Serum Triglyceride and Risk of Coronary Heart Disease, Stroke, and Total Mortality in Japanese-American Men

George G. Rhoads and Manning Feinleib

The role of serum triglyceride as a risk factor for coronary heart disease (CHD), stroke, and total mortality was examined in men of Japanese ancestry who were 45 to 78 years old. During the first 10 years following a baseline nonfasting triglyceride determination, there were 490 incidence cases of CHD in 7615 men at risk. Average annual incidence rates were 2.1 times higher in men with nonfasting values above the 75th percentile (279 mg/dl) than in those under the 25th percentile (129 mg/dl, \( p < 0.001 \)). This association largely disappeared when associations of triglyceride with other CHD risk factors were accounted for.

Fasting triglycerides were measured in a representative sample of 1729 men partway through the study. With an average follow-up of 5.7 years there were 72 new CHD cases in this group with the risk for men in the top quartile (above 195 mg/dl) being 1.9 times higher than for those in the bottom quartile (below 94 mg/dl). This gradient was of borderline significance \( (p < 0.10) \) and completely disappeared in a multivariate analysis which included HDL and other factors. It appears that the association of triglyceride with CHD in this cohort is of a noncausal nature. Triglycerides were not predictive of stroke or of total mortality in these men.

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death certificates, and from re-examination near the second and sixth anniversaries. The follow-up for hospitalized cases of myocardial infarction and stroke and for all mortality cases is believed to be essentially complete. Diagnostic judgments were made by study physicians who applied established criteria in ignorance of baseline triglyceride values. Informed consent was obtained from all participants. Men came to the baseline examination in a non-fasting state and blood was drawn one hour after a 50 g glucose load. Frozen serum was shipped to the U.S. Public Health Service Hospital in San Francisco where triglyceride was measured by an automated fluorometric method. Because triglyceride varied by the time of day and the time since the last meal, a linear adjustment has been made to correct for these effects. This turned out to have little overall impact, the correlation between the original and adjusted values being 0.99. Triglyceride values were not obtained in 352 men.

Between 1970 and 1972 a probability sample of 1859 of these men participated in the Cooperative Lipoprotein Phenotyping Study for which blood was collected after a 12-hour fast. Plasma was shipped to San Francisco on ice where total cholesterol and triglyceride were determined and where additional cholesterol measurements were done on the d > 1.006 fraction before and after precipitation of LDL with heparin and manganese. Thus, total and HDL cholesterol were measured directly, while VLDL and LDL cholesterol were obtained by difference. In addition to these procedures, frozen serum was shipped to the Center for Disease Control for separate determinations of total triglyceride and cholesterol. The average length of follow-up from lipoprotein phenotyping until the tenth anniversary in the study was 5.7 years.

Direct age adjustments were weighted differently for the baseline and lipoprotein examinations. In each case the age-structure of the group involved was used as the standard. The resulting weights (squared) were used to combine the variances of age-specific mean differences for the adjusted t tests. For multiple logistic analyses, coefficients were estimated using the iterative maximum likelihood approach.

Table 1. Median and 95th Percentile Values for Serum Triglycerides in Men from Several Populations

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>95th%</th>
<th>Median</th>
<th>95th%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50-59</td>
<td>60-69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albany</td>
<td>127</td>
<td>338</td>
<td>118</td>
<td>287</td>
</tr>
<tr>
<td>Framingham</td>
<td>121</td>
<td>315</td>
<td>124</td>
<td>281</td>
</tr>
<tr>
<td>Honolulu</td>
<td>133</td>
<td>451</td>
<td>133</td>
<td>352</td>
</tr>
<tr>
<td>California</td>
<td>136</td>
<td>346</td>
<td>133*</td>
<td>261*</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>136</td>
<td>377</td>
<td>115</td>
<td>335</td>
</tr>
</tbody>
</table>

*Less than 100 persons.
Adapted from reference 20.

Results

In the Cooperative Lipoprotein Phenotyping Study fasting serum triglyceride was compared among the study sites as shown in Table 1. Puerto Rican men and Japanese men in Honolulu and in the San Francisco Bay Area had higher median values than did Caucasian men in Albany and Framingham. The proportion of men 50 to 59 years old with triglycerides above 315 mg/dl was about twice as high in Honolulu (10%) as in Framingham (5%). A similar excess was found in men who were 60 to 69 years old.

During the average of 5.7 years of follow-up from the lipoprotein determinations, there were 72 new cases of CHD, 27 new strokes, and 89 deaths (all causes). The mean triglycerides for these groups are shown in Table 2. Men developing CHD had higher levels than the others, a difference which was of borderline significance after age adjustment. There was no evidence that increased triglycerides were associated with subsequent stroke or with overall mortality. The age-adjusted rates for CHD and total death are shown in Figure 1. There is an increase in CHD through the first three quartiles of triglyceride, but no further increase in the top quartile, which corresponds roughly with Type IV hyperlipoproteinemia.

Table 2. Mean Fasting Triglycerides By Follow-up Status

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Age-adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
</tr>
<tr>
<td>CHD incidence</td>
<td>72</td>
<td>198.8</td>
</tr>
<tr>
<td>No CHD*</td>
<td>1866</td>
<td>171.7</td>
</tr>
<tr>
<td>TE stroke incidence‡</td>
<td>27</td>
<td>186.7</td>
</tr>
<tr>
<td>No stroke*</td>
<td>1803</td>
<td>173.1</td>
</tr>
<tr>
<td>Decedents</td>
<td>89</td>
<td>159.3</td>
</tr>
<tr>
<td>Survivors</td>
<td>1770</td>
<td>173.4</td>
</tr>
</tbody>
</table>

*Prevalence cases excluded.
†p < 0.10.
‡Thromboembolic stroke.
The effect of other risk factors on the relation of fasting triglycerides to CHD incidence was examined using the multiple logistic model (Table 3). With just age as a covariate, triglyceride was a weak predictor of CHD ($0.10 > p > 0.05$). This result is consistent with that shown in Table 2. After addition of total cholesterol, systolic blood pressure, and HDL cholesterol to the model, the coefficient for triglycerides became nonsignificant and slightly negative. Thus, in this population the modest univariate association of fasting triglyceride with CHD appears to be entirely explained by the association of elevated triglycerides with these other more powerful risk factors.

In the first 10 years of the Honolulu Heart Program, triglycerides were measured four times. At the baseline examination the determination was done in the nonfasting state one hour after a 50 g glucose load. For a sample of 1770 participants, the nonfasting measurements were repeated 2 years later at the second examination (without the glucose load). As part of the lipoprotein phenotyping study, a probability sample of 1859 men had fasting triglycerides done between 1970 and 1972 and a subsample of these measurements was repeated (again fasting) between 1976 and 1978. The correlation coefficients for the repeated measures are presented in Table 4.
Since triglyceride distributions are skewed, the log-transformed data are also shown. The correlation for repeated fasting measurements which were done about 6 years apart in 294 men was 0.58. This is somewhat smaller than the correlation coefficient for total serum cholesterol, but after transformation it is comparable to the one for HDL.

While the correlation coefficients for the nonfasting and fasting data appear comparable, it should be noted that the time interval between measurements was shorter for the nonfasting data. The reliability of the nonfasting data, as well as their correlations with the fasting values, were both improved with the log transformation, so the transformed data were used in analyzing the relation of nonfasting triglycerides to disease. This produced a slightly stronger relationship to myocardial infarction (MI) and CHD death than did the original values.

Table 5 shows age-adjusted mean log triglyceride values for those men developing disease during the 10 years of follow-up and for those remaining healthy. Men sustaining fatal and nonfatal myocardial infarcts had higher premorbid levels of triglyceride. While this was also true for men developing angina, the difference was not statistically significant. There was no evidence that high nonfasting triglycerides predisposed to thromboembolic stroke or to total mortality.

The relation of the nonfasting values to total CHD is shown graphically in Figure 2. The cutpoints used correspond to the 25th, 50th, 75th, and 90th percentiles. There was a steady increase in incidence with triglyceride up to the 75th percentile (279 mg%) but not above that level. The relative risk between the top and bottom quartiles was about the same for nonfasting triglycerides (2.1) as for fasting values (1.9). The much higher level of statistical significance found for the former was mostly due to the larger number of incidence cases available. A comparison of the original nonfasting values restricted to the men with the later fasting studies showed age-adjusted means of 300 mg/dl and 238 mg/dl in the CHD incidence cases and the noncases, respectively (t = 1.74; p < 0.10). In terms of statistical significance this result is almost identical to that shown in Table 2 for the fasting comparison in these same men.

| Table 5. Mean Loge Nonfasting Triglyceride By 10-Year Follow-Up Status |
|---------------------------------|-------|--------|-------|
| Patient characteristics | No. | Mean  | sd    | t     | Mean | t     |
| All CHD*                | 474  | 5.41  | 0.64  | 5.51† | 5.43 | 6.05† |
| Angina                  | 97   | 5.32  | 0.69  | 1.11  | 5.35 | 1.49  |
| MI                      | 199  | 5.46  | 0.65  | 4.80† | 5.47 | 5.02† |
| CHD death               | 125  | 5.44  | 0.63  | 3.45† | 5.49 | 3.86† |
| No CHD‡                 | 6806 | 5.25  | 0.62  |       | 5.25 |       |
| TE Stroke§              | 190  | 5.23  | 0.54  | -0.67 | 5.22 |       |
| No Stroke or CHD‡       | 7007 | 5.26  | 0.61  | -0.69 | 5.26 | 1.11  |
| Decedents               | 672  | 5.25  | 0.66  | -0.41 | 5.29 |       |
| Survivors               | 6982 | 5.26  | 0.61  |       | 5.26 |       |

Of the 8006 first examination participants, 352 are excluded because of missing triglyceride values.
*Includes coronary insufficiency which is not shown separately.
†p < 0.001 as compared to "No CHD."
‡Excludes prevalence cases.
§Thrombo-embolic stroke.
Table 6. Multiple Logistic Analyses Relating Non-Fasting Triglycerides to CHD 10-Year Follow-Up

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Log&lt;sub&gt;e&lt;/sub&gt; triglyceride coefficients</th>
<th>Variables included in multivariate model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CHD incidence (460)</td>
<td>0.4636†</td>
<td>Systolic BP, skinfolds, cigs/day, cholesterol, alcohol, glucose, years in Japan</td>
</tr>
<tr>
<td>Angina pectoris (96)</td>
<td>0.2335</td>
<td>Skinfolds, cigs/day cholesterol</td>
</tr>
<tr>
<td>Myocardial infarct (195)</td>
<td>0.5680†</td>
<td>Systolic BP, skinfolds, cigs/day, cholesterol, alcohol</td>
</tr>
<tr>
<td>CHD death (123)</td>
<td>0.5863†</td>
<td>Systolic BP, cigs/day, cholesterol, alcohol, glucose</td>
</tr>
</tbody>
</table>

Numbers for each endpoint shown in parentheses. Covariates chosen because of significant contribution to step-wise discriminant analysis.

*p < 0.10.
†p < 0.05.
‡p < 0.001.

Multivariate analyses for the nonfasting data are shown in Table 6. The analyses which include only age as a covariate show highly significant coefficients relating triglyceride to overall CHD, to CHD death and to MI. The association with angina is not significant. In each case, however, inclusion of other variables produces a major reduction in these coefficients. Only the association with nonfatal myocardial infarction remains statistically significant. This attrition took place despite the omission of two important covariates which were not available for this analysis. Physical activity was not well measured in this study, and HDL was done on a subset at a later date. Inclusion of these variables, especially HDL, would almost certainly have further reduced the triglyceride coefficients.

Discussion

Less attention has been paid to the potential association of serum triglycerides with thromboembolic stroke than with CHD. Feldman and Albrink followed early CHD papers with a similar case-control study of stroke and found a positive association with triglyceride. Similar results were reported by others. Possible associations of triglyceride levels with physical inactivity in stroke victims and with total and HDL cholesterol were not considered in these reports. Rossner et al. found no significant difference in triglycerides between young patients with ischemic cerebrovascular disease and controls, although HDL was lower in the patients. More recently, Ueda et al. found that triglycerides were more likely to be elevated in patients with transient ischemic attacks than in those with strokes. At Framingham, triglyceride was measured as the S<sub>20</sub>-400 fraction. It was not related to brain infarction after taking cholesterol into account. In the present study there is no suggestion that triglyceride is an important stroke risk factor. No significant differences were found, and the nonfasting values were actually lower in men who later had a stroke than in their more fortunate peers. It is interesting that triglyceride levels are higher in the Honolulu Japanese than in their counterparts in Hiroshima despite the fact that stroke is more common in Japan. Blood pressure levels are similar in the two sites. Overall, the evidence implicating triglyceride in the causation of stroke is unimpressive in as much as the positive case-control studies did not control for confounding variables.

With respect to CHD, we found a simple association between elevated triglycerides and the later development of disease. This association tended to disappear in multivariate analysis. We believe that the multivariate approach is appropriate for these data and that it provides a better overall indication of the importance of triglyceride for CHD than does the simple association. Persons with high triglyceride tend to be obese and to have elevated LDL and low HDL levels. If it was posited that triglyceride caused CHD by affecting one of these other risk factors, then it would be clearly inappropriate to control for that factor in assessing the triglyceride–CHD relationship. (For instance, one would not want to control for blood pressure in estimating the total effect of obesity on stroke.) However, we are not aware of any evidence that the triglyceride level per se has an important effect on any of these other correlated risk factors. It seems much more likely that triglyceride itself is determined in part by obesity and that its correlation with LDL and HDL is produced by hepatic and other poorly understood antecedent mechanisms. This interpretation dictates the need to control for these other factors so that the risk which they confer is not falsely attributed to triglyceride.

Multivariate analysis is potentially sensitive to within-person variation and measurement errors which are somewhat larger for triglyceride than for
total cholesterol and LDL. However, in analyses including LDL, HDL, and triglyceride, HDL appears to be a more potent measure of CHD risk than does triglyceride despite their similar reproducibility. Thus, low reproducibility is not an adequate explanation for the failure of triglyceride to hold up in the multivariate case, and the implication persists that other variables account for most of the association with CHD.

Zilversmit has recently suggested that chylomicron remnants may play an important role in atherogenesis, implying that measurements made in the nonfasting state might have some advantages. In Western societies, few individuals live any significant portion of their lives in a fasting state so that nonfasting values should provide a better idea of their usual triglyceride levels. A measurement done casually during the day is subject to more variability than a fasting specimen, but as shown in Table 4 its reliability over time is only slightly worse. Like the 24-hour dietary recall, it may be a reasonable approach for characterizing groups of people such as are used in this study. In the present data the strength of association between triglyceride and CHD was similar for the fasting and nonfasting measurements and suggested no important difference in their relation to CHD. In both cases the association seemed to be largely explained by confounding variables, with the exception of a persistent relationship between the nonfasting determination and nonfatal MI: HDL was found in Honolulu as opposed to Framingham, and yet the CHD rates are twofold higher in the Massachusetts groups. The hypertriglyceridemia in Honolulu has not led to high rates of CHD in this population (by U.S. standards).

Overall, these comparisons with other male cohorts lead to the same conclusion as the analyses within the Honolulu group alone. Neither approach suggests that the association between triglyceride (and by inference VLDL) and coronary disease is of a causal nature. Triglyceride plays a central role in lipoprotein metabolism and its measurement will doubtless continue to be important in understanding the lipoprotein status of individuals. However, treatment of hypertriglyceridemia per se is unlikely to have much effect on coronary risk.

References

27. Ueda K, Howard G, Toole JF. Transient ischemic attacks (TIAs) and cerebral infarction (CI): a comparison of predisposing factors. J Chronic Dis 1980;33:13–19

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