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 (TG >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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Despite considerable advances during the past 40 years, there is increasing awareness among scientists, epidemiologists, and clinicians that current approaches to evaluation of coronary heart disease (CHD) risk in asymptomatic individuals remain suboptimal.1 There is also controversy around recommending widespread use of additional metabolic markers, such as apolipoprotein (APO) levels, indices of fibrinolytic activity and of susceptibility to thrombosis (eg, plasminogen activator inhibitor–1 and lipoprotein[a] levels), markers of inflammation (eg, C-reactive protein levels), and markers of insulin resistance (waist circumference and fasting insulin levels).2-9 Although all of these markers have been shown to predict CHD events, whether these variables contribute to CHD risk independently of the variation in traditional risk factors and lipid variables remains a matter of debate.

Regarding the traditional fasting plasma lipid profile (triglycerides [TGs], total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C] [which is most often calculated rather than measured directly], and high-density lipoprotein cholesterol [HDL-C]), there is no universal acceptance of how this information should be used and interpreted, although several consensus documents have been produced.2,10-13 Because there is overwhelming evidence14,15 that an elevated LDL-C concentration in plasma is atherogenic, whereas a high HDL-C level is cardioprotective,16-17 the measurement and interpretation of LDL-C and HDL-C levels is emphasized in the US National Cholesterol Education Program guidelines.11 According to these guidelines,11 LDL-C concentration should be considered the primary

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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, hyperten-

sion, 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 studies 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
The TC/HDL-C ratio combined with elevated TG is associated with high CHD risk. This dyslipidemic state (lipid triad) has been described as atherogenic dyslipidemia.20 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.5 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.21 These observations are concordant with results from the Copenhagen Male Study,33 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.34 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.33 This variation may therefore have a major effect on the calculated 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.

### Table 1. Characteristics of 114 Men in the Quebec Cardiovascular Study Who Developed IHD Compared With 1989 Men Who Remained IHD Free During 5-Year Follow-up*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Without IHD (n = 1989)</th>
<th>With IHD (n = 114)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56 ± 7</td>
<td>59 ± 8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Body mass index†</td>
<td>26 ± 4</td>
<td>27 ± 4</td>
<td>.07</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>4</td>
<td>16</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>34</td>
<td>44</td>
<td>.07</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>130 ± 17</td>
<td>137 ± 17</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>81 ± 10</td>
<td>82 ± 12</td>
<td>.47</td>
</tr>
<tr>
<td>Triglycerides, mg/dL§</td>
<td>154 ± 66</td>
<td>177 ± 66</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL‡</td>
<td>220 ± 38</td>
<td>235 ± 41</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LDL-C, mg/dL§</td>
<td>149 ± 35</td>
<td>162 ± 37</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HDL-C, mg/dL§</td>
<td>40 ± 10</td>
<td>37 ± 9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Apolipoprotein B, mg/dL</td>
<td>1.16 ± 0.30</td>
<td>1.30 ± 0.32</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total cholesterol/HDL-C ratio</td>
<td>5.81 ± 1.68</td>
<td>6.67 ± 1.91</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LDL-C/HDL-C ratio</td>
<td>3.96 ± 1.35</td>
<td>4.60 ± 1.51</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD, except where indicated otherwise. IHD indicates ischemic heart disease; LDL-C, low-density lipoprotein cholesterol; and HDL-C, high-density lipoprotein cholesterol.
†Calculated as weight in kilograms divided by the square of height in meters.
‡To convert triglycerides from milligrams per deciliter to millimoles per liter, multiply milligrams 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.

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![Image of Table 2 and Figure 2]
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.
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 = 653)</th>
<th>115-168 (2) (n = 735)</th>
<th>&gt;168 (3) (n = 697)</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>42 ± 7</td>
<td>40 ± 7‡</td>
<td>38 ± 7§</td>
<td>−11.0</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>HDL-C, mg/dL¶</td>
<td>156 ± 30</td>
<td>152 ± 21‡</td>
<td>142 ± 31§</td>
<td>−8.9</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.

Figure 5. Fasting apolipoprotein B and insulin levels and low-density lipoprotein (LDL) peak particle size among 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). 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 millimoles per deciliter by 0.01129. To convert insulin from microunits per milliliter to picomoles per liter, multiply microunits per milliliter by 6.945.

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 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 involving LDL-C/HDL-C ratios by covariance analysis (Table 3). Thus, when the TC/HDL-C ratios across TG tertiles were standardized for an LDL-C/HDL-C ratio of 5.49, the second TG tertile (TG, 115–168 mg/dL [1.3–1.9 mmol/L]) had a TC/HDL-C ratio of 5.73, whereas the top TG tertile (TG, >168 mg/dL [>1.9 mmol/L]) had a TC/HDL-C ratio that reached 6.33. 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 al38 also previously reported that patients with high TG–low HDL-C are characterized by clustering metabolic abnormalities described as the atherogenic metabolic triad of nontraditional risk factors, which included hyperinsulinemia, elevated APOB level, and small, dense LDL particles. Thus, a higher proportion of men with elevated TG levels were also characterized by the atherogenic metabolic triad. Figure 5 shows that men with high TG concentrations had elevated APOB and insulin levels and smaller LDL particles than men characterized by low TG levels.
in the features of the insulin resistance syndrome than the LDL-C/HDL-C ratio.

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


