Relationship between Serum Lipoprotein Ratios and Insulin Resistance in Obesity

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Background: The fasting serum lipid profile [triglycerides (TGs), total cholesterol (TC), and LDL- and HDL-cholesterol (LDL-C and HDL-C)] is used to calculate lipid ratios (TC/HDL-C, LDL-C/HDL-C, TG/HDL-C) that allow identification of individuals at increased risk for cardiovascular disease. Because these individuals are also frequently insulin resistant, this study analyzed the relationships between lipid ratios and insulin sensitivity.

Methods: In 132 obese [mean (SE) body mass index, 37.5 (0.6) kg/m²] outpatients without known diabetes mellitus, fasting serum lipid profiles and 75-g oral glucose tolerance tests were performed. Insulin sensitivity was assessed from surrogate estimates for fasting (QUICKI) and dynamic (OGIS) conditions.

Results: After exclusion of other endocrine diseases (n = 35), the remaining patients were classified as glucose tolerant (n = 56), glucose intolerant (n = 22), or as having type 2 diabetes (n = 19). QUICKI and OGIS indicated severe insulin resistance in all individuals with type 2 diabetes and impaired glucose tolerance compared with glucose-tolerant individuals: QUICKI, glucose tolerant, 0.302 (0.002); glucose intolerant, 0.290 (0.002); type 2 diabetes, 0.281 (0.003); P < 0.001; OGIS (mL · m² · min⁻¹), glucose tolerant, 343 (7), glucose intolerant, 293 (9); type 2 diabetes, 256 (12); P < 0.001. Serum TG (P < 0.005) and TG/HDL-C ratios (P < 0.05) were increased in individuals with impaired glucose tolerance. TG/HDL-C ratios negatively correlated with QUICKI (r = −0.370; P < 0.001) and OGIS (r = −0.333; P < 0.005) in nondiabetic individuals.

Conclusions: This study demonstrates that the TG/HDL-C ratio positively correlates with insulin resistance in severely obese nondiabetic individuals.

Obesity has recently become so prevalent across the world that it is replacing undernourishment and infectious diseases as the most significant contributor to poor health (1). In particular, obesity is part of the metabolic syndrome and of type 2 diabetes mellitus, which both cluster several abnormalities, including insulin resistance, dyslipidemia, and markers of cardiovascular disease (2, 3).

Increased serum concentrations of LDL-cholesterol (LDL-C) are atherogenic (4, 5), whereas increased HDL-cholesterol (HDL-C) is considered cardioprotective (5, 6). Increased serum concentrations of triglycerides (TGs) have also been recognized as a risk factor for cardiovascular disease (7, 8). However, several epidemiologic studies demonstrated that the total cholesterol (TC)/HDL-C and the LDL-C/HDL-C ratios are better predictors of atherosclerosis and cardiovascular disease than any other single lipid marker (9–11). Likewise, the TG/HDL-C ratio was demonstrated to be as significant a predictor of cardiovascular disease as the two other lipid ratios (7).

The better ability of lipid ratios to predict cardiovascular disease compared with single lipid markers is of particular clinical relevance and can be possibly explained by association of lipid ratios with a cluster of cardiovascular risk factors that are at least in part unrelated to cholesterol metabolism (12). The TC/HDL-C ratio was shown to correlate negatively with rates of insulin-stimulated glucose disposal in a small group of healthy

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individuals (13). Subsequently, nondiabetic individuals who were of normal weight or overweight and had an increased TC/HDL-C ratio were shown to exhibit resistance to insulin-stimulated glucose disposal and to have higher blood pressure, increased TG concentrations, and hyperinsulinemia; each of these factors is part of the metabolic syndrome and is an independent risk factor for cardiovascular disease (12).

Increased TG/HDL-C ratios are able to identify insulin-resistant overweight individuals with normal glucose tolerance and are markers of insulin resistance with specificities and sensitivities similar to those for fasting tolerance and are markers of insulin resistance with normal glucose tolerance status but exclude patients with other endocrine or metabolic disorders. The present study therefore aimed to assess whether the TC/HDL-C, LDL-C/HDL-C, and TG/HDL-C ratios relate to surrogate estimates of insulin sensitivity in an obese population and whether these relationships vary across categories of glucose tolerance.

**Participants and Methods**

**Participants**

Individuals (n = 132) with a body mass index > 30 kg/m² who had been referred to the endocrine outpatient service were examined. None of them was previously known to have either diabetes mellitus or impaired glucose tolerance or was taking hypoglycemic agents. Thirty-four individuals were excluded from further analysis because of treatment with lipid-lowering drugs (n = 10), hypothyroidism (n = 4), hyperthyroidism (n = 2), Cushing syndrome (n = 4), steroid therapy (n = 3), adrenal incidentalomas (n = 7), pheochromocytoma, primary hyperparathyroidism, hyperprolactinemia, or cyclosporine therapy after kidney transplantation (n = 1 for each).

All procedures were performed according to the Helsinki Declaration of 1975 as revised in 1996 and according to guidelines of Good Clinical Practice.

**Protocol**

After an overnight fast, an indwelling catheter was inserted at 0800 into an antecubital vein, and a baseline blood sample was obtained to determine fasting concentrations of plasma glucose and of serum insulin, C-peptide, TC, HDL-C, and TGs. All participants received a standard glucose solution containing 75 g of glucose (GlucoDrink 75; Roche Diagnostics). Blood samples for the measurement of plasma glucose and serum insulin and C-peptide concentrations were taken at 60, 90, and 120 min after glucose ingestion.

Participants were classified as having diabetes when the venous fasting plasma glucose concentration was ≥1260 mg/L and/or the 120-min plasma glucose concentration during the oral glucose tolerance test was ≥2000 mg/L. Impaired fasting glycaemia was diagnosed when the fasting plasma glucose concentration was greater than or equal to 1100 mg/L but less than 1260 mg/L and the 120-min plasma glucose concentration during the oral glucose tolerance test was < 1400 mg/L. Impaired glucose tolerance was diagnosed when the fasting plasma glucose concentration was < 1260 mg/L and the 120-min plasma glucose concentration during the oral glucose tolerance test was greater than 1400 mg/L but less than 2000 mg/L (19).

**Analytical Procedures**

Glucose was measured in venous fluoride EDTA plasma by the hexokinase method. Insulin (Adaltis) and C-peptide (PerkinElmer) concentrations were measured in serum by commercially available RIAs. Serum TC, HDL-C, and TG concentrations were determined enzymatically in the routine laboratory (20, 21). Serum LDL-C was calculated according to the Friedewald formula. One individual with serum TG > 4000 mg/L was excluded from data analysis because use of the Friedewald formula is not applicable under these conditions.

**Calculations**

Insulin sensitivity was calculated both in the fasting state and during the oral glucose tolerance test.

For the former, the quantitative insulin sensitivity check index (QUICKI) was used and calculated as the inverse of the sum of the logarithmic transformation of fasting concentrations of serum insulin and plasma glucose (22). This index has previously been shown to be a surrogate measure of insulin sensitivity, given the significant correlation with glucose disposal during euglycemic hyperinsulinemic glucose clamp tests (22–24).

The oral glucose insulin sensitivity index (OGIS; mL m⁻² min⁻¹) was used as a descriptor of dynamic insulin sensitivity during the oral glucose tolerance test (25). This index has also been shown to positively correlate with glucose clearance obtained during hyperinsulinemic euglycemic glucose clamp tests in lean, obese, and type 2 diabetic individuals and is used as another surrogate measure of insulin sensitivity (25, 26). The OGIS is calculated according to a model-derived formula that includes the oral glucose dose; the body surface area; six fixed rate constants; the measured plasma concentrations of glucose at 0, 90, and 120 min; and the measured concentration of serum insulin at 0 and 90 min during the oral glucose tolerance test (25).
The relationship between both surrogate measures of insulin sensitivity and direct measures of insulin sensitivity have previously been shown to vary only slightly between obese individuals with normal and impaired glucose tolerance, first-degree relatives of patients with type 2 diabetes, and overweight to obese type 2 diabetic patients (23–25).

**Statistical Analysis**
All statistical analyses were performed using SPSS 11.0 software (SPSS Inc.). Data are presented as means (SE).

Comparisons between groups of glucose tolerant, impaired glucose tolerant, and type 2 diabetic individuals were performed with one-way ANOVA with Tukey correction for several comparisons. Linear correlations are Pearson product–moment correlations.

To exclude possible effects of age and body mass index on the relationship between the three lipid ratios and the two indices of insulin sensitivity, multiple linear regression analyses were performed. QUICKI or OGIS was entered as the dependent variable, and age, body mass index, and the respective lipid ratio were entered as predictors. Partial correlation coefficients of the lipid ratios with QUICKI and OGIS from these analyses are presented. $P <0.05$ was considered to indicate a statistically significant difference.

**Results**

**Clinical Characteristics and Glucose Tolerance**
On the basis of the oral glucose tolerance test, 56 (58%) individuals were glucose tolerant, 22 (23%) exhibited previously unknown impaired glucose tolerance, and 19 (20%) were newly diagnosed with overt diabetes mellitus. Interestingly, none of the participants fulfilled the criteria for the diagnosis of impaired fasting glycemia. The clinical characteristics, fasting serum lipid profiles, and calculated lipid ratios are summarized in Table 1. The individuals newly diagnosed with type 2 diabetes mellitus were older than individuals with normal glucose tolerance ($P <0.01$), whereas mean ages of the individuals with normal and impaired glucose tolerance were comparable ($P = 0.376$).

### Table 1. Clinical characteristics and fasting serum concentrations of TC, HDL-C, LDL-C, and TGs in individuals with normal or impaired glucose tolerance and patients with type 2 diabetes mellitus.$^a$

<table>
<thead>
<tr>
<th></th>
<th>NGT$^b$</th>
<th>IGT</th>
<th>T2DM</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (F/M)</td>
<td>56 (35/21)</td>
<td>22 (16/6)</td>
<td>19 (12/7)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>39 (2)</td>
<td>46 (3)</td>
<td>51 (3)$^c$</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Body mass index, kg/m$^2$</td>
<td>37.5 (0.7)</td>
<td>36.4 (1.0)</td>
<td>38.7 (1.0)</td>
<td>0.376</td>
</tr>
<tr>
<td>Body surface area, m$^2$</td>
<td>2.19 (0.03)</td>
<td>2.13 (0.06)</td>
<td>2.18 (0.06)</td>
<td>0.575</td>
</tr>
<tr>
<td>TC, mg/L</td>
<td>2084 (52)</td>
<td>2246 (68)</td>
<td>2063 (84)</td>
<td>0.179</td>
</tr>
<tr>
<td>HDL-C, mg/L</td>
<td>504 (18)</td>
<td>474 (19)</td>
<td>489 (26)</td>
<td>0.607</td>
</tr>
<tr>
<td>LDL-C, mg/L</td>
<td>1311 (46)</td>
<td>1394 (67)</td>
<td>1231 (78)</td>
<td>0.305</td>
</tr>
<tr>
<td>TGs, mg/L</td>
<td>1350 (67)</td>
<td>1891 (174)$^d$</td>
<td>1716 (154)</td>
<td>&lt;0.050</td>
</tr>
<tr>
<td>TC/HDL-C ratio</td>
<td>4.33 (0.14)</td>
<td>4.90 (0.24)</td>
<td>4.44 (0.28)</td>
<td>0.134</td>
</tr>
<tr>
<td>LDL-C/HDL-C ratio</td>
<td>2.73 (0.11)</td>
<td>3.04 (0.20)</td>
<td>2.65 (0.21)</td>
<td>0.279</td>
</tr>
<tr>
<td>TG/HDL-C ratio</td>
<td>3.01 (0.25)</td>
<td>4.25 (0.48)$^d$</td>
<td>3.93 (0.53)</td>
<td>&lt;0.050</td>
</tr>
</tbody>
</table>

$^a$ Data are means (SE), except for number and gender of individuals in each group.

$^b$ NGT, normal glucose tolerance; IGT, impaired glucose tolerance; T2DM, type 2 diabetes mellitus.

$^c,d$ Significant differences ($P <0.05$) between groups (ANOVA, post hoc Tukey correction): $^c$ T2DM vs NGT; $^d$ IGT vs NGT.
Individuals with impaired glucose tolerance did not differ between patients with type 2 diabetes and individuals with normal glucose tolerance. Mean (SE) fasting insulin sensitivity indices (QUICKI) did not differ between patients with type 2 diabetes and individuals with normal glucose tolerance. Individuals with impaired glucose tolerance and lowest in glucose-tolerant individuals. Serum insulin concentrations of glucose, insulin, and C-peptide responses were generally highest in individuals with impaired glucose tolerance compared with individuals with normal glucose tolerance.

**Table 2. Pearson product moment correlation coefficients (r) and age- and body mass index-corrected partial correlation coefficients (r_p) between the three lipid ratios and surrogate measures of fasting (QUICKI) and dynamic (OGIS) indices of insulin sensitivity in obese individuals with normal glucose tolerance, impaired glucose tolerance, or type 2 diabetes.**

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Group</th>
<th>QUICKI</th>
<th>OGIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC/HDL-C</td>
<td>NGT&lt;sup&gt;a&lt;/sup&gt;</td>
<td>r: -0.152, P: NS&lt;sup&gt;b&lt;/sup&gt;, r_p: -0.161, P: NS</td>
<td>r: -0.145, P: NS, r_p: -0.158, P: NS</td>
</tr>
<tr>
<td></td>
<td>IGT</td>
<td>r: -0.330, P: 0.13, r_p: -0.193, P: NS</td>
<td>r: 0.013, P: NS, r_p: 0.076, P: NS</td>
</tr>
<tr>
<td></td>
<td>T2DM</td>
<td>r: 0.132, P: NS, r_p: 0.242, P: NS</td>
<td>r: -0.070, P: NS, r_p: -0.050, P: NS</td>
</tr>
<tr>
<td>LDL/HDL-C</td>
<td>NGT</td>
<td>r: -0.018, P: NS, r_p: -0.032, P: NS</td>
<td>r: -0.094, P: NS, r_p: -0.100, P: NS</td>
</tr>
<tr>
<td></td>
<td>IGT</td>
<td>r: -0.212, P: 0.084, r_p: 0.10</td>
<td>r: 0.195, P: NS, r_p: -0.274, P: NS</td>
</tr>
<tr>
<td></td>
<td>T2DM</td>
<td>r: 0.272, P: NS, r_p: 0.440, P: 0.10</td>
<td>r: -0.084, P: NS, r_p: -0.081, P: NS</td>
</tr>
<tr>
<td>TG/HDL-C</td>
<td>NGT</td>
<td>r: -0.396&lt;sup&gt;c&lt;/sup&gt;, P: 0.002, r_p: -0.400&lt;sup&gt;c&lt;/sup&gt;, P: 0.003</td>
<td>r: -0.203, P: 0.13, r_p: -0.235, P: 0.086</td>
</tr>
<tr>
<td></td>
<td>IGT</td>
<td>r: -0.399, P: 0.066, r_p: -0.323, P: 0.094</td>
<td>r: -0.375, P: 0.086, r_p: -0.365, P: 0.10</td>
</tr>
<tr>
<td></td>
<td>T2DM</td>
<td>r: -0.155, P: NS, r_p: -0.188, P: NS</td>
<td>r: -0.020, P: NS, r_p: 0.026, P: NS</td>
</tr>
</tbody>
</table>

<sup>a</sup> NGT, normal glucose tolerance; IGT, impaired glucose tolerance; T2DM, type 2 diabetes mellitus.
<sup>b</sup> NS, not significant (P ≥ 0.2).
<sup>c</sup> Correlations considered significant at P < 0.05.

0.175). Height, weight, body mass index, and body surface area also did not differ among the three groups.

**Fasting Serum Lipid Profile and Lipid Ratios**

TC, HDL-C, and LDL-C concentrations did not differ among individuals who were glucose tolerant, had impaired glucose tolerance, or had type 2 diabetes (Table 1). Compared with individuals with normal glucose tolerance, patients with impaired glucose tolerance (P < 0.005) had higher TG values; these values also tended to be higher in patients with type 2 diabetes (P = 0.072). Neither the TC/HDL-C (P = 0.134) nor the LDL-C/HDL-C ratio (P = 0.279) differed among the groups. Individuals with impaired glucose tolerance had ~1.5-fold higher TG/HDL-C ratios (P < 0.05) than did individuals who were glucose tolerant. The TG/HDL-C ratio was not different between glucose-tolerant individuals and patients with type 2 diabetes.

**Concentrations of Glucose, Insulin, and C-peptide during the Oral Glucose Tolerance Test**

Concentrations of plasma glucose, serum insulin, and serum C-peptide during the oral glucose tolerance test in individuals with normal glucose tolerance, individuals with impaired glucose tolerance, and individuals with type 2 diabetes are shown in Fig. 1. By definition, plasma glucose concentrations in response to the oral glucose challenge were highest in patients with type 2 diabetes and lowest in glucose-tolerant individuals. Serum insulin and C-peptide responses were generally highest in individuals with impaired glucose tolerance and lowest in individuals with normal glucose tolerance.

**Insulin Sensitivity in the Patient Groups**

Mean (SE) fasting insulin sensitivity indices (QUICKI) did not differ between patients with type 2 diabetes and individuals with impaired glucose tolerance [0.290 (0.002) for individuals with impaired glucose tolerance vs 0.281 (0.005) for patients with type 2 diabetes; P = 0.198] but were higher in individuals with normal glucose tolerance [0.302 (0.005)] compared with both individuals with impaired glucose tolerance (P < 0.05) and patients with type 2 diabetes (P < 0.001). Dynamic insulin sensitivity (OGIS) was lowest in patients with type 2 diabetes [256 (12) mL·m⁻²·min⁻¹] compared with individuals with impaired glucose tolerance [293 (9) mL·m⁻²·min⁻¹; P < 0.05] and glucose-tolerant individuals [343 (7) mL·m⁻²·min⁻¹; P < 0.01] and was lower in individuals with impaired glucose tolerance compared with individuals with normal glucose tolerance (P < 0.05).

**Correlation Analysis between Lipid Ratios and Measures of Insulin Sensitivity**

The relationship between the three lipid ratios and both surrogate measures of insulin sensitivity was assessed within the groups of individuals who had normal glucose tolerance, had impaired glucose tolerance, or had type 2 diabetes (Table 2). Neither the TC/HDL-C nor the LDL-C/HDL-C ratio showed any significant relationships to both indices of insulin sensitivity in individuals who had normal glucose tolerance, had impaired glucose tolerance, or had type 2 diabetes.

The TG/HDL-C ratio negatively correlated with fasting insulin sensitivity in glucose-tolerant individuals and also tended (P ≤ 0.1) to be negatively correlated with fasting and dynamic indices of insulin sensitivity in individuals with impaired glucose tolerance. No relationship between the TG/HDL-C ratio and measures of insulin sensitivity was found in the group with type 2 diabetes. When individuals with normal and impaired glucose tolerance were combined, correlation analysis revealed a negative relationship between TG/HDL-C ratios and indices of fasting insulin sensitivity (QUICKI, r = -0.370; P < 0.001; Fig. 2A). This also was true for the relationship between the TG/HDL-C ratios and indices of
Discussion

These data show that the relationship between lipid ratios and insulin sensitivity varies between groups with different glucose tolerance status in an exclusively obese population (body mass index range, 30–57 kg/m²). Only the TG/HDL-C ratio correlated negatively with surrogate measures of insulin sensitivity in nondiabetic individuals but not in patients with type 2 diabetes mellitus. The groups were comparable with regard to measures of adiposity, such as body mass index and body surface area. Fasting serum TG concentrations were ~40% higher in individuals with impaired glucose tolerance and also tended to be ~27% higher in patients with type 2 diabetes, whereas TC and LDL-C values were similar in all groups. This is in line with the positive association between serum TG concentrations and insulin resistance (27–30) and the unchanged serum concentrations of TC and LDL-C in insulin-resistant states (14, 28, 31–36).

The relationships between the three lipid ratios (TC/HDL-C, LDL-C/HDL-C, TG/HDL-C) and both surrogate measures of insulin sensitivity were analyzed with multiple linear regression analyses, which allowed us to exclude the confounding effects of age and body mass index on these relationships. TC/HDL-C ratios were similar in all groups and not correlated with QUICKI and OGIS. Interestingly, two previous studies that both used a specific measure of insulin sensitivity demonstrated that increased TC/HDL-C ratios are associated with insulin resistance in individuals whose weight is normal (12, 13) and negatively correlate with rates of insulin-stimulated glucose disposal in lean nondiabetic individuals (13). Although the present study might suggest that these relationships do not hold true in severe obesity, the small number of patients limits the statistical power and inference from these data. The LDL-C/HDL-C ratios were comparable and exhibited no relationships with surrogate measures of insulin sensitivity. Again the limited number of patients does not exclude the possibility of such relationships.

In the present study, we found that the TG/HDL-C ratio was ~40% higher in individuals with impaired glucose tolerance. In individuals with normal glucose tolerance, the TG/HDL-C ratio was related closely to QUICKI and less to OGIS, in particular when corrected for the confounding effects of age and body mass index. In individuals with impaired glucose tolerance, correlation coefficients between surrogate measures of insulin sensitivity and TG/HDL-C ratios were similar or higher than in glucose-tolerant individuals. These relationships achieved only borderline statistical significance, which most likely resulted from the small number of individuals with impaired glucose tolerance. When individuals with normal and impaired glucose tolerance were combined, the TG/HDL-C ratio negatively correlated with both surrogate measures of insulin sensitivity. The authors of a recent study with a larger cohort reported that TG concentrations or the TG/HDL-C ratio offer the most practical approach to identify insulin resistance in overweight nondiabetic volunteers (14). The present study extends these findings to a severely obese nondiabetic population (mean body mass index, ~38 vs ~29 kg/m²) comprising patients with normal and impaired glucose tolerance. In addition, the present study was performed in a cohort exhibiting marked insulin resistance with TG/HDL-C ratios higher than the TG/HDL-C cutoff values for detecting insulin resistance (14). Despite the similar efficacy for detecting insulin resistance, the more consistent association of TG/HDL-C compared with TG concentrations
makes this ratio a promising marker of insulin resistance. Moreover, the TG/HDL-C ratio is associated with a higher risk for myocardial infarction than TG concentrations in a population including 8–14% diabetic patients (7). These data suggest that the TG/HDL-C ratio may serve as a marker that is easy to determine and links insulin resistance and cardiovascular risk in nondiabetic individuals (14). Of note, we found no correlation between TG/HDL-C ratio and either QUICKI or OGIS in patients with type 2 diabetes mellitus.

Several limitations must be considered in the interpretation of the results: (a) as stated above, the number of patients per group was rather small; (b) patients with type 2 diabetes were older than individuals with normal glucose tolerance, which, however, did not influence the results of the statistical evaluation after correction for age; and (c) gender differences in the relationship of lipid ratios and insulin sensitivity may exist but could not be addressed appropriately in the present study. Of note, McLaughlin et al. (14) did not detect any interaction between sex and the ability of the TG/HDL-C ratio to predict insulin resistance in 127 men and 131 women (14).

In conclusion, this study demonstrates that only the TG/HDL-C ratio positively correlates with insulin resistance in severely obese nondiabetic individuals but not in patients with overt diabetes. Our data therefore support recent findings in overweight glucose-tolerant individuals, indicating that the TG/HDL-C ratio serves as an easily available laboratory marker for identifying insulin resistance (14).

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