Conjoint High Triglycerides and Low HDL Cholesterol Across Generations

Analysis of Proband Hypertriglyceridemia and Lipid/Lipoprotein Disorders in First-degree Family Members

Dennis L. Sprecher, MD; Misty J. Hein, BA; Peter M. Laskarzewski, PhD

Background To discern whether hypertriglyceridemia (hyper-TG, TG >95th percentile) and hypoalphalipoproteinemia (hypoalpha, high-density lipoprotein [HDL-C] ≤10th percentile) are jointly transmitted in families, we studied 385 probands with marked elevations in TG or cholesterol levels (TG or cholesterol >99th percentile in a previous visit) and their 2072 first-degree relatives in the Lipid Research Clinics' Family Study. Repeat TG measurement, with exclusion criterion of TG ≤95th percentile, resulted in 162 probands with hyper-TG.

Methods and Results When the proband demonstrated the conjoint trait (CT; ie, TG >95th percentile, HDL-C ≤10th percentile, n=82), an average of 10.6% of first-degree relatives conjointly expressed hyper-TG and hypoalpha in contrast to only 4.1% of first-degree relatives of a proband who expressed high TG levels with normal HDL-C levels (TG >95th percentile, HDL-C >10th percentile, n=80). Hyper-TG was expressed in 24.2% of first-degree relatives of probands with CT. However, hyper-TG was expressed in only 14.4% of first-degree relatives of probands with hyper-TG alone. CT probands and their family members tended to have more reported cardiac events and symptoms (P = .02 and .09, respectively) than those subjects associated with hyper-TG alone.

Conclusions The differences in HDL-C-TG abnormalities between families related to hyper-TG probands with or without hypoalpha indicate that bottom decile HDL-C is not simply secondary to hyper-TG. A familial interaction is suggested between HDL-C and TG levels consistent with the transmission of hyper-TG and hypoalpha among first-degree relatives. Among subjects and their families with hyper-TG, those who in addition have low HDL-C demonstrate a tendency for more coronary artery disease than do those with normal HDL-C levels. (Circulation. 1994;90:1177-1184.)

Key Words • lipoproteins • familial hypertriglyceridemia • conjoint trait

Hypertriglyceridemia is commonly observed in postmyocardial infarction patients. However, its independent, direct causal relation to atherosclerotic vascular disease has been questioned. Acquired hypertriglyceridemia may be secondary to alcohol ingestion, obesity, high fat diets, diabetes mellitus, and immunologic disease. Among plasma lipids and lipoproteins, triglyceride (TG) is an environmentally dependent parameter and thus is labile. Clinical trials including the Stockholm Ischemic Heart Disease Study, the Helsinki Trial, the Cholesterol-Lowering Angiographic Study (CLAS), and the more recent FATS Study have provided some support for the notion that treatment of more than simply one lipoprotein or lipid value is beneficial in the protection against cardiovascular disease, including lowering low-density lipoprotein cholesterol (LDL-C), raising high-density lipoprotein cholesterol (HDL-C), and lowering TG.

Plasma TG concentration and HDL-C levels have been found generally to be inverse parameters. Elevations in TG concentration associated with an increase in the number of very-low-density lipoprotein (VLDL) particles result in a remodeling of the HDL particle, producing a TG-enriched and cholesterol ester–poor HDL. One might speculate that the TG level is the major and most frequent basis for hypoalpha concentrations. Thus, the TG level may be the critical parameter, whereas the HDL-C level is simply secondary.

The common clinical familial hyperlipoproteinemia observed that demonstrate an interaction of LDL-C, HDL-C, and TG levels are variously entitled familial hypertriglyceridemia, familial combined dyslipidemia, familial hypohapalpha, and more recently, familial dyslipoproteinemic hypertension. It remains to be discerned whether there are unique molecular genetic differences between these various familial dyslipoproteinemias. Nonetheless, a frequent common denominator in each of these genetic entities is a combined low HDL-C–high TG state. This combined phenotype also correlates well with a new atherogenic marker related to dense LDL particles, phenotype B, which has a significant association with the premature development of coronary artery disease.

The elucidation of the HDL-C–TG familial interaction through epidemiologic methods may provide some insight into its basic mechanisms as well as the role played in the various previously reported familial dyslipemias. If plasma TG level is the major determinant of HDL-C concentration, we would expect that first-degree relatives of hypertriglyceridemic probands would express a similar distribution of lipoprotein values regardless of the HDL-C concentration in the proband.
Our primary objective was to determine if first-degree family members expressed enriched HDL-C–TG phenotypes when related to a proband with high TG alone compared with those related to a proband with high TG and low HDL-C.

Methods

The Lipid Research Clinics’ (LRC) Family Study, which has been previously described, was used for this analysis.23 The Family Study 99th Percentile Hyperlipidemic sample consists of 468 probands of all ages with elevated TG or cholesterol levels (TG or cholesterol >99th percentile, visit 1), their spouses (if applicable), and first-degree family members. The percentiles used for classification were based on preliminary visit 1 data from five clinics and were age- and sex-specific but not race- or clinic-specific. Selecting all white families, regardless of age or sex, 385 probands and 2072 first-degree relatives were included in the analysis. Spouses were excluded, as were probands who had no first-degree relatives.

After a 12-hour fast, blood was obtained for quantitation of plasma total cholesterol, TG, HDL-C, and LDL-C following previously defined LRC methodology.22 Subjects with TG levels >400 mg/dL had direct assessment of LDL-C and VLDL-C performed through ultracentrifugation. All subjects were classified into LRC age- and sex-specific percentile distributions for their HDL-C and TG values.22 Quetelet Index (QI) was calculated as (weight/height²) x 1000. The 385 probands were then classified into one of the following two groups or were excluded from further evaluation based on their visit 2 levels: group 1, hypoalpa, hyper-TG (HDL-C <10th percentile, TG >95th percentile, joint trait [CT]) and group 2, normal HDL-C, hyper-TG (HDL-C >10th percentile, TG >95th percentile). (Note: High TG and hyper-TG are used interchangeably in this report.)

Thus, the 385 probands had their TG levels measured twice and were only included in the final analysis if subjects were included in the >99th percentile LRC Family Study subgroup and TG >95th percentile observed on the second evaluation. The grouping was done to assess the degree to which hypoalpa occurs among hyper-TG probands. Mean age, lipoproteins, QI, and blood pressure were calculated separately for the CT and hyper-TG probands. Indications of family history for coronary events were compared for the CT and hyper-TG probands using the two-tailed Z score as a test of significance. First-degree relatives of these probands were then classified as hypoalpa, hyper-TG, or both, and the average percentages associated with each trait were computed. The distributions of LDL-C, HDL-C, and QI for all probands and LDL-C and QI only for family members with the hypoalpa–hyper-TG trait were also determined.

Kindred distributions of HDL-C and TG were compiled as follows: First, the number of probands was counted, as were their first-degree relatives. Second, the age- and sex-specific percentile of each variable for each family member was determined (using the LRC percentile distributions). The overall distribution of family members then was obtained by averaging the percentage of a family in a given percentile range over the total number of families. For example, if family 1 had 20% of its members below the 10th percentile of the HDL-C distribution, family 2 had 50% of its members below the 10th percentile, and family 3 had 0% of its members below the 10th percentile, the average percent below the 10th percentile of the HDL-C distribution for the three families would be 23.33%. Method of averaging allows each family to be weighted equally regardless of family size.

The average percentage of family members with one of the following six traits was computed: (1) hypoalpa alone, (2) hyper-TG alone, (3) hypoalpa and hyper-TG, (4) hypoalpa (combining normal TG and hyper-TG), (5) hyper-TG (combining normal HDL-C and hypoalpa), and (6) hypoalpa and/or hyper-TG. Significance associated with the pairwise difference in percentages between the two groups was assessed using the Wilcoxon rank-sum test23 for each of the six traits.

Results

Of the 385 original probands (Fig 1), 223 were excluded due to TG ≤95th percentile on the second visit. Of the remaining 162 probands, 82 had CT and had a total of 458 first-degree relatives, resulting in an average family size of 6.6 (including the proband). The balance of 80 probands had normal HDL-C with hyper-TG and had a total of 451 first-degree relatives, also resulting in an average family size of 6.6. Table 1 displays mean ± SEM of age, lipoproteins, QI, and blood pressures for the CT and normal HDL-C–hyper-TG proband groups. Because the original population was enriched for elevated TG and total cholesterol, the repeat hypertriglyceridemic population demonstrated an unanticipated elevation in total cholesterol. A reevaluation of the original 385 probands’ visit 1 total cholesterol and TG levels using the LRC’s age-, sex-, and race-specific percentiles indicated that 26.8% had total cholesterol >95th percentile alone, 50.4% had TG >95th percentile alone, and 22.7% had both total cholesterol and TG >95th percentile. Thus, 73.1% of these probands had visit 1 TG levels >95th percentile. Accordingly, 96% of the 162 probands (155 of 162) had both visit 1 TG >95th percentile and visit 2 TG >95th percentile. Misclassification due to the use of the preliminary visit 1 data percentiles did not have a significant effect on the results.

Fig 2 represents all 162 families in which the proband had one of the two HDL-C–TG abnormalities. Each column of this figure represents a family of a proband with either CT or normal HDL-C–high TG. The respective family sizes are indicated beneath the columns. The top row of each column designates family members with hypoalpa alone; the middle row designates family members with hypoalpa and hyper-TG; and the bot-
TABLE 1. Unadjusted Mean Age, Lipoproteins, Quetelet Index, and Blood Pressure for the Conjoint Trait and Hypertriglyceride Probands

<table>
<thead>
<tr>
<th></th>
<th>Conjoint Trait Probands (n=82)</th>
<th>Hypertriglyceride Probands (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SEM M IQR</td>
<td>Mean±SEM M IQR</td>
</tr>
<tr>
<td>Age, y</td>
<td>40.2±1.5 39.5 28.8, 47</td>
<td>37.0±1.6 39.0 26.5, 50.8</td>
</tr>
<tr>
<td>HDL-C</td>
<td>29.9±0.6* 30.5 26.3, 34</td>
<td>44.8±1.0 43.0 37.4, 49</td>
</tr>
<tr>
<td>LDL-C</td>
<td>108.4±4.9* 105.5 76.5, 130.3</td>
<td>127.8±5.3 130.0 96.0, 158</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>240.9±10.4 224.5 197.0, 257</td>
<td>236.2±5.7 232.0 199.0, 269.0</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>614.4±68.7* 406.5 267, 689.3</td>
<td>365.8±21.4 328.5 214.3, 479.3</td>
</tr>
<tr>
<td>Quetelet Index</td>
<td>2.96±0.05* 2.86 2.53, 3.23</td>
<td>2.72±0.05 2.74 2.44, 3.04</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>141.1±1.6 140.0 131.5, 148.5</td>
<td>138.9±2.0 139.3 124.5, 151.9</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>104.8±1.3 103.5 97.5, 111.1</td>
<td>102.6±1.5 104.3 91.6, 113.4</td>
</tr>
</tbody>
</table>

M indicates median; IQR, interquartile range; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.

*Conjoint trait vs hypertriglyceride mean comparison, P<.05.

The latter row designates family members with hyper-TG alone. Indications of upper decile LDL-C and upper decile QI are given for both probands and first-degree family members. Sixty-seven of the 82 families (82%) identified by probands with CT had first-degree relatives with an HDL-C-TG abnormality. Similarly, 49 of the 80 families (61%) identified by probands with normal HDL-C and hyper-TG had first-degree relatives with an HDL-C-TG abnormality.

To distinguish familial combined hyperlipidemia from HDL-C-TG abnormalities (especially CT) and begin to understand the influence of body mass on these parameters, upper decile LDL-C and QI in probands and family members are also presented in Fig 2. The per-

![Fig 2](http://circ.ahajournals.org/)

Fig 2. Each column represents a family of a proband with either conjoint trait (CT) or normal high-density lipoprotein cholesterol (HDL-C)–high triglyceride (TG). Top row designates family members with hypoalpha alone; middle row designates family members with hypoalpha and hyperTG; bottom row designates family members with hyperTG alone. The numbers bracketed under column clusters represent the number of family members represented in each column. A bold symbol above a column indicates the proband has upper decile low-density lipoprotein cholesterol (LDL-c, "L"), upper decile Quetelet index (QI, "Q"), or both ("B"). Absence of a symbol above the column indicates a lack of these characteristics in the proband. A symbol beneath the column indicates that at least one family member (exclusive of the proband) has upper decile LDL-c ("L"), upper decile Quetelet index ("Q"), or both ("B"). The latter ("B") denotes a family with at least one member with both, or at least two members, each with at least one of the two characteristics. Absence of a symbol indicates the lack of these characteristics in any of the family members.
Table 2. Number of Proband-Defined Families With Specific Family Member Phenotype

<table>
<thead>
<tr>
<th>Number of Affected Family Members</th>
<th>Affected Family Member Phenotype</th>
<th>Conjoint Trait (n=82)</th>
<th>Hypertriglyceride (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1</td>
<td>Hypoalpha</td>
<td>53</td>
<td>31</td>
</tr>
<tr>
<td>≥2</td>
<td>Hypoalpha alone</td>
<td>34</td>
<td>19</td>
</tr>
<tr>
<td>≥1</td>
<td>CT</td>
<td>31</td>
<td>15</td>
</tr>
<tr>
<td>≥2</td>
<td>Hyper-TG</td>
<td>60</td>
<td>39</td>
</tr>
<tr>
<td>≥1</td>
<td>Hyper-TG alone</td>
<td>45</td>
<td>31</td>
</tr>
<tr>
<td>≥2</td>
<td></td>
<td>15</td>
<td>7</td>
</tr>
</tbody>
</table>

CT indicates conjoint trait; hyper-TG, hypertriglyceridemia.

percentages of proband with upper decile LDL-C in the CT and normal HDL-C–hyper-TG groups are 15% (12 of 82) and 24% (19 of 80), respectively. Similarly, the percentages of probands with upper decile QI in the CT and normal HDL-C–hyper-TG groups are 43% (35 of 82) and 31% (25 of 80), respectively. The percentage of families (exclusive of probands) in which one or more members express upper decile LDL-C is 45% (37 of 82) for the CT and 35% (28 of 80) for the normal HDL-C–hyper-TG proband–defined family groups. For QI, the percentage of families is 55% (45 of 82) and 33% (26 of 80) for the CT and normal HDL-C–hyper-TG proband–defined family groups, respectively. Likewise, the percentage of families (exclusive of probands) in which one or more members express upper decile LDL-C and hyper-TG (in combination or separately) is 37% (30 of 82) and 19% (15 of 80) for CT and normal HDL-C–hyper-TG proband–defined family groups, respectively.

Table 2 displays the number of proband-defined families with specific family member phenotypes. Within the two proband-defined phenotypes, ie, CT and normal HDL-C–hyper-TG, the number of families with one or more affected family members and the number of families with two or more affected family members are given for the following phenotypes: (1) hypoalpha alone, (2) hyper-TG alone, (3) hypoalpha and hyper-TG, (4) hypoalpha (combining normal TG and hyper-TG), (5) hyper-TG (combining normal HDL-C and hypoalpha), and (6) hypoalpha and/or hyper-TG. For example, 53 of the 82 families in which the proband has CT had at least 1 family member with hypoalpha, whereas 24 families had at least 2 family members with hypoalpha. Conversely, of the 80 families in which the proband has hyper-TG alone, 31 families had at least 1 family member with hypoalpha and 7 families had at least 2 family members with hypoalpha.

Fig 3 summarizes the data given in Fig 2 for all 162 families in which the proband had one of the two HDL-C–TG phenotypes. The left pair of intersecting circles represents families of probands with CT; the right pair represents families of probands with normal HDL-C–hyper-TG. Hypoalpha, hyper-TG, and the hypoalpha–hyper-TG trait are displayed as they occur in the first-degree relatives of the probands in each phenotypic group. The two sets of intersecting circles represent 458 and 451 first-degree relatives, respectively.

Comparison of CT and normal HDL-C–hyper-TG proband–associated families indicates that each subgroup (hypoalpha alone, hyper-TG and hypoalpha, and hyper-TG alone) is relatively enriched in the CT proband–associated first-degree relatives (P=.0149, P=.0043, and P=.0347, respectively). Hypoalpha overall (P=.0003) and hyper-TG overall (P=.0011) are observed more frequently in CT proband–associated family members. A comparison of all HDL-C–TG abnormalities between these two groups also demonstrates a significant difference (35.3% versus 20.8%, P=.0001).

As a means of establishing whether or not the CT and normal HDL-C–hyper-TG proband groups differ with respect to family history for coronary heart disease, the percentage of probands who had ever had a heart attack and the percentage of probands whose father and/or mother had a positive family history for coronary heart disease were compared. Table 3 displays these results.
TABLE 3. Summary of Family History of Coronary Heart Disease in Conjoint Trait Probands and Hypertriglyceride Probands

<table>
<thead>
<tr>
<th></th>
<th>Conjoint Trait Probands</th>
<th>Hypertriglyceride Probands</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=82)</td>
<td>(n=80)</td>
</tr>
<tr>
<td>Proband had:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart attack</td>
<td>Yes 5</td>
<td>Total 82</td>
</tr>
<tr>
<td>Father and/or mother</td>
<td>Yes 34</td>
<td>Total 82</td>
</tr>
<tr>
<td>Heart attack or angina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD before age 60 years</td>
<td>19</td>
<td>Total 82</td>
</tr>
<tr>
<td>Stroke or other CVD</td>
<td>21</td>
<td>Total 82</td>
</tr>
</tbody>
</table>

CHD indicates coronary heart disease; CVD, coronary vascular disease. Probands not responding "Yes" responded "No" or "Unknown." One conjoint trait proband did not respond to question "Proband has had a heart attack."

Five of the 82 CT probands responded as having had a heart attack compared with 0 of the 80 normal HDL-C-hyper-TG probands ($P=0.02$). The CT probands responded with a higher percentage of fathers and/or mothers with heart attack or angina (41% versus 29%, $P=0.09$), coronary heart disease before age 60 years (23% versus 14%, $P=.12$), and stroke or other coronary vascular disease (26% versus 20%, $P=0.40$). Although not statistically significant, this is indicative of a trend toward an increased family history for cardiovascular disease in the CT families.

Fig 4 displays the LDL-C percentile distribution of the probands with either CT or normal HDL-C-hyper-TG. Among CT probands, 26% (21 of 82) have LDL-C in the upper half of the LDL-C distribution. This compares with 51% (41 of 80) among the normal HDL-C-hyper-TG probands. Any evidence of heterogeneity suggests that the CT probands tend to have lower LDL-C ($\chi^2=18.77, df=7, P = 0.009$). In addition, when probands with TG >400 mg/dL were directly evaluated for LDL-C using ultracentrifugation (CT probands, $n=42$; normal HDL-C-hyper-TG probands, $n=27$), the percentage with LDL-C >95th percentile were 2.4% (1 of 42) and 11.1% (3 of 27), respectively. This indirectly suggests that CT subjects had lower LDL-C values from those with hyper-TG alone.

Fig 5 displays the QI percentile distribution of the probands with either CT or normal HDL-C-hyper-TG. Both proband groups have higher QIs than normal. The CT probands have 87% (71 of 82) in the upper half of the QI distribution; the normal HDL-C-hyper-TG probands have 80% (60 to 80) in the upper half of the QI distribution. There is no evidence to suggest a difference in QI distribution between the two groups.

Forty-five of the 458 first-degree relatives of probands with CT had the hypoalpha-hyper-TG trait, whereas 17 of the 451 first-degree relatives of probands with normal HDL-C-hyper-TG had the hypoalpha-hyper-TG trait. The LDL-C and QI distributions do not suggest a difference between the two groups.

Fig 6 displays the HDL-C percentile distribution of the probands with either CT or normal HDL-C-hyper-TG. The distribution is bimodal, with the valley between the peaks at the 10th percentile.
Discussion

We have assessed first-degree family members of probands with two types of lipoprotein profiles: (1) hyper-TG and hypoalpha and (2) hyper-TG and normal HDL-C. The data strongly suggest that elevated TG concentrations in patients do not totally determine the HDL-C concentration, a finding consistent with previous studies.26 The family lipid-lipoprotein distribution is clearly different, depending on whether the hyper-TG proband does or does not also express hypoalpha. Furthermore, the percentage with the hypoalpha–hyper-TG trait among hypoalpha and hyper-TG family members as well as the percentage of hypoalpha and hyper-TG alone is greater in first-degree relatives of CT probands than in first-degree relatives of hyper-TG probands. The hypoalpha–hyper-TG trait exists as a unique transmissible entity or is the result of a linked transmission of both low HDL-C and high TG independently.

In the present study, the patients had extremely elevated TG levels (TG in the upper 5th percentile rather than upper 10th percentile) but in addition had values that were measured twice. This avoids the dilutional effect of regression to the mean. Many patients with high TG levels on first measurement are excluded on the second measurement due to lability of values or nonfasting samples.7 If such probands are designated as hyper-TG, values from their respective families can dilute out any potential enrichment. When two values, such as TG values, are reproducibly high, there is an increased probability that hyper-TG exists. There would presumably be a higher incidence of genetic defects in this population.

We have previously reported on the random sample of the LRC Family Study, where 2.7% to 3.6% of probands demonstrated the CT defined by extreme deciles for both TG and HDL-C measured only once.27 These differences in definition of hyper-TG between the current and previous studies may explain the significant enrichment in the total average percentage of hyper-TG individuals among the family members of probands with hyper-TG alone (14.4% currently versus 9.8% previously).27 The 10.6% of CT family members of CT probands found is consistent with the 12.7% reported previously, given the TG cutoff point was more stringent in the current study. Therefore, these data suggest some interaction presumably between VLDL and HDL particles as relevant to the association of TG and HDL-C levels among generations.28 Path analysis performed on the random sample from the LRC Family Study suggests that the VLDL–HDL-C interaction is determined by factors beyond the family environment.29 This would be consistent with a genetic basis for these associations.

A substantial portion of the inverse relation between HDL-C and TG is based on a transfer of TG and cholesterol ester between the VLDL and HDL particles.3031 Deckelbaum et al32 have indicated that as TG increases there is a continuous remodeling of the HDL particle, which would lead to a reduction in the cholesterol moiety. Sane and Nikkila33 evaluated first-degree relatives of hyper-TG probands and found that the fractional catabolic rate (FCR) of VLDL-TG was clearly reduced in these relatives, while production rates were either normal or enhanced. This led the group to postulate modifications in lipoprotein lipase function relevant to both VLDL catabolism and HDL maturation as potentially critical in explaining this phenomenon. This has taken on further support in the evaluation of LpL heterozygote patients in that they appear to represent a portion of the familial hypertriglyceridemic population, particularly after the age of 40 years.34 Structural defects in LpL, the presence and function of the apolipoprotein (apo) C-II cofactor,35 and LpL inhibition by apoC-III36–38 could each be relevant factors in modifying LpL activity and producing hyper-TG. Hormonal influence or regulatory factors that operate in some tissue-specific manner could be critical.39 Other factors important in intermediate metabolism may also be relevant, for example, apoE.4041

Familial dyslipoproteinemias traditionally described such as familial combined hyperlipidemia and familial hyper-TG as well as familial hypoalphalipoproteinemia often present with phenotypes associated with TG abnormalities and/or the CT. Familial combined subjects frequently express elevated LDL-C levels, and whereas LDL-C levels >90th percentile are distributed similarly among families in both of our groups, hyper-TG-alone subjects tended to have higher calculated LDL-C levels than CT subjects. Even though these calculated LDL-C levels, according to the Friedewald equation, could be inaccurate down to TG levels of 250 mg/dL,42 this contrast in LDL-C continued to be evident when only subjects with TG levels >400 mg/dL were evaluated, ie, LDL-C more directly measured through beta quantification. Lack of apolipoprotein B data on our subjects as well as the generally modest size of our families precludes more definitive assessment of the association between CT and the previously described entities of familial hyper-TG or combined hyperlipidemia. Furthermore, the more recent description of familial dyslipidemic hypertension permits one or more of the extreme decile LDL-C, TG, and HDL-C values into the classification schema.18 The noted dense LDL particles in hyper-TG compare favorably with the phenotype B recommended by Austin,43 with high correlations for low HDL and high TG. This phenotype is associated with an increased incidence of premature coronary heart disease. Hyperbetalipoproteinemia may represent a similar entity.44 Furthermore, the formal definition of familial hypoalphalipoproteinemia only includes patients with TGs <90th percentile.17 However, in careful evaluation of previous studies of hypoalpha, TGs are often in the upper quartile. Therefore, it is indeed possible that all of the above clinical entities including the hyper-TG and hypoalpha trait are simply epiphenomena of similar single or multiple enzymatic defects.

High TG levels, commonly associated with patient populations found to have cardiovascular disease, are often not statistically informative, since other measurements, notably HDL-C, are more relevant after multiple regression.2 In our population, probands with concomitant low HDLC and high TG had more reported myocardial infarctions (5 of 82) than probands with high TG alone (0 of 80, P = .02). In addition, there was a suggestive trend (P = .09) toward more cardiovascular disease in families of CT probands. This is consistent with Framingham data, suggesting enhanced incidence of heart disease in high TG subjects who also have low HDL-C.45 Similarly, in non–insulin-dependent diabetes,
7-year follow-up data suggested high TG as a risk predictor only in the presence of low HDL-C.46 In contrast, an enhanced mortality in male subjects with low HDL-C-hyper-TG was no longer observed after adjustments were made for fasting plasma glucose concentrations.47 Low HDL-C-hyper-TG subjects are noted to demonstrate insulin resistance48 concurrently associated with increased body mass index. Obesity is associated with elevations in TG and reductions in HDL-C. It was noted that both proband groups had an increased Quetelet (Fig 5), and the mean levels of QI as well as TG were higher in the CT proband group. However, distributional comparison provided no evidence for a significant difference in QI. Furthermore, even though the CT probands demonstrated a more skewed TG distribution than the hyper-TG probands, all TG values were >95th percentile. Therefore, group differences in QI and TG levels cannot totally explain the marked distinction between the family member HDL-C-TG distribution.

The independent correlation of HDL-C with cardiovascular risk49 may be the critical and relevant issue, excluding TG values as influential. However, the intricate metabolic connection between HDL and TG rich lipoproteins50 prompts speculation on some interactive effect for the development of vascular disease.43 A patient with high TG alone or low HDL-C alone may communicate a different basic mechanism and ultimate cardiovascular risk profile than one who concurrently expresses both high TG and hypoalpha.

In summary, high TG found in a clinic patient has relevance to family members. When high TG is found with low HDL-C in the proband, each of the HDL-C/TG phenotypes is enriched in the family. When high TG is noted alone in the proband, high TG and high QI are found in family members, however, the prevalence of low HDL-C is not enriched among associated family members. Therefore, the findings of high TG should prompt careful inspection of the HDL-C level since conjoined abnormalities in both HDL-C and TG tend to be associated with an enhanced risk for cardiovascular disease.

Acknowledgments

This study was supported by the Lipid Research Clinic, Cincinnati, Ohio. We appreciate the editorial assistance of Charles J. Glueck, MD.

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_Circulation._ 1994;90:1177-1184
doi: 10.1161/01.CIR.90.3.1177

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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