Blood Glucose and Risk of Coronary Heart Disease

Leon D. Ostrander, Jr., Donald E. Lamphiear, Wendy J. Carman, and George W. Williams

Health status of 1877 Tecumseh Study subjects aged 35–64 years was ascertained in 1977. They represented 77% of the persons in this age range who were apparently healthy and had participated in comprehensive examinations of nearly the entire population of the community in 1959–1960 and 1962–1965. Subjects who developed coronary heart disease had a significantly higher mean blood glucose concentration than other members of the cohort, even after exclusion of diabetics. Similarly, when examined as single variables, age, sex, serum cholesterol, systolic blood pressure, number of cigarettes smoked per day, and relative weight were significantly related to incidence of coronary events. In the multiple logistic function, however, age, cigarette smoking, blood pressure, and blood glucose were the only significant variables. In a two-way interaction model, glucose and cholesterol were a highly predictive pair. After exclusion of diagnosed diabetics, glucose by itself or in interaction with other variables was not significant in the multiple logistic functions.

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Overt diabetics have a higher incidence of atherosclerotic heart disease than nondiabetics, and the difference is not entirely due to the diabetics’ propensity to obesity, hypertension, and hyperlipidemia. Metabolic changes due to persistent hyperglycemia probably account for much of the risk associated with overt diabetes. Blood glucose concentration has not been significantly related to the incidence of coronary events among persons who were not overtly diabetic, so that high normal levels of glucose or transient elevations may be no more harmful than constant normoglycemia. On the other hand, persons with ischemic heart disease have a higher prevalence of hyperglycemia than members of the general population of similar age and sex. In addition, apparently healthy persons with mild-to-moderate glucose intolerance have higher levels of a number of suspected coronary risk factors than subjects with normal glucose tolerance, and differences are partially independent of age and adiposity.

These diverse observations suggest a relationship between blood glucose level and development of ischemic heart disease that is nonlinear, complex, and possibly mediated through other physiological variables. We postulated that persistent hyperglycemia and the interaction of high blood glucose level with other factors increase the risk of ischemic heart disease in the general population. This hypothesis was tested among a cohort of 1877 middle-aged participants in the Tecumseh population who had been followed nearly 18 years.

Methods

During 1959 and 1960, 8641 residents of Tecumseh, Michigan (88% of the total population of all ages) participated in comprehensive studies of multiple factors that may be related to the incidence of coronary heart disease. A second series of examinations was conducted from 1962 to 1965, and the response rate was comparable to the first cycle. Because of mobility, death, and noncompliance, 6563 persons participated in both examinations.

Assessment of individuals was similar at each examination and included detailed medical and
social histories, physical examinations, electrocardiograms, chest x-rays, anthropometric measurements, and a blood sample drawn 1 hour after a 100 g oral glucose challenge. Glucose was administered without regard for time of day or interval since the previous meal. Diagnosed diabetics were not challenged but gave a casual blood sample. Blood glucose and serum cholesterol concentrations were determined from the specimens.

The subjects of the present report are 869 men and 1008 women aged 35 through 64 years in 1977. All had complete data and were free of apparent cardiovascular disease at the time of the 1959–1960 and 1962–1965 examinations. Previously, 2608 persons in the appropriate age range had participated in the earlier examinations, but 112 were excluded because of incomplete data collection and 46 had suspected or probable cardiovascular disease. Thus, 77% of the 2450 eligible persons were included. Other exclusions consisted of 2886 persons who were too young and 1069 who were too old for the specified age range.

Status of the 1877 subjects was ascertained from death certificates, which were obtained for all deceased participants, or findings at a clinic visit when each subject had an electrocardiogram and answered a detailed health questionnaire administered by an interviewer.

Angina pectoris was diagnosed if the subject's chest pain fulfilled criteria of the Health Insurance Plan of Greater New York. History of myocardial infarction was based on strict criteria previously used in the Tecumseh studies. Electrocardiograms were classified according to the Minnesota Code. Diagnosed diabetics were subjects who reported that they were considered diabetics by their physicians and were treated with insulin or oral hypoglycemic drugs.

Sixty-nine subjects had developed definite coronary heart disease. Twenty-five had died, 29 survivors had sustained electrocardiographically confirmed myocardial infarction (codes 1-1 or 1-2, prominent Q waves), and 15 had a history of myocardial infarction (nine) or angina pectoris (six) and major electrocardiographic abnormalities other than 1-1 or 1-2, namely, items 1-3, (equivalent Q waves); 4-1 or 4-2; 5-1 or 5-2 (RST-segment or T wave abnormalities); or 7-1 (complete left bundle branch block).

The 69 patients with coronary heart disease were compared to 1534 living members of the cohort who had no evidence of ischemic heart disease in 1977. The remaining 274 persons could not be classified with confidence because of suspect findings, death from other causes, or incomplete data. Of these 274, 83 had suspected coronary heart disease, but they did not differ significantly from subjects without heart disease according to any measured variable. Age, number of cigarettes smoked per day, systolic blood pressure, serum cholesterol concentration, relative weight, and 1-hour postchallenge blood glucose level were determined at each examination and means of the variables were used in the analyses.

Incidence as a function of risk factor variables was estimated by the multiple logistic function according to the method of Truett et al. A forward stepwise procedure was used to determine risk factors significantly (p < 0.05) related to the development of coronary events during the period of observation. Each of the seven variables was tested separately for statistical significance in predicting coronary heart disease. Then risk was determined as the joint function of the variables selected in the stepwise procedure. Finally, variable interactions were tested in a model that included the seven variables and all

<table>
<thead>
<tr>
<th>Table 1. Means and Standard Deviation of Variables in Relation to Incidence of Coronary Heart Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td>Men/women</td>
</tr>
<tr>
<td>Age (yrs)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
</tr>
<tr>
<td>Relative weight index</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dl)</td>
</tr>
<tr>
<td>Blood glucose (mg/dl)</td>
</tr>
<tr>
<td>Cigarettes/day</td>
</tr>
</tbody>
</table>

*Significance level for differences between features listed in the two columns. For continuous variables, data are presented as means with the standard deviation.
Table 2. Statistical Significance of Risk Factor Variables in the Logistic Function Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>All persons</th>
<th>Without diagnosed diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>1603</td>
<td>1592</td>
</tr>
<tr>
<td>Sex</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Age</td>
<td>sig &lt; 0.0000</td>
<td>sig &lt; 0.0000</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>sig &lt; 0.0000</td>
<td>sig &lt; 0.0000</td>
</tr>
<tr>
<td>Relative weight index</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>sig &lt; 0.0307</td>
<td>ns</td>
</tr>
<tr>
<td>Cigarettes/day</td>
<td>sig &lt; 0.0000</td>
<td>sig &lt; 0.0000</td>
</tr>
</tbody>
</table>

ns = not significant.

Possible two-way cross products. Independent linear effects of variables appear in the interaction model as additive contributions to the discrimination of persons at high risk for coronary heart disease. The cross product terms represent interactions that occur when the effect of one risk factor variable is influenced by the level of another. Risk ratios were calculated from the number of observed coronary events in the upper quartile of the distribution of predicted risk divided by the observed number of events in the lowest quartile. All analyses were repeated after exclusion of the 11 diagnosed diabetics.

Results

The means of the variables for persons who developed coronary heart disease are compared to those who did not (table 1). Persons who manifested coronary events included a higher proportion of men and had higher mean levels of all variables than those who did not develop coronary heart disease. Each variable was a highly significant predictor of coronary events and was not appreciably changed by exclusion of overt diabetics.

Significance of Seven Variables

Table 2 shows the significance of seven variables with regard to risk of coronary heart disease. Age, number of cigarettes smoked, systolic blood pressure, and blood glucose concentration were significant factors in risk function for the entire cohort. Exclusion of diagnosed diabetics eliminated blood glucose as a significant factor.

Interaction of Variables

Table 3 shows the interaction of variables. Only four of all possible two-way interaction terms and three single factors appear in a function for prediction of risk. Systolic blood pressure × age, systolic blood pressure × cigarettes, cholesterol × blood glucose, age × cigarettes, age, systolic blood pressure, and cigarettes were statistically significant. After exclusion of diagnosed diabetics, the cholesterol × blood glucose interaction was not significant.

Risk Ratios

Risk ratio for coronary heart disease according to blood glucose level alone was low for the entire cohort and only slightly reduced after exclusion of diagnosed diabetics (table 4). Risk ratios calculated from functions of single variable models and from the interaction models were much higher. Exclusion of diabetics had no consistent effect.

Table 3. All Statistically Significant Single Factors and Two-Way Interactions As Determined from Logistic Function

<table>
<thead>
<tr>
<th>Interaction</th>
<th>All persons</th>
<th>Without diagnosed diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure × age</td>
<td>sig &lt; 0.0010</td>
<td>sig &lt; 0.0015</td>
</tr>
<tr>
<td>Cigarettes/day × age</td>
<td>sig &lt; 0.0056</td>
<td>sig &lt; 0.0008</td>
</tr>
<tr>
<td>Cigarettes/day × systolic blood pressure</td>
<td>sig &lt; 0.0019</td>
<td>sig &lt; 0.0006</td>
</tr>
<tr>
<td>Serum cholesterol × blood glucose</td>
<td>sig &lt; 0.0066</td>
<td>ns</td>
</tr>
<tr>
<td>Age</td>
<td>sig &lt; 0.0019</td>
<td>sig &lt; 0.0028</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>sig &lt; 0.0141</td>
<td>sig &lt; 0.0194</td>
</tr>
<tr>
<td>Cigarettes/day</td>
<td>sig &lt; 0.0001</td>
<td>sig &lt; 0.0000</td>
</tr>
</tbody>
</table>

ns = not significant.
Discussion

Preliminary reports from the Tecumseh Study suggested that blood glucose was significantly related to the prevalence and incidence of coronary heart disease. Among the cohort reexamined in 1977, we found that blood glucose concentration was a significant risk factor for coronary events when diagnosed diabetics were included in the analyses. The hypothesis that blood glucose is a conjoint predictor of coronary events was true when diabetics were included. Only 11 persons were diagnosed diabetics and free of apparent coronary heart disease at the time of the first two examinations; four of these 11 subsequently developed coronary events. As noted in other epidemiological studies in Bedford, London, Chicago, and Helsinki, diagnosed diabetes is associated with excess risk of coronary heart disease that is not attributable to other factors, but lesser degrees of hyperglycemia have little predictive power. Casual and various postchallenge glucose determinations yield remarkably similar results in different studies.

Persistent hyperglycemia as found in many overt diabetics is probably a significant risk factor for coronary heart disease because of associated metabolic abnormalities such as accumulation of polyols in tissues or hypoxia due to excess hemoglobin A_1c. The effect appears to be independent of other apparent precursors. Lesser hyperglycemia has some predictive power, but after other risk factors are accounted for, it is not significant. Like obesity, hyperglycemia identifies persons with a high probability of having other risk factors. In a carefully studied sample of the Tecumseh population, mild-to-moderate glucose intolerance was significantly associated with numerous physiological abnormalities that have been implicated in the development of atherosclerosis. It would be prudent to assess coronary risk factors in the many persons who are found to be hyperglycemic when tested in diabetes detection programs.

The findings in the present study should reconcile differences between earlier reports from Tecumseh and other studies in respect to the status of the 1-hour postchallenge blood glucose as a risk factor for coronary heart disease. In preliminary reports of Tecumseh data, blood glucose level was analyzed as a single variable, which was significantly related to prevalence and incidence of coronary heart disease. In the present report, victims of coronary disease also had a significantly higher mean blood glucose concentration at entry to the study than subjects who did not develop coronary events. However, when other variables were included in the multiple logistic function, blood glucose level was a lesser factor and was not significant after exclusion of diagnosed diabetics. The findings are still consistent with earlier reports of Tecumseh data, but current analyses indicate a more complex relationship between glucose concentration and ischemic heart disease. The results are generally in accord with recent reports from other epidemiological studies.

Serum cholesterol concentration was not a significant risk factor in the multiple logistic function for selection of single variables, but the highly significant relationship between the glucose-cholesterol interaction and incidence of coronary events suggests that risk is a complex function of multiple factors. Further investigation of interactions between variables may uncover critical physiological disturbances that are responsible for ischemic events, a step toward better identification of high-risk persons. By means of different statistical methods, Scott and associates recently demonstrated the complexity and power of risk-factor interactions as determinates of severity of coronary artery disease in a large number of male patients. A substantial improvement in predictive power by means of more sophisticated statistical analysis would be a strong incentive for more specific and aggressive prophylactic measures.

References


Index Terms: blood glucose • diabetes mellitus • coronary heart disease • variable interactions
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