Coronary Artery Disease Mortality in Relatives of Hypertriglyceridemic School Children: The Muscatine Study

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with the technical assistance of Kathleen M. Schreiber

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WHETHER an elevated triglyceride level is an important risk factor for the development of coronary artery disease has been studied for more than 20 years and is still being debated. Fifty percent of patients with symptomatic atherosclerosis may be hypertriglyceridemic.1-8 However, prospective studies have produced conflicting results. In one study,9 a triglyceride elevation was considered a risk factor only in the presence of associated cholesterol elevations, while in other studies, hypertriglyceridemia was considered an independent risk factor.10, 11 Recently, high-density lipoprotein (HDL) cholesterol levels have been shown to be inversely correlated with the development of coronary artery disease: HDL cholesterol levels have been negatively correlated with total triglyceride levels.12 We have shown that children with persistently elevated cholesterol levels have family members with an increased frequency of fatal ischemic heart disease.13 In this investigation we describe the relationship between the triglyceride levels in healthy school children and the lipid levels and the frequency of coronary mortality among their adult relatives. Two groups of school children were selected for family studies: those with fasting triglyceride levels either above the ninetieth percentile or lower than the tenth percentile in the 1973 and 1975 school survey. We were particularly interested in whether children with elevated triglyceride levels in the absence of coexisting elevated cholesterol levels had increased coronary mortality in their relatives. We subdivided the index cases with high triglyceride levels into two approximately equal

Definitive

1. Stroke: when all three of the following criteria are met:

   I. One or more of the following symptoms or signs:
      (a) Carotid-cerebral arterial system: weakness or numbness in the contralateral limbs (arm, leg or both), homonymous or monocular visual loss, dysphasia or agnosia.
      (b) Vertebral-basilar arterial system: weakness or numbness of one or more limbs; episodes of vertigo and nausea; numbness of the face, particularly about the mouth; diplopia, dysphagia; dysarthrias; homonymous hemianopsia; ataxia; nystagmus or altered consciousness.

   II. The above symptoms or signs for more than 24 hours.

   III. Objective neurologic deficits are present.

   Events due to another known cause, for example, trauma, were excluded.

   2. Intermittent cerebral ischemic attacks (ICIA); when all three of the following criteria are met:

   I. One or more of the above symptoms or signs were present with signs confirmed by physician's observations.
   II. The symptoms or signs persist for less than 24 hours.
   III. There are repetitive episodes.

   3. Death from stroke.

   Reported

   Stroke or ICIA reported by physician but no documentation of clinical event available.
groups: those without high cholesterol (below the seventy-fifth percentile) and those with high cholesterol (above the seventy-fifth percentile) levels.

**Materials and Methods**

**Survey and Family Study**

In 1973 and 1975, 2655 children in Muscatine, Iowa participated in school surveys in which height, weight, triceps skinfold thickness, blood pressure, and fasting plasma cholesterol and triglyceride levels were measured. In 1973, 421 of 4053 school children were at or above the age- and sex-specific ninetieth percentile for triglyceride level; 272 of these children were resampled in 1975 and 97 were again above the age- and sex-specific ninetieth percentile for the 1975 survey (n = 4546). These 97 children were called the high-triglyceride group; 75 (77.4%), 34 male and 41 female, participated in the family study. In 1973, 377 school children were at or below the age- and sex-specific tenth percentile; 251 were resampled in 1975 and 58 were again at or below the tenth percentile for 1975. These 58 children were designated the low-triglyceride group; 47 (81%), 20 male and 27 female, participated in the family study. This participation rate compares favorably with past studies. The percentile distributions are reported elsewhere. We found no significant differences in age, height, weight, relative weight, triceps skinfold thickness, cholesterol and triglyceride level, or systolic and diastolic blood pressure between index cases whose families participated and index cases whose families did not.

The method of family study has been described elsewhere. Briefly, the vital status of all first- and second-degree relatives was determined. Death certificates were sought on all adult relatives who died at age 30 years and older. In addition, a medical history and fasting plasma cholesterol and triglyceride determinations were performed on all willing first- and second-degree relatives. All participants gave informed consent.

Blood specimens and questionnaires were obtained from 538 of 605 siblings and parents (89%) and 840 of 1216 grandparents, aunts and uncles (70%). The reduced participation in second-degree relatives probably reflects the greater proportion contacted and responding by mail rather than in person.

**Documentation of Cause of Death**

 Coronary mortality was recorded when the following conditions were listed on the death certificate: coronary occlusion, coronary thrombosis, myocardial infarction, sudden occlusion, coronary embolism or coronary atherosclerosis. Less specific terms, such as generalized arteriosclerosis, arteriosclerotic cardiovascular disease, arteriosclerosis, myocarditis, atherosclerotic heart disease, and acute myocardial failure, were not considered to specify myocardial infarction as a cause of death. The reliability problems of death certificates have been examined. The diagnostic accuracy on death certificates for coronary artery disease improves as the age at death decreases, and when the more specific disease category of myocardial infarction is used instead of the all-inclusive category of arteriosclerotic heart disease. We recorded all conditions reported on the death certificate to avoid problems of judgment and possible introduction of further bias when attempting to select a single cause of death.

Death certificates were obtained for 178 of 196 of all deceased adult first- and second-degree relatives (91%): 107 of 118 in the high-triglyceride group and 71 of 78 in the low-triglyceride group. Among those who died in the high-triglyceride group for whom a death certificate was unavailable, the nearest relative gave the following as a cause of death: myocardial infarction in four patients, cancer in one patient, diabetes in one, childbirth in one, war death in one, hypertension in one, suicide in one and accident in one. Among those in the low-triglyceride group, their relatives reported myocardial infarction in one patient, cancer in one, stroke in one, renal failure in one, old age in one and war deaths in two patients.

**Biologic Measurements**

Plasma cholesterol and triglyceride levels were determined by the Iowa Lipid Research Clinic Core Lipid Laboratory, which participates in the standardization and surveillance programs of the Center for Disease Control. The second year of surveillance ended in June 1975, and the average coefficients of variation for nine different plasma pools done weekly over 12 months for cholesterol and triglyceride were 1.67% and 2.9% respectively. These values have persisted.

**Data Analysis**

Although the ages of the living relatives were comparable, consideration of both living and dead relatives indicated that the low-triglyceride group had experienced more years at risk than the high-triglyceride group. To correct for this, age and time standardizations were performed. Mortality in each of the study cohorts was compared with the expected mortality for the Iowa population during the same period. Results for 1936–1975 were the same as for each decade; but the mortality comparisons for the 1966–1975 decade are reported because cause of death was most accurate and most years at risk had accrued in this decade.

The independent effect of the index case’s cholesterol level on coronary mortality was examined by subdividing the high-triglyceride group into those with high cholesterol (HTG-HC group, n = 37), in whom the cholesterol level for both 1973 and 1975 were in higher than the seventy-fifth percentile, and those with normal or low cholesterol (HTG-LC group, n = 38), in whom the cholesterol level was lower than the seventy-fifth percentile.

The t test was used to compare means of measurement variables. Where necessary, logarithms were used to transform skewed data toward normal, and analyses were performed on both the transformed and untransformed data. Because inferences from both analyses agreed, only the results for the untrans-
formed data are reported. Although a large number of comparisons are made, we have not attempted to adjust for multiple comparisons. The significance levels reported are for each individual comparison. Chi-square tests of homogeneity were used in comparing mortality experience in the various groups. In comparing observed to expected mortality in the standardization scheme, the chi-square approximation was used when expected frequencies were at least 5 and the Poisson approximation when expected frequencies were less than 5.

Results

Characteristics of Index Cases

For selected characteristics of index cases (table 1), significant differences for relative weight, triceps skinfold thickness and the cholesterol levels were noted. When the high-triglyceride group was subdivided into the HTG-HC and HTG-LC groups, the groups differed by design with respect to mean lipid levels and were not significantly different with respect to the other variables. For the HTG-HC group the mean cholesterol level (± SD) was 216 ± 37 mg/dl and the mean triglyceride level was 160 ± 47 mg/dl; for the HTG-LC group the mean cholesterol level was 174 ± 21 mg/dl and the mean triglyceride level was 140 ± 36 mg/dl. No index case had thyroid disease, diabetes mellitus or renal disease, and none was receiving medication.

Lipid Values and Coronary Risk Factors in Living Relatives

Cholesterol and triglyceride values (table 2) of siblings, parents, and aunts and uncles of the high-triglyceride group were significantly higher than those for corresponding relatives of the low-triglyceride group. For grandparents, the lipid values in the two groups were not significantly different.

Because index cases in the high-triglyceride group weighed somewhat more than those in the low-triglyceride group (table 1), we examined ponderosity in family members (table 2). First-degree relatives in the high-triglyceride group tended to weigh more compared with the low-triglyceride group (NS); this trend was not present in the second-degree relatives. Correction for ponderosity did not alter the meaningful lipid differences.

Subdivision of the high-triglyceride group index cases into HTG-HC and HTG-LC revealed important lipid differences in the relatives, while other biologic measurements were not significantly different. The cholesterol values of HTG-HC vs HTG-LC relatives were: siblings, 184 ± 52 vs 158 ± 26 mg/dl (p < 0.001); parents, 216 ± 38 vs 192 ± 37 mg/dl (p < 0.001); aunts and uncles, 204 ± 35 vs 193 ± 36 mg/dl (p < 0.001); and grandparents, 231 ± 39 vs 217 ± 40 mg/dl (p < 0.02). The triglyceride values in the HTG-HC vs HTG-LC relatives were: siblings, 86 ± 55 vs 88 ± 49 mg/dl (NS); parents, 176 ± 183 vs 130 ± 66 mg/dl (NS); aunts and uncles, 147 ± 104 vs 126 ± 104 mg/dl (NS); and grandparents, 184 ± 151 vs 142 ± 75 mg/dl (NS).

The frequency of other coronary risk factors in adult first- and second-degree relatives of the high- and low-triglyceride groups, respectively, was: hypertension treated with drugs, 16.6% vs 16.9%; current smokers, 33.6% vs 29.2%; former smokers, 21.8% vs 26.1%; and diabetes mellitus treated with drugs, 1.9% vs 2.9%.

Mortality Analysis

Total mortality in the adult relatives was comparable; 13.2% of first- and second-degree high-triglyceride group relatives and 14.2% of the low triglyceride group relatives had died. Examination by age and cause of death also showed no significant differences. However, division of the high-triglyceride group into HTG-HC and HTG-LC subgroups (table 3) showed a trend toward greater coronary mortality in the HTG-HC group in the age group younger than 60 years (NS). Classification by age and sex (table 4) also showed a slight increase of coronary mortality in HTG-HC male relatives compared with HTG-LC male relatives.

More elaborate standardization of mortality experience by age, sex and time of birth (table 5) also showed no significant differences. There was a lower death rate compared with the population in the HTG-LC group. The number of deaths from myocardial infarction, stroke or cancer was not significantly different from that expected in this group. Observed mortality in the HTG-HC group were very near the population-expected values except for a slight but non-significant increase in deaths from myocardial infarction.

Discussion

A study of young heart attack survivors showed that more progeny of the combined hyperlipidemia group had elevated triglyceride levels than control subjects. In our study, the relatives of children with high triglyceride levels showed no excess total or coronary mortality. This suggests that families of young myocardial infarction victims may have a different disorder of lipid metabolism, which is manifest in childhood as hypertriglyceridemia. Our data show that children with hypertriglyceridemia, the upper seg-

Table 1. Characteristics of Index Cases

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>High group (n = 75)</th>
<th>Low group (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>10.5 ± 2.5</td>
<td>10.8 ± 2.7</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>194.8 ± 38.5</td>
<td>160.9 ± 25.1†</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>149.5 ± 42.5</td>
<td>33.2 ± 8.4</td>
</tr>
<tr>
<td>Relative weight (%)</td>
<td>115.9 ± 22.9</td>
<td>99.9 ± 11.4‡</td>
</tr>
<tr>
<td>Triceps skinfold (mm)</td>
<td>13.3 ± 7.1</td>
<td>8.1 ± 3.7†</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>112.4 ± 13.8</td>
<td>109.9 ± 12.5</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>74.7 ± 9.5</td>
<td>69.7 ± 7.9</td>
</tr>
</tbody>
</table>

The entries are mean ± SD from the 1973 school survey.

*Relative weight is defined as the child's weight divided by the median weight for the given age, height and sex, multiplied by 100.

†Significantly different from the high-triglyceride group: p < 0.05.
‡p < 0.01.

Abbreviation: BP = blood pressure.
TABLE 2.  Mean Biologic Measurements in Family Members

<table>
<thead>
<tr>
<th></th>
<th>Siblings</th>
<th>Parents</th>
<th>Grandparents</th>
<th>Aunts, uncles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>n</td>
<td>128</td>
<td>196</td>
<td>89</td>
<td>135</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>152.7±28.2</td>
<td>167.3±39.2</td>
<td>187.3±34.7</td>
<td>202.0†±39.3</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>62.0±27.7</td>
<td>86.6‡±52.8</td>
<td>107.0±71.6</td>
<td>149.2‡±129.4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>155.2±20.1</td>
<td>166.6±21.1</td>
<td>168.7±10.1</td>
<td>169.3±9.4</td>
</tr>
<tr>
<td>Weight (lbs)</td>
<td>115.6±45.9</td>
<td>123.4±50.5</td>
<td>163.9±43.1</td>
<td>173.7±38.3</td>
</tr>
<tr>
<td>Skinfold (mm)</td>
<td>10.8±7.4</td>
<td>11.2±6.7</td>
<td>16.1±9.6</td>
<td>16.6±9.2</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>113.3±13.9</td>
<td>112.8±15.9</td>
<td>128.3±19.6</td>
<td>129.7±16.2</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>72.7±10.7</td>
<td>72.9±12.2</td>
<td>84.9±12.6</td>
<td>84.8±10.8</td>
</tr>
<tr>
<td>Age (years)</td>
<td>15.2±6.4</td>
<td>15.7±6.5</td>
<td>42.6±7.6</td>
<td>41.2±7.5</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
Difference from low group:
*p < 0.01.
†p < 0.005.
‡p < 0.001.

Abbreviations: Low = low-triglyceride group; High = high-triglyceride group; BP = blood pressure.

TABLE 3.  Mortality in First- and Second-degree Relatives

<table>
<thead>
<tr>
<th></th>
<th>All causes</th>
<th>MI</th>
<th>Cancer</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages 30–59 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High TG, high C</td>
<td>10.1% (30/297)</td>
<td>4.4% (13)</td>
<td>2.4% (7)</td>
<td>0.3% (1)</td>
</tr>
<tr>
<td>High TG, low C</td>
<td>7.4% (27/365)</td>
<td>0.9% (3)</td>
<td>1.4% (5)</td>
<td>0.8% (3)</td>
</tr>
<tr>
<td>Low TG</td>
<td>6.8% (26/380)</td>
<td>2.1% (8)</td>
<td>1.1% (4)</td>
<td>0.3% (1)</td>
</tr>
<tr>
<td>Ages 60 years and older</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High TG, high C</td>
<td>26.4% (32/121)</td>
<td>9.9% (12)</td>
<td>8.3% (10)</td>
<td>3.3% (4)</td>
</tr>
<tr>
<td>High TG, low C</td>
<td>25.0% (30/120)</td>
<td>8.3% (10)</td>
<td>6.7% (8)</td>
<td>4.2% (5)</td>
</tr>
<tr>
<td>Low TG</td>
<td>30.4% (52/171)</td>
<td>10.5% (18)</td>
<td>7.6% (13)</td>
<td>5.2% (9)</td>
</tr>
</tbody>
</table>

Abbreviations: TG = triglyceride; C = cholesterol; MI = myocardial infarction.

Elevated triglyceride levels might be a coronary risk factor only when there is an associated elevation of cholesterol level. Studies that suggest a relationship between elevated triglyceride level and coronary disease were not adjusted for the confounding effects of elevated cholesterol levels. Half of the hypertriglyceridemic index cases had cholesterol levels above the seventy-fifth percentile (15% had cholesterol levels above the ninety-fifth percentile), suggesting an excess of type II-B hyperlipoproteinemia in this population. Relatives also showed this trend. Our data suggest that the relatives of children with both elevated cholesterol and triglyceride levels have an increased risk for coronary disease compared with the HTG-LC group relatives. This is in agreement with our observations that elevated cholesterol levels in children identify relatives with increased coronary mortality.

Our results should be interpreted cautiously. First, the method of defining coronary mortality using death certificates is not without sensitivity and specificity problems; but by narrowing the coronary mortality...
## Table 5. Mortality, 1966-1975

<table>
<thead>
<tr>
<th>Cause</th>
<th>High triglyceride</th>
<th>High TG, low C</th>
<th>High TG, high C</th>
<th>Low triglyceride</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed/expected</td>
<td>Observed/expected</td>
<td>Observed/expected</td>
<td>Observed/expected</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All causes</td>
<td>37</td>
<td>47.9</td>
<td>14</td>
<td>25.0*</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>14</td>
<td>13.0</td>
<td>5</td>
<td>6.7</td>
</tr>
<tr>
<td>Stroke</td>
<td>4</td>
<td>3.7</td>
<td>3</td>
<td>1.9</td>
</tr>
<tr>
<td>Cancer</td>
<td>10</td>
<td>9.1</td>
<td>2</td>
<td>4.7</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All causes</td>
<td>20</td>
<td>25.1</td>
<td>11</td>
<td>13.2</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5</td>
<td>4.6</td>
<td>1</td>
<td>2.4</td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
<td>2.8</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>Cancer</td>
<td>7</td>
<td>6.8</td>
<td>4</td>
<td>3.6</td>
</tr>
</tbody>
</table>

*Significantly less than expected (p < 0.05).

Abbreviations: TG = triglyceride; C = cholesterol.

Definition and focusing attention on recent death certificates, we have minimized these problems and enhanced the usefulness of the method. In addition, any biases should be similar for the high- and low-triglyceride groups. Second, since our selection criteria included all children at or above the ninetieth percentile, effects of severe hypertriglyceridemia in the children and their relatives on coronary mortality might have been diluted by the inclusion of some families with mild triglyceride elevations. Finally, although we showed a trend toward higher coronary mortality in the families of the HTG-HC group, the difference was not statistically significant, possibly because of the small number of families in this category or because no real difference exists.

In childhood, hypertriglyceridemia is a heterogenous phenomenon. Elevations of either triglyceride or cholesterol levels or both have been observed in the progeny of coronary disease victims with familial hypercholesterolemia. Our data suggest that children in the general population with persistent high triglyceride levels may have at least one of three types of disorders: familial combined hyperlipidemia (some relatives with either elevated cholesterol or triglyceride or both), familial hypertriglyceridemia (some relatives with elevated triglyceride levels), or sporadic hypertriglyceridemia (relatives free of lipid elevation). In the first disorder, the family is at excess risk for coronary disease, and in the latter two disorders no increased coronary risk among relatives has been demonstrated. Thus, if a child has hypertriglyceridemia, the significance in terms of coronary heart disease risk must be viewed in relation to the child's cholesterol levels and to the cholesterol levels of the child's relatives.

Acknowledgment

We thank the Muscantine Field team — Theresa Gibbs, Darlene Linville, Mary Ann Reiter, Lynn Russell, Karen Stanhope and Verna Mae Wilson — for their skill and diligent assistance in screening the locally living relatives. We also thank June Slach and Joy Eyman for data management and programming and Beverly Kuddes and Irma Kromer for typing the manuscript.

## References

Tellurium-123m-labeled-9-Telluraheptadecanoic Acid: A Possible Cardiac Imaging Agent

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SUMMARY To study the value of the fatty acid analog tellurium-123m-labeled-9-telluraneptadecanoic acid (123mTe-THDA) as a cardiac imaging agent, five dogs had partial occlusion of the left anterior descending coronary artery. One hour later, scission-46 (46Sc) microspheres were injected into the left atrium, followed immediately by the i.v. 123mTe-THDA. After injection, regional myocardial 123mTe activity was monitored continuously with implanted miniature cadmium telluride radiation detectors in both ischemic and nonischemic zones. After 4 hours, stannum-113 microspheres were injected into the left atrium and the dogs were killed. Ischemic and nonischemic areas of myocardium were sectioned and counted in a well counter. Nonischemic myocardial 123mTe activity reached 88±10% (mean±SD) of peak activity within 1 minute after injection, peaked in 8±9 minutes, then decreased 2±8% over the next 4 hours. Ischemic myocardial 123mTe activity reached 97±4% of peak activity within 1 minute after injection, peaked in 5±5 minutes, then decreased 5±7% over the next 4 hours. There was a linear correlation between 123mTe activity at 1 hour and at 4 hours and the initial 46Sc microsphere-determined regional myocardial blood flow (r = 0.93 ± 0.96). Ischemic and nonischemic zone myocardial blood flows did not change significantly during the experiment. Cardiac images of excellent quality were obtained after 123mTe-THDA administration in three additional dogs with left anterior descending occlusions and two additional dogs with no occlusions using a conventional gamma scintillation camera and a low-energy collimator. The linear relationship with regional myocardial blood flow, the minimal myocardial washout after a rapid peak, and the 159-keV gamma make 123mTe-THDA a promising new cardiac perfusion imaging agent.

UNDER AEROBIC CONDITIONS, nonesterified long-chain fatty acids are the major substrate for myocardial energy production.1,2 As a result of the high utilization by the heart, rapid turnover from the blood, and minimal concentration in normal lung, fatty acids labeled with gamma-emitting radioisotopes might be excellent myocardial imaging agents. However, most of these radiopharmaceuticals are rapidly metabolized with translocation of the tracer label to other sites. The changing distribution of the radiolabel during the imaging interval may decrease image quality and the redistribution may have little relationship to fatty acid metabolism. We prepared a long-chain fatty acid, substituting a metallic heteroatom within the alkyl chain.3-6 We postulated that such an organometallic-substituted fatty acid would enter the myocardial cells but would be only partially metabolized, leaving the tracer within the cell. One such family of compounds, tellurium-123m-labeled long-chain fatty acids, has been shown to have high myocardial uptake in preliminary studies in rats.3-6 The purposes of the present study were to determine if the initial distribution of tellurium-123m-labeled-9-telluraneptadecanoic acid (123mTe-THDA) was proportional to regional myocardial blood flow; to determine if the inter-alkyl location of the 123mTe would protect it from translocation during metabolism of the

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