Glucose-Cholesterol Interaction Magnifies Coronary Heart Disease Risk for Hypertensive Patients

Hillel W. Cohen, Susan M. Hailpern, Michael H. Alderman

Abstract—Elevated cholesterol and glucose are known independent risk factors for coronary heart disease. This study examines whether an adverse synergistic interaction of cholesterol and glucose magnifies coronary heart disease risk among treated hypertensive patients. Subjects were hypertensive patients (n=6672) in a worksite treatment program, with entry fasting glucose <6.99 mmol/L (126 mg/dL) and total cholesterol <6.72 mmol/L (260 mg/dL) observed for mean 5.6±4.5 years follow-up (range 0.5 to 21.7 years). Outcome events were incident hospitalization or death due to coronary heart disease. Cox proportional hazard models were constructed for the whole sample to assess interaction and then stratified by fasting glucose categories with thresholds defined either at impaired fasting glucose (≥6.11 mmol/L [110 mg/dL]) or upper quartile (≥5.72 mmol/L [103 mg/dL]). An interaction product term of total cholesterol and fasting glucose as continuous variables significantly (P=0.009) improved a Cox proportional hazards model, adjusting for total cholesterol, fasting glucose, and other coronary heart disease risk factors. Adjusted hazard ratios for 3 upper total cholesterol categories (with total cholesterol <5.17 mmol/L [200 mg/dL] as reference) in the higher fasting glucose stratum were more than double the corresponding hazard ratios in the lower stratum, whether using impaired fasting glucose or upper quartile fasting glucose as the cut point. These results suggest that an adverse synergistic interaction between glucose and cholesterol magnifies coronary heart disease risk associated with total cholesterol among hypertensive patients, raising the possibility that coronary heart disease prevention might be enhanced if cholesterol intervention criteria were modified by glucose status. (Hypertension. 2004;43:1-6.)

Key Words: coronary disease • risk factors • hypercholesterolemia • glucose • hypertension

Hypercholesterolemia and hyperglycemia are well-established independent risk factors for coronary heart disease (CHD) and are often observed among hypertensive patients with metabolic syndrome. 1-3 While the confluence of these risk factors has been noted, the question arises whether interaction among them can lead to an adverse synergism that magnifies risk.

The pioneering Framingham risk models based on additive effects of independent risk factors have been the prevalent paradigm to explain cardiovascular disease (CVD) risk.4-6 While CVD outcome studies typically use regression models that take into account multiple factors, these models usually explain only a fraction of observed events—a discrepancy that continues to inspire searches for novel factors.7,8 It is possible that the interaction of known factors, with an adverse, synergistic effect, may account for at least part of the difference between the adverse outcomes predicted by multivariate risk models and the larger number that occur.

To date, we have reported evidence of such interaction in 2 very different populations. Analysis of the Honolulu Heart Project® data on almost 7000 Japanese-American men revealed an interaction of the upper quartile of baseline postprandial serum glucose with total cholesterol (TC) for 10-year CHD mortality and morbidity.9 A separate study10 observed a statistically significant association of the interaction of TC/high-density lipoprotein cholesterol (HDL-C) ratio and the upper quartile of hemoglobin A1c (HbA1c) with atherosclerotic raised lesions from autopsy data collected by the Pathobiological Determinants of Atherosclerosis in Youth (PDAY)11 study of 1530 individuals ≥35 years old who died from causes unrelated to CVD.

The current study examines the hypothesis that an interaction with glucose magnifies the risk of CHD events associated with cholesterol among treated hypertensive patients.

Methods

Design, Study Sample, and Measures

This observational cohort study used data prospectively collected from 1978 to 1999 by the Worksite Hypertension Program (Worksite), a union-sponsored, nurse-managed, and doctor-supervised systematic hypertension treatment program in New York City. Worksite participants had an untreated blood pressure (BP) ≥160/95 mm Hg or were taking antihypertensive medications at screening. Entry BP thresholds were modified to ≥140/90 mm Hg in 1993 in response to recommendations of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V).13

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Detailed methods of Worksite have been described previously, and data from this program have been used for many published studies.14–17

Inclusion criteria for the current study included serum fasting glucose (FG) and TC measures at entry and at least 6 months of follow-up. Those at entry with a history of CVD were excluded from these analyses, as were those with TC ≥6.72 mmol/L (260 mg/dL), FG ≥6.99 mmol/L (126 mg/dL), or history of diabetes. The remaining 6672 participants constituted the study sample.

Outcome Measures and Follow-Up

Principle discharge diagnoses from hospital charts and primary cause of death from death certificates were recorded using the International Classification of Diseases (ICD-9). 18 Outcome events were hospitalizations or deaths due to an incident CHD event (ICD-9 codes 410 to 414), or an angioplasty or coronary bypass procedure while enrolled in Worksite or within 6 months after leaving the program. Follow-up time was calculated from date of entry to date of event or, if no event, to date of last visit (mean = 5.6 ± 4.5 years; range 0.5 to 21.7).

Statistical Analyses

FG at entry was dichotomized using the threshold 6.11 mmol/L (110 mg/dL), currently accepted for impaired fasting glucose (IFG). TC was categorized into groups I through IV (I, <5.17 mmol/L [200 mg/dL]; II, 5.17 to 5.68 mmol/L [200 to 219 mg/dL]; III, 5.69 to 6.20 mmol/L [220 to 239 mg/dL]; and IV, 6.21 to 6.71 mmol/L [240 to 259 mg/dL]) coinciding with traditional thresholds and also dichotomized as groups II–IV versus I. A Cox proportional hazards model was constructed including TC and FG as continuous variables, adjusting for sex; ethnicity (white versus non-white); and entry measures of age, systolic BP, body mass index (BMI), smoking, left-ventricular hypertrophy, and prior BP treatment with incident CHD as the outcome event. A product term of TC×FG was added to the model to represent interaction. The null hypothesis of no interaction was tested using the change in likelihood ratio test (LR) statistic. The HRs in the upper glucose strata were more than twice those of the corresponding categories in the lower glucose strata.

In sensitivity analyses, statistically significant interactions were observed for models with dichotomous glucose and dichotomous cholesterol if subjects with FG ≥6.99 mmol/L (126 mg/dL), history of diabetes, or those with cholesterol ≥6.72 mmol/L (260 mg/dL) were included. However, the

### TABLE 1. Entry Characteristics by Blood Glucose

<table>
<thead>
<tr>
<th>Blood Glucose</th>
<th>&lt;6.11 mmol/L (≤110 mg/dL) n=5870</th>
<th>≥6.11 mmol/L (≥110 mg/dL) n=792</th>
<th>Total n=6672</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>63.2%</td>
<td>67.8%</td>
<td>63.8%</td>
<td>0.013</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.5 ± 9.6</td>
<td>54.2 ± 8.9</td>
<td>51.8 ± 9.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoker</td>
<td>20.2%</td>
<td>18.5%</td>
<td>20.0%</td>
<td>0.252</td>
</tr>
<tr>
<td>White</td>
<td>33.3%</td>
<td>34.4%</td>
<td>33.4%</td>
<td>0.532</td>
</tr>
<tr>
<td>Treated blood pressure</td>
<td>42.0%</td>
<td>46.3%</td>
<td>42.5%</td>
<td>0.024</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.3±4.6</td>
<td>29.1±4.9</td>
<td>28.4±4.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>11.5%</td>
<td>10.8%</td>
<td>11.5%</td>
<td>0.813</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>150±20.1</td>
<td>153±20.7</td>
<td>151±20.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>96±15.8</td>
<td>96±11.4</td>
<td>96±15.3</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L [mg/dL])</td>
<td>5.38±0.78</td>
<td>5.44±0.77</td>
<td>5.39±0.78</td>
<td>0.043</td>
</tr>
<tr>
<td>Blood glucose (mmol/L [mg/dL])</td>
<td>5.15±0.50</td>
<td>6.42±0.25</td>
<td>5.30±0.63</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Categorical variables presented as %, with P values calculated by χ². Continuous variables presented as mean±SD, with P values calculated by t test between the glucose categories.

Results

Table 1 presents baseline characteristics of the 6672 Worksite participants who constituted the study sample, stratified by IFG. Those with IFG, compared with those with normal glucose, were significantly more likely to be male, older, and taking antihypertensive medication. This group also had higher mean systolic BP, BMI, and TC. Diastolic BP, smoking status, ethnicity, and left ventricular hypertrophy (LVH) were similar.

In a Cox proportional hazards model with incident CHD as outcome, adding an interaction product term of continuous glucose with continuous TC significantly (P=0.009) improved the model that included both main effects terms along with age, sex, ethnicity, smoking status, systolic BP, LVH, BP treatment at entry, and BMI.

Age-sex adjusted rates for 4 TC categories are shown in Table 2 stratified separately by IFG and upper quartile FG. Using the IFG threshold, CHD rates in the higher glucose stratum were substantially higher in the 3 upper TC categories but not for TC <5.17 mmol/L (200 mg/dL). Results were similar using the upper quartile FG threshold. Table 3 shows hazard ratios for these TC categories and the upper 3 categories, combined with TC <5.17 mmol/L (200 mg/dL) as reference and adjusting for other cardiovascular risk factors. At each of the 3 upper TC categories and for the 3 categories combined, point estimates of the HRs in the upper glucose strata were more than twice those of the corresponding categories in the lower glucose strata.

In sensitivity analyses, statistically significant interactions were observed for models with dichotomous glucose and dichotomous cholesterol if subjects with FG ≥6.99 mmol/L (126 mg/dL), history of diabetes, or those with cholesterol ≥6.72 mmol/L (260 mg/dL) were included. However, the
interaction term of the 2 continuous variables was no longer statistically significant when these upper glucose or cholesterol values were included.

Discussion

The principal finding of this study is that elevated FG magnifies the relative risk (estimated by HRs) of CHD associated with TC in a population of treated hypertensive patients without frank diabetes. This was observed for both IFG and upper quartile thresholds of FG.

This finding is consistent with a biological interaction of glucose and cholesterol, although a merely statistical interaction cannot be excluded. A biological interaction would have the clinical implication that optimal cholesterol goals may differ according to levels of glucose. While a clinical trial would be necessary to determine whether using glucose to inform cholesterol management would improve outcomes, these findings support the usefulness of such a trial.

There is reason to believe that the interaction we observed has a biological basis. It is widely believed that the oxidation of low-density lipoprotein cholesterol (LDL-C) plays an important part in atherogenesis, and it is possible that excess circulating glucose may facilitate peroxidation of cholesterol. It has also been observed that diabetes is associated with oxidative stress, which is in turn associated with atherogenesis. IGF and even modestly elevated glucose could be a marker for insulin resistance, and the distinction with frank type II diabetes in this context may be one of quantity rather than quality. Even if elevated glucose is simply a marker for higher risk from moderately elevated cholesterol, such an observation would still have important clinical implications in identifying those who might benefit more from cholesterol lowering interventions.

In our study we purposely excluded those with very high cholesterol (≥6.72 mmol/L [260 mg/dL]) since the high level of independent risk at this level could mask an interaction. Our hypothesis is that elevated glucose magnifies the cholesterol-associated risk of CHD, possibly by facilitating oxidation of cholesterol in atherogenesis. Those with very high cholesterol would likely experience substantial CHD risk irrespective of glucose. In sensitivity analyses including TC values ≥6.72 mmol/L (260 mg/dL), results were similar for dichotomized TC, but were not statistically significant with TC as a continuous variable, suggesting that the interaction effect is strongest at more moderate elevations of TC.

Similarly, we have previously shown diabetes to be among the strongest CVD risk factors among treated hypertensives. We excluded individuals with a history of diabetes or FG ≥6.99 mmol/L (126 mg/dL) at entry, since the magnitude of independent risk of CVD associated with diabetes might also confound the observation of an interaction. Including individuals

| TABLE 2. Age and Sex Adjusted CHD Rates by Total Cholesterol Within Glucose Stratata* |
|---------------------------------|----------------|----------------|----------------|----------------|
|                                | I              | II             | III            | IV             |
|                                | <5.17 mmol/L   | 5.17–5.68 mmol/L | 5.69–6.20 mmol/L | 6.21–6.71 mmol/L |
| Fasting Glucose (<200 mg/dL)   |                |                |                |                |
| Impaired†                       | 3.29 (0.73, 6.21) | 9.13 (3.29, 14.61) | 8.04 (2.56, 13.51) | 7.67 (1.46, 13.88) |
| Not impaired                    | 4.38 (2.92, 5.48) | 5.48 (4.02, 7.31) | 4.38 (2.92, 5.84) | 4.38 (2.56, 6.21) |
| Upper quartile§                 | 4.02 (0.73, 6.94) | 8.77 (4.75, 12.42) | 6.57 (3.29, 9.86) | 5.48 (2.56, 8.77) |
| Lower 3 quartiles               | 4.38 (3.29, 5.84) | 5.11 (3.29, 6.94) | 4.02 (2.56, 8.4) | 4.43 (4.37, 4.50) |
*Data presented as CHD rates per 1000 person years with 95% confidence intervals in parentheses.
†Impaired fasting glucose ≥6.11 mmol/L (110 mg/dL).
§Upper quartile fasting glucose ≥5.72 mmol/L (103 mg/dL).

| TABLE 3. Adjusted CHD Hazard Ratios for Categories of Total Cholesterol in Glucose Stratified Models* |
|---------------------------------|----------------|----------------|----------------|----------------|
|                                | I              | II             | III            | IV             |
|                                | <5.17 mmol/L   | 5.17–5.68 mmol/L | 5.69–6.20 mmol/L | 6.21–6.71 mmol/L |
| Fasting Glucose (<200 mg/dL)   |                |                |                |                |
| Impaired†                       | 1.00 (reference) | 2.70 (0.96, 7.59) | 2.64 (0.93, 7.52) | 2.79 (0.92, 8.49) |
| Not impaired                    | 1.00 (reference) | 1.25 (0.82, 1.88) | 1.00 (0.63, 1.57) | 0.92 (0.57, 1.50) |
| Upper quartile§                 | 1.00 (reference) | 2.95 (1.40, 6.21) | 2.21 (1.02, 4.78) | 2.18 (0.95, 5.00) |
| Lower 3 quartiles               | 1.00 (reference) | 1.00 (0.64, 1.59) | 0.84 (0.51, 1.40) | 0.79 (0.47, 1.35) |
*Hazard ratios (95% confidence intervals) from Cox proportional hazards models adjusted for sex, race, and entry values for age, systolic blood pressure, treatment status, smoking status, left ventricular hypertrophy, and body mass index. For each model the lowest TC category (<5.17 mmol/L (<200 mg/dL)] is the reference for the other TC categories.
†P value comparing II–IV combined to I as reference.
‡Impaired fasting glucose ≥6.11 mmol/L (110 mg/dL).
§Upper quartile fasting glucose ≥5.72 mmol/L (103 mg/dL).
with diabetes led to greater statistical significance of the interaction based on dichotomized values, but diminished the statistical significance of the interaction based on continuous values.

Further, including the highest values of cholesterol and glucose would have little clinical importance. TC ≥6.72 mmol/L (260 mg/dL) is already a strong indication for cholesterol-lowering interventions. Similarly, current cholesterol guidelines call for lower cholesterol goals for diabetic patients. We wanted to address whether lower cholesterol goals should be extended to those with elevated glucose but without frank diabetes. Our findings provide support for a trial to see whether lower cholesterol goals for hypertensive patients with IFG would improve outcomes.

We chose IFG (6.11 mmol/L [110 mg/dL]) as a primary glucose cut point since IFG has been identified as a potential independent risk factor for CVD even though it is not currently used to inform cholesterol treatment decisions. Repeating the analyses using an upper quartile threshold, as was done in our previous studies that measured HbA1c or post-load glucose, gave similar results. Consistency of these findings within and across studies lends support to the likelihood that our findings are not an artifact of an arbitrary threshold.

Table 3 shows elevated hazard ratios in each of the 3 cholesterol categories ≥5.17 mmol/L (200 mg/dL) for the upper glucose stratum (whether dichotomized by IFG or upper quartile). The lack of statistical significance for the individual categories II, III, and IV, despite point estimates similar to the combined group, likely reflects inadequate statistical power in the impaired glucose stratum, which comprises less than 12% of the sample. In contrast, the observed HR in the not-impaired stratum for TC ≥6.21 mmol/L (240 mg/dL) is close to 1, and even the upper limit of the 95% confidence interval shows only a modest increase over the reference. Combining the 3 upper cholesterol categories provides a statistically significant contrast between with the reference in the higher glucose strata, whether using the IFG or upper quartile threshold. Our findings thus suggest that glucose status might aid in identifying those who would most strongly benefit from interventions, especially at modest elevations of cholesterol that would not be treated under current guidelines. Nonetheless, only a randomized clinical trial can adequately test a hypothesis to modify clinical recommendations.

It should be noted, however, that results of recent clinical trials of lipid lowering interventions are consistent with the implications of our findings. A randomized trial among hypertensive subjects with at least 3 other cardiovascular risk factors had a lipid-lowering arm (versus placebo) among the subgroup with TC <6.5 mmol/L. This study arm was stopped early because the treatment group showed significant improvement in all stroke, total CVD, and total coronary event outcomes. The mean entry glucose for the whole study arm was 6.2 mmol/L, above the threshold for IFG, although the improvement in outcomes among the frank diabetes subgroup was not statistically significant. This seeming anomaly is consistent with our findings that the interaction effect is strongest in the moderate levels of both glucose and cholesterol, rather than at the highest levels. In the Heart Protection Study, statin treatment was found to be better than placebo irrespective of cholesterol levels for high-risk CHD patients. The observed benefit of treating even "normal" levels of cholesterol may reflect that thresholds differentiating normal from elevated cholesterol should be lower for those with high glucose status. Although the diabetic subset (29%) showed similar benefit of statins for subjects without diabetes, it is noteworthy that among diabetic subjects without diagnosed occlusive arterial disease at entry, statins provided substantially greater reductions in events (33%; 95% CI: 17 to 46) compared with the high-risk, nondiabetic participants (25%; 95% CI: 19 to 30). These results are consistent with a hypothesis that the association of an interaction effect of glucose and cholesterol with CHD risk is based on atherogenesis and is most important at the early phase of atherosclerotic accumulation.

Our study has several limitations. The study took place over an extended period of time (>20 years) and laboratory drift or secular trends may have affected recorded levels of cholesterol and glucose. An analysis of these entry values showed a modest secular trend toward lower mean values from 1978 to 1999, with mean FG going from 5.31 ± 0.72 mmol/L (95.6 ± 12.9 mg/dL) to 5.16 ± 0.57 mmol/L (92.9 ± 10.2 mg/dL) and mean cholesterol going from 5.51 ± 0.69 mmol/L (213 ± 26.7 mg/dL) to 5.22 ± 0.71 mmol/L (202 ± 27.5 mg/dL). However, much of this decline took place after 1993 when new entry criteria, based on JNC V, included subjects with lower entry BPs who could be expected to have lower values of FG and TC. There were too few events among those entering 1993 or before to repeat the analysis in this subgroup, but results for those entering before 1993 were consistent with the whole sample. Further, since the difference of effect between glucose groups was seen on the multiplicative scale of HRs (Table 3) as well as on an additive scale of rates (Table 2), modest differences in the absolute value of TC and glucose measures would not be expected to have a major impact on the analyses.

It is possible that the interaction we observed may be based on unknown confounding, sampling variability, or other limitations common to observational studies. Observational studies are particularly prone to confounding. Statistical adjustment in multivariate models can only help reduce the impact of confounding but not eliminate it. Nonetheless, with the exception of the interaction terms, the models and methods in this study were those used in previous published studies by our team using data from this cohort. That the interaction was observed irrespective of whether FG and TC were coded as continuous or dichotomous variables reduces the likelihood that our findings were due solely to the coding and modeling procedures.

Another limitation of this study is that we were not able to account for lipid fractions such as HDL-C, LDL-C, and triglycerides, especially since current guidelines use LDL-C thresholds to indicate treatment. Lipid fractions were not collected in the Worksite program until 1988, leading to insufficient statistical power to analyze the subset with entry lipid fraction values. Inadequate numbers with baseline lipid fraction values is a limitation shared by other studies, including the original Framingham cohort. Also, while in-treatment factors could have influenced the results, we chose not to examine in-treatment values since the primary clinical implication of our hypothesis concerns using baseline glucose and cholesterol to inform cholesterol interventions to improve outcomes.

Notwithstanding the limitations, our study has several important strengths. First, it was based on an a priori hypothesis and on analytical methods developed from 2 earlier studies. The con-
sistency of the results across 3 studies despite the widely different populations and differences in measures lends support to the generalizability of the findings. The consistency of the findings for 2 different dichotomizations of glucose (IFG and upper quartile), also adds confidence that the observed interaction is not merely statistical or based on arbitrary thresholds, though such happenstances cannot be ruled out. Given the generally low statistical power to detect statistically significant interactions in multivariate models while adjusting for main effects in the same model,19 a finding of statistical significance for interaction is notable.

Perspectives

Our findings suggest an adverse synergistic interaction of FG with TC that magnifies the risk of incident CHD events associated with TC for hypertensive patients. We cannot tell from these data whether the glucose is part of a biological interaction with cholesterol or whether it is a marker for some other process that confers greater risk of CHD at moderately elevated levels of cholesterol. In either case, our findings suggest that using glucose status to modify criteria for cholesterol interventions might improve CHD outcomes. Current guidelines recommend a lower cholesterol target for hypertensive patients with diabetes. Our findings lend support to a hypothesis that these guidelines should be extended to patients with IFG or similar manifestations of hyperglycemia or insulin resistance at levels less severe than frank diabetes. In light of the rapidly rising prevalence of the metabolic syndrome, our findings, if confirmed, could have important clinical implications for cholesterol guidelines for CHD prevention among hypertensive patients.

Acknowledgments

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References

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