Total Cholesterol/HDL Cholesterol Ratio vs LDL Cholesterol/HDL Cholesterol Ratio as Indices of Ischemic Heart Disease Risk in Men

The Quebec Cardiovascular Study

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**Background:** Total cholesterol (TC)/high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C)/HDL-C ratios are used to predict ischemic heart disease risk. There is, however, no consensus on which of these 2 indices is superior. The objective of the present study was to present evidence that the LDL-C/HDL-C ratio may underestimate ischemic heart disease risk in overweight hyperinsulinemic patients with high triglyceride (TG)–low HDL-C dyslipidemia.

**Methods:** A total of 2103 middle-aged men in whom measurements of the metabolic profile were performed in the fasting state were recruited from 7 suburbs of the Quebec metropolitan area.

**Results:** The relationship of LDL-C/HDL-C to TC/HDL-C ratios was examined among men in the Quebec Cardiovascular Study classified into tertiles of fasting TG levels. For any given LDL-C/HDL-C ratio, the TC/HDL-C ratio was higher among men in the top TG tertile (>168 mg/dL [>1.9 mmol/L]) than in men in the first and second TG tertiles. Adjustment of the TC/HDL-C ratio for LDL-C/HDL-C by covariance analysis generated significant differences in average TC/HDL-C ratios among TG tertiles (P<.001). Greater differences in features of the insulin resistance syndrome (insulinemia, apolipoprotein B, and LDL size) were noted across tertiles of the TC/HDL-C ratio than tertiles of the LDL-C/HDL-C ratio.

**Conclusion:** Variation in the TC/HDL-C ratio may be associated with more substantial alterations in metabolic indices predictive of ischemic heart disease risk and related to the insulin resistance syndrome than variation in the LDL-C/HDL-C ratio.

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PARTICIPANTS AND METHODS

THE QUEBEC CARDIOVASCULAR STUDY

The population and evaluation procedures of the Quebec Cardiovascular Study have been described previously. Briefly, 2443 men were evaluated in 1985 for IHD risk factors, including familial history of IHD, history of smoking, diabetes mellitus, blood pressure measurement, height and weight, determination of the fasting plasma lipid and lipoprotein profile, and an electrocardiogram. Each participant completed a standardized questionnaire administered by trained nurses. After exclusion of men with fasting TG levels greater than 399 mg/dL (≥4.5 mmol/L) and patients with clinical signs of IHD, 2103 middle-aged men who were asymptomatic for IHD were followed for 5 years for the occurrence of IHD events. During this period, 114 men developed a first ischemic event, which included typical effort angina, coronary insufficiency, nonfatal myocardial infarction, and coronary death.24 Logistic regression analysis using the Cox proportional hazards model revealed that diabetes mellitus, LDL-C level, age, systolic blood pressure, HDL-C level, smoking, and medication use at baseline (β-adrenergic blocking agents and diuretics) were the best independent predictors of IHD in this cohort.25

LABORATORY ANALYSES

After participants had fasted for 12 hours, blood samples were obtained from an antecubital vein while participants were sitting. A tourniquet was used, but it was released before withdrawal of blood into Vacutainer tubes (Becton Dickinson, Mountain View, Calif) containing EDTA. Plasma was separated from blood cells by centrifugation and immediately used for measurement of lipoprotein-lipid and APOB levels. Aliquots of fasting plasma were frozen at the time of collection for subsequent assessment of insulin levels. Plasma TC and TG concentrations were determined using a Technicon RA-500 analyzer (Bayer Corp, Tarrytown, NY), as previously described.26 The HDL-C level was measured in the supernatant after precipitation of APOB-containing lipoproteins with heparin–manganese chloride.27 The LDL-C concentration was estimated using the equation of Friedewald et al28 because men with TG concentrations greater than 399 mg/dL (≥4.5 mmol/L) were excluded from the analyses. Plasma APOB concentrations were measured using the rocket immunoelectrophoretic method of Laurell,29 as previously described.29 Serum standards for the APOB assay were prepared in our laboratory (Lipid Research Center, Sainte-Foy, Quebec) and calibrated against serum samples obtained from the Centers for Disease Control and Prevention (Atlanta, Ga). The standards were lyophilized and stored at −80°C until use. The coefficients of variation for TC, HDL-C, and TG levels were all less than 3%, and for APOB measurements were less than 5%.

therapeutic target, whereas HDL-C levels may also be critical in the assessment of CHD risk. Thus, because TG levels are ignored in the National Cholesterol Education Program algorithm, the clinician is left with LDL-C and HDL-C levels to assess risk while considering the presence or absence of other important risk factors, such as family history of early CHD, age, smoking, hypertension, diabetes mellitus, low physical activity, and obesity. On this basis, the LDL-C/HDL-C ratio is often calculated to estimate CHD risk.

Results of prospective studies18,19 have suggested that a high LDL-C/HDL-C ratio combined with hypertriglyceridemia is associated with highest CHD risk. Thus, algorithms have been produced showing that an elevated...
LDL-C/HDL-C ratio combined with elevated TG is associated with high CHD risk. This dyslipidemic state (lipid triad) has been described as atherogenic dyslipidemia.  

We believe that this approach could be further simplified by using the TC/HDL-C ratio. Because there is more cholesterol in the very LDL (VLDL) fraction in individuals with elevated TG concentrations, the LDL-C/HDL-C ratio may underestimate the magnitude of the dyslipidemic state in these patients. On that basis, we propose that the high prevalence of moderate hypertriglyceridemia among patients with CHD explains why the TC/HDL-C ratio was the best predictor of ischemic heart disease (IHD) risk in several observational prospective studies, including the Quebec Cardiovascular Study.  

However, reduction of this ratio and of the LDL-C/HDL-C ratio in patients initially free of IHD who were treated with a lipid-lowering drug (lovastatin) was found to predict a decreased risk of a first IHD event.  

Therefore, the objective of this article was to present evidence from the Quebec Cardiovascular Study that supports the notion that the TC/HDL-C ratio may be a better and simpler cumulative marker of the presence of atherogenic dyslipidemia and of increased IHD risk than the LDL-C/HDL-C ratio.

Table 1 gives the baseline characteristics of the 114 men who developed IHD compared with those who remained IHD free during 5-year follow-up. Overall, men with IHD were characterized by an unfavorable metabolic profile compared with asymptomatic men. When the TC/HDL-C ratio was included in a multivariate model, it was found to be the best single predictor of IHD risk in the Quebec Cardiovascular Study.  

Neither TG nor HDL-C levels further contributed to IHD risk once the TC/HDL-C ratio had been considered in the analysis. These observations are concordant with results from the Copenhagen Male Study, where it was found that after adjustment for age and nonlipid risk factors, the TC/HDL-C ratio was the strongest predictor of IHD risk. Results presented in Figure 1 indicate that there was a progressive increase in the IHD odds ratio across quintiles of the TC/HDL-C ratio, whereas only men in quintiles 4 and 5 of the LDL-C/HDL-C ratio were characterized by increased IHD risk. We believe that there is a metabolic rationale underlying this finding. It is well documented that high TG–low HDL-C dyslipidemia, which is often linked to abdominal obesity and insulin resistance, is associated with marginal or even no change in LDL-C levels. Furthermore, LDL-C concentrations are often estimated from 3 measurements (TG, TC, and HDL-C) rather than measured directly. Thus, a variation that may reach 25% in estimated LDL-C levels could be explained by these 3 components.

Figure 1. Odds ratios for ischemic heart disease (IHD) during 5-year follow-up in 2103 men in the Quebec Cardiovascular Study classified according to quintiles of low-density lipoprotein cholesterol (LDL-C)/high-density lipoprotein cholesterol (HDL-C) (A) and total cholesterol (TC)/HDL-C (B) ratios. Numbers below the bars indicate the mean LDL-C/HDL-C or TC/HDL-C ratios for each quintile, whereas numbers above the bars indicate the relative odds ratio compared with the first quintile.
the TC/HDL-C ratio are measured directly, and this ratio can be used in men with TG levels greater than 399 mg/dL (>4.5 mmol/L).

As given in Table 2, men in the Quebec Cardiovascular Study with high TG–low HDL-C dyslipidemia (TG, ≥177 mg/dL [≥2.0 mmol/L]) and HDL-C, <35 mg/dL (<0.9 mmol/L) were characterized by a higher body mass index (calculated as weight in kilograms divided by the square of height in meters) and by elevated fasting insulin concentrations compared with normolipidemic men despite identical LDL-C levels in the 2 groups. Moreover, the IHD event rate was 2 times higher among these men. Thus, when the LDL-C/HDL-C ratio was computed in these overweight hyperinsulinemic patients with high TG–low HDL-C dyslipidemia, its increase resulted only from the reduced HDL-C levels associated with this condition (Figure 2). However, the increased TC/HDL-C ratio obtained in overweight hyperinsulinemic men with high TG–low HDL-C dyslipidemia not only resulted from the decreased HDL-C level but also from the slight increase in the TC level as more TC was associated with the calculated VLDL fraction in hypertriglyceridericemic individuals than in normolipidemic men (Figure 2). Thus, the relative difference in the TC/HDL-C ratio in overweight patients with high TG–low HDL-C dyslipidemia vs normotriglyceridericemic men (62%) was greater than the difference in the LDL-C/HDL-C ratio between these 2 groups (54%).

This phenomenon is further illustrated in Figure 3, in which participants in the Quebec Cardiovascular Study were stratified into tertiles of fasting TG levels. In all TG tertiles, significant correlations were observed between LDL-C/HDL-C and TC/HDL-C ratios between normolipidemic men and men of the Quebec Cardiovascular Study with high triglyceride (TG)–low HDL-C dyslipidemia. VLDL indicates very low-density lipoprotein; ellipses, not applicable. To convert cholesterol from milligrams per deciliter to millimoles per liter, multiply milligrams per deciliter by 0.02586. To convert insulin from microunits per milliliter to picomoles per liter, multiply microunits per milliliter by 0.02586.

Table 2. Characteristics of 1426 Men in the Quebec Cardiovascular Study Classified on the Basis of TG and HDL-C Levels

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normolipidemic Men† (n = 1127)</th>
<th>High TG–Low HDL-C Dyslipidemic Men†† (n = 299)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56.4 ± 6.9</td>
<td>56.3 ± 7.4</td>
</tr>
<tr>
<td>Body mass index§</td>
<td>23.5 ± 3.6</td>
<td>27.6 ± 3.4</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL¶</td>
<td>217 ± 36</td>
<td>227 ± 39†</td>
</tr>
<tr>
<td>TG, mg/dLопередко</td>
<td>116 ± 31</td>
<td>244 ± 53†</td>
</tr>
<tr>
<td>LDL-C, mg/dLопередко</td>
<td>149 ± 34</td>
<td>149 ± 34</td>
</tr>
<tr>
<td>HDL-C, mg/dLопередко</td>
<td>45 ± 9</td>
<td>29 ± 4</td>
</tr>
<tr>
<td>Total cholesterol/HDL-C ratio</td>
<td>4.94 ± 1.11</td>
<td>7.98 ± 1.59‡</td>
</tr>
<tr>
<td>LDL-C/HDL-C ratio</td>
<td>3.41 ± 1.00</td>
<td>5.25 ± 1.45†</td>
</tr>
<tr>
<td>Apolipoprotein B, mg/dL</td>
<td>108 ± 26</td>
<td>135 ± 30†</td>
</tr>
<tr>
<td>Fasting insulin, µU/mL**</td>
<td>10 ± 5</td>
<td>13 ± 6†</td>
</tr>
<tr>
<td>Event rate, ††</td>
<td>3.19</td>
<td>6.02†</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD, except where indicated otherwise. TG indicates triglyceride; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.
†To convert total, LDL, and HDL cholesterol from milligrams per deciliter to millimoles per liter, multiply milligrams per deciliter by 0.02586.
‡To convert TG from milligrams per deciliter to millimoles per liter, multiply milligrams per deciliter by 0.02586.
§Calculated as weight in kilograms divided by the square of height in meters.
¶To convert total, LDL, and HDL cholesterol from milligrams per deciliter to millimoles per liter, multiply milligrams per deciliter by 0.02586.
**To convert insulin from microunits per milliliter to picomoles per liter, multiply microunits per milliliter by 6.945.
††P<.05.

Figure 2. Relative differences in the total cholesterol (TC)/high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C)/HDL-C ratios between normolipidemic men and men of the Quebec Cardiovascular Study with high triglyceride (TG)–low HDL-C dyslipidemia. VLDL indicates very low-density lipoprotein; ellipses, not applicable. To convert cholesterol from milligrams per deciliter to millimoles per liter, multiply milligrams per deciliter by 0.02586. To convert insulin from microunits per milliliter to picomoles per liter, multiply microunits per milliliter by 6.945. Body mass index is calculated as weight in kilograms divided by the square of height in meters.
Figure 3. Relationships between the low-density lipoprotein cholesterol (LDL-C)/high-density lipoprotein cholesterol (HDL-C) and total cholesterol (TC)/HDL-C ratios among men in the Quebec Cardiovascular Study divided into tertiles of fasting plasma triglyceride (TG) levels. To convert TG from milligrams per deciliter to millimoles per liter, multiply milligrams per deciliter by 0.01129.

Figure 4. Low-density lipoprotein cholesterol (LDL-C)/high-density lipoprotein cholesterol (HDL-C) and total cholesterol (TC)/HDL-C ratios according to triglyceride (TG) tertiles in men in the Quebec Cardiovascular Study. Asterisk indicates significantly different from the first tertile; dagger, significantly different from the second tertile (P<.001). The relative difference between the third and first tertiles of LDL-C/HDL-C or TC/HDL-C ratios is indicated above the bar. Numbers within parentheses indicate the mean TG level for each tertile. Error bars represent SE. To convert TG from milligrams per deciliter to millimoles per liter, multiply milligrams per deciliter by 0.01129.
Thus, the results indicate that individuals with similar LDL-C/HDL-C ratios may have markedly different TC/HDL-C ratios depending on their fasting TG levels. Lamarche et al. also previously reported that patients with high TG–low HDL-C are characterized by clustering metabolic abnormalities described as the atherogenic metabolic triad (insulin, APOB, and LDL size) across tertiles of TC/HDL-C and LDL-C/HDL-C ratios. There was a progressive increase in plasma APOB (+47 mg/dL; +50%) and insulin (+3 µU/mL [+21.3 pmol/L]; +32%) levels from the first to the third TC/HDL-C tertiles, which was accompanied by a significant decrease in LDL peak particle size (−4.65 Å; −2%). There was also a progressive increase in APOB (+48 mg/dL; +52%) and insulin (+2 µU/mL [+14.7 pmol/L]; +21%) concentrations and a decrease in LDL peak particle diameter (−3.52 Å; −1%) in the first vs third tertiles of the LDL-C/HDL-C ratio. However, there was a greater deterioration in 2 of the 3 features of the atherogenic metabolic triad (insulin and LDL size) across TC/HDL-C ratio tertiles than among tertiles of the LDL-C/HDL-C ratio. Therefore, although both LDL-C/HDL-C and TC/HDL-C ratios were significantly correlated with the features of the atherogenic metabolic triad related to the insulin resistance syndrome (hyperinsulinemia, elevated APOB level, and small, dense LDL particles), variation in the TC/HDL-C ratio seems to better reflect underlying metabolic alterations.

Accordingly, Figure 6 compares these features of the atherogenic metabolic triad (insulin, APOB, and LDL size) across tertiles of TC/HDL-C and LDL-C/HDL-C ratios. There was a progressive increase in plasma APOB (+47 mg/dL; +50%) and insulin (+3 µU/mL [+21.3 pmol/L]; +32%) levels from the first to the third TC/HDL-C tertiles, which was accompanied by a significant decrease in LDL peak particle size (−4.65 Å; −2%). There was also a progressive increase in APOB (+48 mg/dL; +52%) and insulin (+2 µU/mL [+14.7 pmol/L]; +21%) concentrations and a decrease in LDL peak particle diameter (−3.52 Å; −1%) in the first vs third tertiles of the LDL-C/HDL-C ratio. However, there was a greater deterioration in 2 of the 3 features of the atherogenic metabolic triad (insulin and LDL size) across TC/HDL-C ratio tertiles than among tertiles of the LDL-C/HDL-C ratio. Therefore, although both LDL-C/HDL-C and TC/HDL-C ratios were significantly correlated with the features of the atherogenic metabolic triad related to the insulin resistance syndrome (hyperinsulinemia, elevated APOB level, and small, dense LDL particles), variation in the TC/HDL-C ratio seems to better reflect underlying metabolic alterations.

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Table 3. Characteristics of Men in the Quebec Cardiovascular Study Classified on the Basis of Tertiles of TG Levels After Adjustment for LDL-C/HDL-C Ratio by Covariance Analysis *

<table>
<thead>
<tr>
<th>Variable</th>
<th>&lt;115 (1) (n = 666)</th>
<th>115-168 (2) (n = 735)</th>
<th>&gt;168 (3) (n = 699)</th>
<th>Difference, (1) vs (3), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56.5 ± 7.5</td>
<td>56.7 ± 7.0</td>
<td>56.4 ± 7.4</td>
<td>−0.2</td>
</tr>
<tr>
<td>Body mass index†</td>
<td>25.0 ± 3.9</td>
<td>26.3 ± 3.5‡</td>
<td>27.1 ± 3.7§</td>
<td>8.4</td>
</tr>
<tr>
<td>TG, mg/dL¶</td>
<td>93 ± 46</td>
<td>140 ± 24‡</td>
<td>229 ± 23§</td>
<td>146.7</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL¶</td>
<td>217 ± 30</td>
<td>220 ± 31</td>
<td>226 ± 31§</td>
<td>4.1</td>
</tr>
<tr>
<td>LDL-C, mg/dL¶</td>
<td>156 ± 30</td>
<td>152 ± 21‡</td>
<td>142 ± 31§</td>
<td>−8.9</td>
</tr>
<tr>
<td>HDL-C, mg/dL¶</td>
<td>42 ± 7</td>
<td>40 ± 7†</td>
<td>38 ± 7§</td>
<td>−11.0</td>
</tr>
<tr>
<td>Total cholesterol/HDL-C ratio</td>
<td>5.49 ± 0.26</td>
<td>5.73 ± 0.27‡</td>
<td>6.33 ± 0.26§</td>
<td>15.3</td>
</tr>
<tr>
<td>LDL-C/HDL-C ratio</td>
<td>3.99</td>
<td>3.99</td>
<td>3.99</td>
<td>0</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD, except where indicated otherwise. TG indicates triglyceride; LDL-C, low-density lipoprotein cholesterol; and HDL-C, high-density lipoprotein cholesterol.
†There were 664, 735, and 697 participants for tertiles 1, 2, and 3, respectively. Body mass index calculated as weight in kilograms divided by the square of height in meters.
‡Significantly different from tertile (1).
§Significantly different from tertiles (1) and (2).
*To convert TG from milligrams per deciliter to millimoles per liter, multiply millimoles per deciliter by 0.01129.
†To convert total, LDL, and HDL cholesterol from milligrams per deciliter to millimoles per liter, multiply milligrams per deciliter by 0.02586.
in the features of the insulin resistance syndrome than the LDL-C/HDL-C ratio.

**COMMENT**

An elevated TC/HDL-C ratio in men is observed among overweight, hyperinsulinemic, and hypertriglyceridemic individuals. Additional metabolic alterations found in these individuals include, among others, elevated APOB levels, an exaggerated postprandial lipemia, and small, dense LDL particles. Results of the present study suggest that these atherogenic metabolic disturbances may not always be adequately reflected by the variation in the LDL-C/HDL-C ratio.

In the Quebec Cardiovascular Study, Lamarche et al previously reported that variables such as APOB and fasting insulin levels and LDL size could provide a more refined evaluation of IHD risk than traditional lipid variables. In clinical practice, however, these markers are not measured, and we propose that, in addition to the well-established conventional risk factors, the TC/HDL-C ratio may represent an important cumulative index of the presence of an atherogenic dyslipidemic profile associated with insulin resistance. Because the high TG–low HDL-C dyslipidemia associated with small, dense LDL particles has been suggested to represent the most prevalent lipoprotein phenotype among patients with CHD, the importance of measuring and properly interpreting the TC/HDL-C ratio (rather than the LDL-C/HDL-C ratio) is emphasized.

In summary, the TC/HDL-C ratio was a useful and simple index of IHD risk in men in the Quebec Cardiovascular Study. It is proposed that the ability of this ratio to predict risk is explained by the fact that it is a relevant cumulative marker of the cluster of metabolic abnormalities found in individuals with high TG–low HDL-C dyslipidemia. This condition has been shown to be the consequence of abdominal obesity and insulin resistance and is also commonly associated with an increased concentration of small, dense LDL particles. Because little variation is found in plasma LDL-C levels in overweight hyperinsulinemic men compared with normolipidemic individuals, we propose that calculation of the LDL-C/HDL-C ratio may underestimate IHD risk in some patients compared with the quality of the estimation achieved with the simple use of the TC/HDL-C ratio.

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REFERENCES


