</td>
<td>72.6 (10.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic</td>
<td>127.5 (16.5)</td>
<td>121.9 (19.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking, current, n, %</td>
<td>252 (19.6)</td>
<td>313 (19.3)</td>
<td>0.87</td>
</tr>
<tr>
<td>Alcohol use, drinks/week, n (SD)</td>
<td>7.9 (9.6)</td>
<td>3.6 (5.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, mean (SD), mg/dL</td>
<td>201.3 (34.4)</td>
<td>205.0 (36.8)</td>
<td>0.007</td>
</tr>
<tr>
<td>LDL-C, mean (SD), mg/dL</td>
<td>128.9 (30.9)</td>
<td>122.9 (33.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C, mean (SD), mg/dL</td>
<td>44.0 (11.5)</td>
<td>57.3 (15.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides, mean (SD), mg/dL</td>
<td>149.9 (103.6)</td>
<td>123.9 (69.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-HDL-C, mean (SD), mg/dL</td>
<td>157.4 (35.8)</td>
<td>147.6 (38.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nontriglyceride cholesterol, mean (SD), mg/dL</td>
<td>171.4 (34.0)</td>
<td>180.2 (34.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting glucose, mean (SD), mg/dL</td>
<td>96.9 (8.9)</td>
<td>92.8 (9.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting insulin, mean (SD), pmo/L</td>
<td>9.9 (8.6)</td>
<td>7.6 (6.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>HOMA-IR, n, %</td>
<td>422 (32.7)</td>
<td>320 (19.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension therapy, n, %</td>
<td>183 (14.2)</td>
<td>215 (13.3)</td>
<td>0.47</td>
</tr>
<tr>
<td>Hormone replacement therapy, n, %</td>
<td>276 (17.1)</td>
<td>327 (20.4)</td>
<td>0.035</td>
</tr>
</tbody>
</table>

*Nontriglyceride cholesterol is defined as cholesterol not associated with fasting triglyceride-rich lipoproteins or as approximated by the Friedewald formula.15 calculated as 20% of the concentration of fasting plasma triglycerides minus the concentration of total cholesterol.16

†HOMA-IR was calculated using the equation of Matthews et al14 and is defined here as the upper quartile of the sex-pooled population without diabetes.

Statistical Analysis

Demographic and clinical characteristics were compared by sex using a 2-sample t test for continuous variables and a χ² test for categorical variables. Composite 4-level variable models combining the levels of HOMA-IR and the level of HDL-C were created, where categories were 0=normal HOMA-IR, high HDL-C; 1=high HOMA-IR, high HDL-C; 2=normal HOMA-IR, low HDL-C; and 3=high HOMA-IR, low HDL-C. Similarly, another composite variable was created combining the levels of HOMA with the levels of triglycerides as follows: 0=normal HOMA-IR, low triglycerides; 1=high HOMA-IR, low triglycerides; 2=normal HOMA-IR, high triglycerides; and 3=high HOMA-IR, high triglycerides. In all analyses, 0 was the reference category. Hazard ratios (HR) and 95% CIs were calculated for Cox proportional hazard models that were used to predict the risk of CHD with the composite HOMA-IR+HDL-C variable, adjusting first for age only and then for the following covariates: age, systolic blood pressure, hypertension treatment, diabetes, cigarette smoking, alcohol use, hormone use,
waist circumference, and non-HDL-C. Sex-specific Cox proportional hazard models were similarly used to predict the risk of CHD with the composite HOMA-IR+triglyceride variable, adjusting first for age only and then for the covariates shown above for the HOMA-IR+HDL-C variable but substituting nontriglyceride-associated cholesterol for non-HDL-C.

For a secondary analysis with again CHD as an outcome, we used Cox proportional hazard models containing (1) continuous HDL-C and dichotomous HOMA as risk factors, and (2) log-transformed continuous triglycerides and dichotomous HOMA as risk factors (adjustment in each model was made for those same covariates listed above). We further assessed the significance of HDL-C–HOMA and log triglycerides–HOMA interactions, respectively, in each model. Given that in both models the interaction terms approached significance (P=0.064), the analysis was then stratified by the level of HOMA, assessing the relationships of continuous HDL-C and continuous triglycerides to predict incident CHD.

Kaplan-Meier plots, unadjusted for covariates, were used to show the cumulative incidence of CHD events by the levels of the HOMA-IR + HDL-C variable and the HOMA-IR + triglyceride variable. Log rank tests were performed to assess the difference in the incidence of CHD by the level of these composite variables. Relationships between HOMA-IR values and plasma insulin and the continuous variables of age, systolic blood pressure, waist circumference, body mass index (BMI), and plasma values of glucose, HDL-C, triglycerides, and LDL-C were determined using Pearson correlations.

In all analyses, a 2-tailed probability value of <0.05 was considered statistically significant. SAS software, version 9.1 (SAS Institute, Cary, NC), was used for all analyses.

Results
Baseline characteristics of the study group are summarized for men and women in Table 1. Of note, men, on average, had higher values of BMI, waist circumference, blood pressure, plasma glucose, LDL-C, and triglycerides and lower values of HDL-C compared with women. Plasma insulin values were higher in men, and the frequency of IR, defined by the upper quartile of HOMA-IR, was also greater in men. In this population, continuous values for HOMA-IR were significantly correlated with age (r=0.10), plasma insulin levels (r=0.98), glucose (r=0.52), HDL-C (r=−0.34), triglycerides (r=0.36), LDL-C (r=0.07), systolic blood pressure (r=0.30), BMI (r=0.50), and waist circumference (r=0.49), all with P<0.001.

As shown in Figure 1A, across a quartile range of increasing plasma HDL-C concentrations, IR was most prevalent in both men and women at the lowest values of HDL-C and least prevalent with HDL-C levels that were highest (P<0.001 for IR trend in both sexes). In contrast, as shown in Figure 1B, with increasing quartiles of triglycerides, IR increased in prevalence in both men and women (P<0.001 for IR trend in both men and women). At the lowest quartile of HDL-C or highest quartile of triglycerides, approximately 50% of men and 40% of women had IR.

During a mean follow-up period of 14 years (maximum, 18.4 years), there were 128 new cases of MI or CHD death (83 in men and 45 in women). The incidence of a CHD event was determined in the presence versus absence of IR, with the entire sample divided at the median of HDL-C and the median of triglyceride values into lower and higher range groups. In Table 2, the incidence rates of CHD are shown with and without IR, at higher and lower levels of HDL-C and triglycerides, for the entire study sample and also for men and women separately. HDL-C values tended to be lower and triglyceride values higher with IR than without IR. For the entire study group, the 10-year incidence of CHD appeared generally greater at both lower and higher ranges of either plasma HDL-C or triglycerides in the presence of IR as compared with the absence of IR.

As shown by Kaplan-Meier plots (Figure 2), the cumulative incidence of a CHD event was greatest for groups with IR and either lowest HDL-C or highest triglyceride values and was significantly different from the CHD incidence rates for the groups with comparable levels of these lipids but without IR. All log rank tests were statistically significant (P<0.001).

The relationship of CHD incidence to the presence and absence of IR across a full range of HDL-C and triglyceride levels is shown by Cox proportional hazards regression analysis in Table 3. All Cox models were constructed with a reference subgroup without IR and without either the highest
levels of HDL-C or the lowest levels of triglycerides. Models were adjusted for age alone and also for multiple commonly associated risk factors. Included in these adjustments are non-HDL-C, with HDL-C as the variable of interest, and nontriglyceride-related cholesterol, for triglycerides as the variable of interest.

As shown in Table 3, in fully adjusted analysis in the entire study group, the risk of a CHD event was significantly increased with IR at the low levels of HDL-C (ie, below the median) compared with the reference group (no IR and HDL-C above the median). In contrast, in the absence of IR, the risk of a CHD event for low HDL-C was not significantly increased compared with high HDL-C. Results in men and women separately closely approximated the results of the entire group, showing an increase in CHD risk compared with the reference category in the presence of IR and a low HDL-C but not at higher levels of HDL-C or in the absence of IR.

Results for triglycerides (Table 3) show in a fully adjusted analysis that compared with a reference group without IR and without a low level of triglycerides, there was a significant increase in the risk of CHD events with IR and high triglycerides. In contrast, in the absence of IR, even with triglycerides in the same high range, the risk of CHD events was not increased. These results were similar in men and women with, again, a significant increase in the risk of CHD events associated with the presence of IR and high triglycerides as compared with those with no IR and triglycerides below the median.

Secondary analysis using continuous HDL-C, dichotomous HOMA (presence versus absence of IR), and their interaction has shown the interaction approaching significance ($P=0.064$). Therefore, analysis assessing the relationship of HDL-C to CHD risk was stratified by the level of HOMA. For those with IR, increasing continuous HDL-C was significantly associated with decreasing risk of CHD ($HR=0.94$, $P<0.0001$). For those without IR, continuous HDL-C was also significantly associated with CHD risk ($HR=0.98$, $P=0.049$), although both the magnitude of the effect was

<table>
<thead>
<tr>
<th>Group</th>
<th>Lipid Level</th>
<th>IR</th>
<th>N</th>
<th>HDL-C or Triglyceride, mean±SD</th>
<th>CHD Events/Person-Years of Follow-Up</th>
<th>Age-Adjusted 10-Year Cumulative Incidence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>≥ Median</td>
<td>No</td>
<td>1283</td>
<td>62.2±13.2</td>
<td>33/12307</td>
<td>0.01 (0.007, 0.021)</td>
</tr>
<tr>
<td></td>
<td>≤ Median</td>
<td>No</td>
<td>883</td>
<td>42.3±7.8</td>
<td>32/8347</td>
<td>0.02 (0.010, 0.031)</td>
</tr>
<tr>
<td></td>
<td>≥ Median</td>
<td>Yes</td>
<td>227</td>
<td>55.1±13.3</td>
<td>12/2057</td>
<td>0.04 (0.010, 0.060)</td>
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<tr>
<td></td>
<td>≤ Median</td>
<td>Yes</td>
<td>513</td>
<td>38.4±7.8</td>
<td>51/4732</td>
<td>0.07 (0.043, 0.093)</td>
</tr>
<tr>
<td>Men</td>
<td>≥ Median</td>
<td>No</td>
<td>543</td>
<td>53.0±9.7</td>
<td>23/5164</td>
<td>0.02 (0.009, 0.038)</td>
</tr>
<tr>
<td></td>
<td>≤ Median</td>
<td>No</td>
<td>323</td>
<td>35.4±4.5</td>
<td>17/2970</td>
<td>0.03 (0.008, 0.048)</td>
</tr>
<tr>
<td></td>
<td>≥ Median</td>
<td>Yes</td>
<td>151</td>
<td>48.4±6.6</td>
<td>12/1347</td>
<td>0.06 (0.016, 0.095)</td>
</tr>
<tr>
<td></td>
<td>≤ Median</td>
<td>Yes</td>
<td>270</td>
<td>33.8±5.07</td>
<td>31/2442</td>
<td>0.07 (0.038, 0.110)</td>
</tr>
<tr>
<td>Women</td>
<td>≥ Median</td>
<td>No</td>
<td>740</td>
<td>69.0±11.1</td>
<td>10/7142</td>
<td>0.01 (0.001, 0.013)</td>
</tr>
<tr>
<td></td>
<td>≤ Median</td>
<td>No</td>
<td>560</td>
<td>46.3±6.4</td>
<td>15/5376</td>
<td>0.02 (0.004, 0.029)</td>
</tr>
<tr>
<td></td>
<td>≥ Median</td>
<td>Yes</td>
<td>76</td>
<td>68.4±13.2</td>
<td>0/710</td>
<td>. . .</td>
</tr>
<tr>
<td></td>
<td>≤ Median</td>
<td>Yes</td>
<td>234</td>
<td>43.6±7.1</td>
<td>20/2290</td>
<td>0.06 (0.026, 0.092)</td>
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<tr>
<td>Triglycerides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>&lt; Median</td>
<td>No</td>
<td>1246</td>
<td>78.5±20.0</td>
<td>34/11939</td>
<td>0.02 (0.008, 0.023)</td>
</tr>
<tr>
<td></td>
<td>≥ Median</td>
<td>No</td>
<td>920</td>
<td>173.7±75.4</td>
<td>31/8714</td>
<td>0.02 (0.008, 0.027)</td>
</tr>
<tr>
<td></td>
<td>&lt; Median</td>
<td>Yes</td>
<td>200</td>
<td>89.6±17.1</td>
<td>11/1849</td>
<td>0.04 (0.013, 0.076)</td>
</tr>
<tr>
<td></td>
<td>≥ Median</td>
<td>Yes</td>
<td>540</td>
<td>173.7±75.4</td>
<td>52/4940</td>
<td>0.06 (0.039, 0.086)</td>
</tr>
<tr>
<td>Men</td>
<td>&lt; Median</td>
<td>No</td>
<td>523</td>
<td>82.0±21.8</td>
<td>24/4924</td>
<td>0.02 (0.009, 0.038)</td>
</tr>
<tr>
<td></td>
<td>≥ Median</td>
<td>No</td>
<td>344</td>
<td>198.7±92.8</td>
<td>16/3210</td>
<td>0.03 (0.008, 0.047)</td>
</tr>
<tr>
<td></td>
<td>&lt; Median</td>
<td>Yes</td>
<td>120</td>
<td>91.5±18.7</td>
<td>8/1090</td>
<td>0.05 (0.005, 0.088)</td>
</tr>
<tr>
<td></td>
<td>≥ Median</td>
<td>Yes</td>
<td>302</td>
<td>235.1±125.7</td>
<td>35/2699</td>
<td>0.08 (0.041, 0.110)</td>
</tr>
<tr>
<td>Women</td>
<td>&lt; Median</td>
<td>No</td>
<td>724</td>
<td>75.9±18.2</td>
<td>10/7014</td>
<td>0.01 (0.001, 0.019)</td>
</tr>
<tr>
<td></td>
<td>≥ Median</td>
<td>No</td>
<td>577</td>
<td>158.8±58.0</td>
<td>15/5504</td>
<td>0.01 (0.002, 0.020)</td>
</tr>
<tr>
<td></td>
<td>&lt; Median</td>
<td>Yes</td>
<td>80</td>
<td>86.7±14.0</td>
<td>3/759</td>
<td>0.04 (0.000, 0.084)</td>
</tr>
<tr>
<td></td>
<td>≥ Median</td>
<td>Yes</td>
<td>240</td>
<td>197.1±85.9</td>
<td>17/2240</td>
<td>0.05 (0.017, 0.074)</td>
</tr>
</tbody>
</table>

IR was defined by the upper quartile of HOMA-IR levels in subjects without diabetes. Mean values±SD of HDL-C and triglycerides are shown as mg/dL.
lower. Similarly, the interaction between HOMA and log triglycerides on CHD risk also approached significance ($P = 0.052$); therefore, the analysis assessing the relationship of triglycerides to CHD risk was also stratified by the level of HOMA. In those with IR, increased log triglycerides were significantly associated with increased CHD risk (HR = 1.95, $P = 0.018$). In those with no IR, the association was not significant (HR = 0.62, $P = 0.15$).

![Figure 2. Unadjusted Kaplan-Meier curves showing the cumulative incidence of CHD events in the entire study sample (N=2910) with and without IR and with lower or higher values of fasting plasma HDL-C (A) and with lower or higher values of plasma triglycerides (TG) (B). IR was defined in the entire study group without diabetes by the upper quartile of HOMA-IR values. Lower or higher values of plasma HDL-C and triglycerides were defined at the median plasma concentration of these values for the combined study group of men and women (ie, at 49 mg/dL for HDL-C and at 112 mg/dL for triglycerides). Mean HDL-C and triglyceride values for each of these subgroups (with and without IR) are shown in parentheses for each curve.](image)

Table 3. Incidence of CHD by Presence or Absence of IR at Lower or Higher Values of Plasma HDL-C or Triglycerides

<table>
<thead>
<tr>
<th>Group</th>
<th>IR</th>
<th>HDL-C*</th>
<th>HR (95% CI)</th>
<th>Age-Adjusted P Value</th>
<th>HR (95% CI)</th>
<th>Multivaried† P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>Yes</td>
<td>≤ Median</td>
<td>3.60 (2.32, 5.59)</td>
<td>&lt;0.001</td>
<td>2.83 (1.70, 4.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>≥ Median</td>
<td>1.73 (0.89, 3.38)</td>
<td>0.11</td>
<td>1.46 (0.73, 2.91)</td>
<td>0.29</td>
</tr>
<tr>
<td>Men</td>
<td>No</td>
<td>≤ Median</td>
<td>2.82 (1.64, 4.84)</td>
<td>&lt;0.001</td>
<td>2.29 (1.24, 4.26)</td>
<td>0.009</td>
</tr>
<tr>
<td>Women</td>
<td>Yes</td>
<td>≤ Median</td>
<td>2.03 (1.01, 4.09)</td>
<td>0.048</td>
<td>1.73 (0.82, 3.65)</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>≤ Median</td>
<td>1.32 (0.70, 2.46)</td>
<td>0.39</td>
<td>1.09 (0.56, 2.10)</td>
<td>0.81</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>IR</th>
<th>Triglycerides</th>
<th>HR (95% CI)</th>
<th>Age-Adjusted P Value</th>
<th>HR (95% CI)</th>
<th>Multivaried† P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>Yes</td>
<td>≤ Median</td>
<td>3.01 (1.94, 4.66)</td>
<td>&lt;0.001</td>
<td>2.50 (1.52, 4.11)</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td>Yes</td>
<td>≥ Median</td>
<td>1.75 (0.89, 3.47)</td>
<td>0.11</td>
<td>1.60 (0.79, 3.25)</td>
<td>0.19</td>
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<tr>
<td>Men</td>
<td>No</td>
<td>≤ Median</td>
<td>1.18 (0.72, 1.92)</td>
<td>0.51</td>
<td>0.96 (0.58, 1.57)</td>
<td>0.86</td>
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<tr>
<td>Women</td>
<td>Yes</td>
<td>≤ Median</td>
<td>2.62 (1.55, 4.42)</td>
<td>&lt;0.001</td>
<td>2.30 (1.27, 4.15)</td>
<td>0.006</td>
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<tr>
<td></td>
<td>Yes</td>
<td>≤ Median</td>
<td>1.50 (0.67, 3.33)</td>
<td>0.32</td>
<td>1.35 (0.58, 3.12)</td>
<td>0.48</td>
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<td></td>
<td>No</td>
<td>≤ Median</td>
<td>1.02 (0.54, 1.91)</td>
<td>0.96</td>
<td>0.84 (0.44, 1.60)</td>
<td>0.59</td>
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<tr>
<td></td>
<td>Yes</td>
<td>≤ Median</td>
<td>3.91 (1.73, 8.58)</td>
<td>&lt;0.001</td>
<td>3.08 (1.23, 7.75)</td>
<td>0.02</td>
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<tr>
<td></td>
<td>Yes</td>
<td>≤ Median</td>
<td>2.37 (0.65, 8.62)</td>
<td>0.19</td>
<td>2.44 (0.64, 9.37)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

*Median values of HDL-C were 49 mg/dL for all subjects, 42 mg/dL for men, and 56 mg/dL for women. Median values of triglycerides were 112 mg/dL for all subjects, 121 mg/dL for men, and 108 mg/dL for women.

†Multivariable-adjusted models were adjusted for age, sex, systolic blood pressure, waist circumference, active smoking, alcohol consumption, treatment of hypertension, hormone replacement therapy, for non-HDL-C with HDL-C as the variable of interest, and for non–triglyceride-related cholesterol with triglycerides as the variable of interest.
Discussion

In our large, community-based sample, we have found in analyses excluding diabetes and adjusted for conventional CHD risk factors, as well as the abdominal obesity that characterizes the MetS, that in the presence of IR lowest values of HDL-C, as well as highest values of triglycerides, were associated with an increased incidence of MI and CHD death. Conversely, we have found that in the absence of IR, comparably high levels of triglycerides or low levels of HDL-C that ordinarily might be expected to be associated with an increase in CHD were not significant risk factors for CHD. In this study, an increase in CHD with IR occurred similarly in men and women with either lower HDL-C or higher triglyceride values, whereas in the absence of IR, neither lower HDL-C values nor higher triglyceride values were associated with an increase in CHD events.

Our findings generally support multiple studies by Reaven and colleagues4,12,16,17 demonstrating in selected subgroups that IR and not the obesity that is associated with lower HDL-C and higher triglyceride values best defines a high-CHD risk state. Furthermore, our present results appear to conform to more general studies showing that IR (or hyperinsulinemia as a surrogate marker for IR) will independently predict the development of CV disease in general populations,8–11 as well as in populations with diabetes,18 Although there is evidence that high fasting insulin concentrations, independent of body weight, will predict the development of decreased HDL-C and increased triglyceride concentrations,7 there appears to be just 1 population study, other than the present one, that has demonstrated differences in CV disease outcomes in relation to different concentrations of HDL-C and triglycerides in the presence and absence of IR. In that population, the placebo-treated group of men in the Veterans Affairs HDL-Intervention Trial19 with uniformly low values of plasma HDL-C (<40 mg/dL), the 5-year incidence of a major CV event was significantly greater in the presence of IR than without IR at both higher and lower levels of either HDL-C or triglycerides.

There is substantial experimental evidence that both higher levels of plasma triglycerides and lower levels of HDL-C can be a consequence of IR. Studies in humans have shown that with IR, there is increased synthesis and secretion of triglyceride-rich VLDL particles by the liver.5 These studies have further shown that there is a strong linear relationship between hepatic triglyceride production and plasma triglyceride levels that is dependent on circulating insulin levels but is independent of obesity.3 With increased plasma triglycerides, HDL-C levels are also frequently low, and 2 mechanisms, both involving the activity of triglyceride lipases, have been proposed to account for this reduction in HDL-C as a consequence of IR. By 1 process, IR may result in increased cholesteryl ester transport protein–mediated triglyceride exchange between VLDL and HDL, enriching HDL with triglycerides and making these particles more susceptible to catabolism by hepatic lipase.6,20 By another process, IR may decrease plasma lipoprotein lipase21 that ordinarily catalyzes the catabolism of plasma VLDL and, as a by-product of VLDL catabolism, generates new material for HDL formation from the surface components of plasma VLDL.22,23

As in other studies in predominantly white, general populations24,25 our results in the FHS show that IR, as defined by the fourth quartile of HOMA-IR, was less frequent in women (19.7%) than in men (32.7%). This sex-related difference in the prevalence of IR is consistent with a generally lower prevalence of an intraabdominal (or visceral) pattern of obesity in women then in men.26,27 Because, as we show, the frequency of both lower plasma values of HDL-C and higher values of triglycerides is increased with IR, it seems possible that women may less frequently have both lower levels of HDL-C and higher levels of triglycerides then men because of a less frequent presence of IR.

In our present analysis, we did not attempt to assess the extent to which the MetS, in comparison with IR, might predict the development of new CHD. This comparison has previously been published in the FHS population but for a broader end point of CV disease that included cerebrovascular and peripheral vascular events, as well as coronary disease.28 In that study, MetS predicted outcomes as well as or better than the HOMA-IR measure of IR. However, given the negative to highly variable relationship of low HDL-C to, especially, the incidence of ischemic stroke,29,30 the apparent superiority of MetS in predicting events in that analysis might be explained by the inclusion of non-CHD cases. Furthermore, although waist circumference (or BMI) is a key distinguishing feature of the MetS and is significantly correlated with insulin levels, the strength of this relationship is relatively weak. In our current analysis, with correlations of HOMA-IR to waist circumference and BMI of 0.49 and 0.50, respectively, only 23% to 25% of the variability in HOMA-IR levels was explained by waist or BMI measurements, which closely conforms to comparisons in 2 large series of healthy individuals,17,31 where insulin-mediated plasma glucose concentrations were related to body weight.

It has been suggested because of the strong association of a high triglyceride or low HDL-C with IR that an increased ratio of triglycerides to HDL-C might provide a clinically useful surrogate measure of IR.12,13 However, in a previous analysis from the FHS, the ratio of triglycerides to HDL-C was shown to lack both substantial precision and sensitivity compared with a high HOMA-IR measurement in the prediction of new-onset CHD.32 The combination of an increased waist circumference and high triglycerides33 has also been suggested as a marker of increased visceral fat and a clinically useful index of increased CHD risk. Although this index was proposed as a surrogate measure for a triad of laboratory measurements that included hyperinsulinemia,34 there appears to be no evidence in any general population that this more readily available index will perform as well in assessing CHD risk as directly measuring plasma insulin levels.

Implications, Strengths, and Limitations of Findings

Our results should not be interpreted to implicate IR as directly causal for a CHD event, with or without a dyslipidemia. It is clear from a number of studies that IR is associated with a heightened inflammatory and prothrombotic state associated with abnormalities in a number of laboratory markers of vascular injury, thrombosis, and fibrinolysis that
may result in clinical disease.35 Although we have adjusted for essentially all of the elements of the MetS and found a fourth quartile value of HOMA-IR to independently predict the development of CHD in conjunction with lower values of HDL-C and higher values of triglycerides, our results should not also imply that the MetS, as a clinical construct, is not useful in identifying individuals who may be at higher risk for a CHD event. Our findings were related to only the traditionally “hard” CV end points of confirmed MI or CHD death. Consequently, although our primary outcome (in sex-merged analysis) may appear to be based on relatively low numbers of events, these events were selected to exclude both the possibly less definitive end point of angina and the end point of stroke, which has an uncertain relationship to dyslipidemia.

As a limitation of this study, we recognize that our analysis was constructed to obtain groups of approximately equally sizes, with lower and higher values of HDL-C and triglycerides that were similar in both men and women. We therefore did not use values for these lipids that are more commonly used in clinical practice to characterize low- and high-risk CHD states. We further recognize that although our results were obtained in a large community-based population, not selected for particular traits, the FHS population is predominantly a white population, and the results obtained in this analysis may differ in other ethnic groups.

Conclusions
Our present study provides clear evidence that for the end points of MI and CHD death, the risk associated with lower and higher levels of HDL-C and triglycerides can be more precisely defined in conjunction with a measure of IR. Although fasting plasma insulin measurements have yet to be standardized, as we show in this analysis, even a locally defined measure of IR that is used in conjunction with lower levels of HDL-C and higher levels of triglycerides is apt to more accurately identify an individual at risk for CHD than the use of these lipid measures alone.

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This research was supported through the National Institute of Health/National Heart, Lung, and Blood Institute (Contract N01-HC-25195).

Disclosures
None.

References


Insulin Resistance and the Relationship of a Dyslipidemia to Coronary Heart Disease: The Framingham Heart Study
Sander J. Robins, Asya Lyass, Justin P. Zachariah, Joseph M. Massaro and Ramachandran S. Vasan

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이상지질혈증은 인슐린 저항성이 있는 사람에서만
관상동맥질환의 위험인자이다

문 인 경 교수
서울대학교 보라매병원 내분비내과

Summary

목적
이 연구는 당뇨병이 없는 사람에서 인슐린 저항성
성이 고형성지질혈증과 저 HDL 콜레스테롤 농도(HDL-
C)를 갖는 이상지질혈증과 관상동맥질환 발
생의 관계에 어떠한 효과를 나타내는지 알아보고
자 하였다.

방법 및 결과
1991년에서 1995년까지 검진에 참여한
Framingham Heart Study 참가자들 중에서
당뇨병이나 관상동맥질환의 병력이 없는 대상자(n=2,910명)에서 낮거나 높은 공복 혈당 HDL-C와
중성지방 농도, 그리고 인슐린 저항성의 유무는
심근경색증 발생 또는 관상동맥질환으로 인한
사망과 관련이 있었다. 평균 14년의 추적관찰
중 128명에서 새로 관상동맥질환이 발생하였고,
Kaplan-Meier plot으로 분석해 본 결과 관상동맥
질환의 발생률은 HDL-C가 가장 낮은 군에서
중성지방이 가장 높은 군에서 모두 인슐린 저항성
이 있는 군이 없는 군에 비해 유의하게 높았다
(P<0.001) 다변량 Cox 모델에서 하리둘레를 포함한
주요 관련성의 사례의 위험인자들을 고정하였을
때 단지 인슐린 저항성이 있는 하위군에서만
관상동맥질환의 발생이 유의하게 높았다. 인슐린
저항성이 없고 중앙값보다 높은 HDL-C 혹은
중앙값보다 낮은 중성지방 농도를 가진 기준군과
비교하여 보았을 때, 인슐린 저항성이 있고 낮은
HDL-C를 갖는 군(HR 2.83, P<0.001) 또는 인슐린
저항성이 있고 높은 중성지방 농도를 갖는 군
(HR 2.50, P<0.001)에서 새로운 사전 발생의
위험도의 증가가 유의하였다. 이런 결과는 남성과
여성에서 비슷하였다.

결론
이 지역사회 기반 연구에서 당뇨병을 배제한
대상군에서 혈장 HDL-C 혹은 중성지방과
관련된 새로운 관상동맥질환의 발생 위험은
인슐린 저항성이 있음에 유의하게 증가하였다.
인슐린 저항성과 심혈관질환의 연관성에 대해서는 잘 알려져 있고, 인슐린 저항성이 있을 때, 중성지방이 증가하고 HDL-C가 감소하는 이상지질 혈증의 발생 역시 잘 알려져 있다. 인슐린 저항성 시 나타나는 이런 이상지질혈증은 또한 심혈관질환의 위험 인자이므로 인슐린 저항성 자체가 심혈관질환의 발생 위험을 증가시키는 것인지 혹은 인슐린 저항성 시 반반되는 이상지질혈증이 심혈관질환의 위험을 증가시키는 것인지에 대해서는 잘 규명되어 있지 않다. 홍양주문에 고객 지방산 유전자 CD36 유전자 조절 미우스 모델을 이용하였다. CD36이 없는 마우스는 저량 조리에서 지방산을 TG의 형태로 저장하지 못하므로 혈액 내 지방산과 TG가 증가되며 근육 내 지방산의 총적이 없기 때문에 인슐린 저항성이 없고 심혈관질환의 발생도 감소한다.

본 연구에서는 당뇨병과 관상동맥질환이 없는 대상군에서 평균 14년간의 정형적인 연구를 통해 HOMA-IR을 통해 평가한 인슐린 저항성의 유무가 관상동맥질환 발생에 중요한 인자임을 보여 주었다. HDL-C가 낮거나 중성지방이 높더라도 인슐린 저항성이 있는 경우에는 인슐린 저항성이 없고 이상지질혈증이 없는 기준군과 관상동맥질환의 발생 위험의 차이가 없었다. 반대로, 통계적

**Figure 1.** (A) 인슐린 저항성 유무 및 HDL-C 농도에 따른 관상동맥질환의 누적 발생률. (B) 인슐린 저항성 유무 및 중성지방 농도에 따른 관상동맥질환의 누적 발생률.
로 유의하지는 않았으나 Figure 1에서 알 수 있는 것처럼 인슐린 저항성이 있는 군에서는 이상지질혈증의 유무에 따라 관심등맥혈관의 발생 위험에 많은 차이가 있었다. 이 연구는 당뇨병이 없는 사람을 대상으로 했기 때문에 중성지방의 농도가 높은 군에서도 평균값이 173.7mg/dL밖에 되지 않아 고성장성방혈증과 관심등맥혈관의 발생이 관찰되지는 않았지만, 인슐린 저항성 유무에 따라 이상지질혈증에 대한 차별화된 치료 전략이 필요할 것으로 생각된다.

가장 정확한 인슐린 저항성의 측정 방법은 정상혈당 상인 인슐린 클러프법이지만, 많은 시간이 소요되고 간척기간이 오래 걸리기 때문에 여러 대규모연구가 대량으로 적용하기는 어렵다. 인슐린 저항성에 대한 합성 모델인 HOMA-IR과 인슐린 감수성에 대한 정량적 기준인 QUICKI가 클러프법 대신 대규모연구를 연구에 많이 이용되고 있다. HOMA-IR은 공복 혈장 인슐린 농도와 포도당 농도로부터 다음과 같은 식으로 계산한다.

\[
\text{HOMA-IR} = \left( \text{공복인슐린} \times \text{공복혈당} \right) / 22.5
\]

일반적으로 HOMA-IR=1로 정정기준치이며, 인슐린저항성에 대한 전략적 기준치는 없다. 외국의 여러 연구에서 대체로 HOMA-IR 2.6-2.7 이상이면 인슐린 저항성이 있다고 보고하고 있고, 한국인의 대상으로 한 연구에서는 HOMA-IR 2.4-2.7 정도가 대사중후군을 증가시키는 기준이며, 제2형 당뇨병 환자 혹은 비당뇨병인의 75 피실판에 해당하는 값이 3.0 정도로 보고하고 있다. 본 논문에서는 HOMA-IR의 수치를 계속하고 있는 임상적

REFERENCES