Increased Cholesteryl Ester Transfer Protein Activity in Impaired Glucose Tolerance: Relationship to High Density Lipoprotein Metabolism

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Aim. To investigate the mechanisms and dynamics of cholesteryl ester (neutral lipid) transfer protein activity in subjects with impaired glucose tolerance.

Methods. Eighty six Caucasian subjects were recruited by advertisement from the local population between January 1998 and December 1999. The activity of cholesteryl ester transfer protein in 44 non-obese subjects with impaired glucose tolerance (plasma triglycerides 1.56±0.64 mmol/L; high density lipoprotein (HDL) cholesterol 0.96±0.25 mmol/L; and plasma insulin 78±8 pmol/L) and in 42 normoglycemic controls (plasma triglycerides 0.88±0.41 mmol/L; HDL cholesterol 1.48±0.29 mmol/L; and plasma insulin 38±14 pmol/L) was measured with a new fluorometric assay.

Results. Cholesteryl ester transfer protein activity was increased in subjects with impaired glucose tolerance by 47% (39.5±7.8 vs 26.8±6.8 nmol/mL × h⁻¹; t-test, p<0.05). Linear regression analysis showed that cholesteryl ester transfer protein activity in subjects with impaired glucose tolerance significantly correlated with the following parameters: plasma triglycerides (r=0.614, p<0.05), HDL-triglycerides (r=0.595, p<0.05), percentage of HDL-triglyceride (r=0.667, p<0.05), percentage of HDL choleseryl ester (r=-0.751, p<0.01), percentage of HDL phospholipid (r=0.648, p<0.05), 2-h-insulin (r=0.668, p<0.05), and 2-h-proinsulin (r=0.658, p<0.01). In a subgroup of 13 subjects with impaired glucose tolerance, cholesteryl ester transfer protein activity correlated with HDL apoA-I fractional catabolic rate (r=0.701, p<0.01). In normoglycemic subjects, significant correlations were found only between cholesteryl ester transfer protein activity and percentage of HDL-triglycerides (r=0.541, p<0.05), percentage of HDL choleseryl ester (r=-0.639, p<0.01), 2-h-proinsulin (r=0.642, p<0.05), and HDL apoA-I fractional catabolic rate (n=10, r=0.587, p<0.05).

Conclusion. Cholesteryl ester transfer is important for HDL composition and HDL catabolism both in normoglycemic subjects and subjects with impaired glucose tolerance. Under insulin resistant conditions, increased cholesteryl ester transfer protein activity modulates HDL metabolism more drastically than in normoglycemic conditions. This modulation may be explained by increased availability of triglyceride-rich lipoproteins for neutral lipid exchange in subjects with impaired glucose tolerance.

Key words: apolipoproteins; carrier proteins; glucose intolerance; hyperlipidemia; insulin resistance; lipoproteins, HDL; metabolism
from HDL to triglyceride-rich lipoproteins, e.g., very low density lipoproteins (VLDL), in exchange for triglycerides. This redistribution process should have consequences for HDL composition and consequently for the HDL metabolism (6,7). Indeed, increased cholesteryl ester transfer protein activity in humans was reported in several metabolic disorders, with low HDL cholesterol (9-13), such as type 1 diabetes (8), overt type 2 diabetes (9), obesity (10), nephrotic syndrome (11), acromegaly (12), and hypercholesterolemia (13).

However, little data are available regarding direct association between cholesteryl ester transfer protein activity and the metabolic decomposition of HDL metabolism under prediabetic conditions, e.g., in subjects with impaired glucose tolerance. Our study was designed to explore further the mechanisms and dynamics of cholesteryl ester transfer and their specific link with low plasma HDL concentrations and an altered HDL composition under insulin resistant/hyperinsulinemic conditions. We aimed at finding associations between cholesteryl ester transfer protein activity and parameters of carbohydrate and lipid metabolism in a carefully selected group of normotriglyceridemic or mildly hypertriglyceridemic patients with impaired glucose tolerance.

### Subjects and Methods

**Subjects**

Eighty six Caucasian subjects were recruited by advertisement from the local population between January 1998 and December 1999. All subjects consented to participate in the study, which was approved by the local Medical Ethics Committee. The study group consisted of 44 non-obese subjects (22 women and 20 men), aged 19 to 63 years (median, 46.5 years), with impaired glucose tolerance and normal or moderately increased plasma triglyceride (TG) concentration. The control group included 42 healthy, normolipidemic subjects (22 women and 20 men), aged 19 to 63 years (median, 40.5 years), with normal glucose tolerance (Table 1). There was no evidence of thyroid, liver, cardiovascular, hematomatologic, or renal abnormalities in any of the subjects, and none were taking medications. All subjects were non-smokers. The diagnosis of impaired glucose tolerance was based on two consecutive oral glucose tolerance tests (oGTT; 75 g oral glucose load) according to the World Health Organization (WHO) guidelines and criteria (two 2-h post-glucose values between 7.8 and 11.1 mmol/L) (14).

### Experimental Protocol

Blood (10-20 mL) was collected into vacuum tubes containing EDTA at a final concentration of 0.1%. Plasma was recovered after centrifugation at 4 °C. Sodium azide (0.01%) and aprotinin (200 KIU/mL) were added immediately. Plasma samples were stored at -80 °C and used to determine plasma glucose, plasma lipids, and concentrations of apoB-100, apoA-I, apoA-II, and apoE. In addition, very low density lipoproteins (VLDL; d < 1.006 kg/L), LDL (1.006<d<1.063 kg/L), and HDL (1.063<d<1.210 kg/L) were isolated from 0.5 mL plasma by sequential very fast ultracentrifugation with fixed angle rotor TLA-120.2 at 120,000 rev/min (Beckman instruments, Palo Alto, CA, USA) (15,16). HDL prepared by this very fast ultracentrifugation technique is free of albumin and other protein contaminations, which allows correct compositional analysis (15,16). Lipid and protein constituents in plasma and lipoprotein fractions were measured as previously described (15).

### Table 1. Characteristics and biochemical parameters (mean±SD) of 42 subjects with impaired glucose tolerance (IGT) and 44 subjects with normal glucose tolerance (NGT)*

<table>
<thead>
<tr>
<th>Subject characteristics</th>
<th>NGT group</th>
<th>IGT group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: women/women</td>
<td>22/20</td>
<td>24/20</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>40±14</td>
<td>48±12</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.2±2.4</td>
<td>25.8±2.4</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>5.35±0.48</td>
<td>6.04±0.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2-h-post glucose (mmol/L)</td>
<td>5.58±1.16</td>
<td>8.86±0.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting insulin (pmol/L)</td>
<td>38±14</td>
<td>78±8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2-h-post insulin (pmol/L)</td>
<td>259±111</td>
<td>610±196</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting proinsulin (pmol/L)</td>
<td>1.85±0.69</td>
<td>2.81±1.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2-h-post proinsulin (pmol/L)</td>
<td>10.1±5.7</td>
<td>20.5±12.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting free fatty acids (mmol/L)</td>
<td>0.41±0.20</td>
<td>0.61±0.17</td>
<td>0.008</td>
</tr>
<tr>
<td>HbA1c (%)†</td>
<td>5.2±0.4</td>
<td>5.8±1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.88±0.41</td>
<td>1.56±0.64</td>
<td>0.002</td>
</tr>
<tr>
<td>VLDL triglycerides (mmol/L)</td>
<td>0.52±0.11</td>
<td>0.98±0.34</td>
<td>0.020</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.26±0.66</td>
<td>5.18±0.76</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.48±0.29</td>
<td>0.96±0.25</td>
<td>0.015</td>
</tr>
<tr>
<td>ApoA-I (g/l)</td>
<td>1.46±0.09</td>
<td>1.00±0.29</td>
<td>0.030</td>
</tr>
<tr>
<td>ApoA-II (g/l)</td>
<td>0.24±0.04</td>
<td>0.22±0.03</td>
<td>NS</td>
</tr>
<tr>
<td>ApoB-100 (g/l)</td>
<td>0.95±0.36</td>
<td>1.48±0.29</td>
<td>0.029</td>
</tr>
<tr>
<td>ApoE (g/l)</td>
<td>0.056±0.011</td>
<td>0.078±0.021</td>
<td>0.045</td>
</tr>
<tr>
<td>CETP activity (nmol/mL h⁻¹)</td>
<td>26.8±6.8</td>
<td>39.5±7.8</td>
<td>0.017</td>
</tr>
<tr>
<td>HDL composition:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL triglycerides (mmol/L)</td>
<td>0.12±0.06</td>
<td>0.21±0.08</td>
<td>0.020</td>
</tr>
<tr>
<td>HDL free cholesterol (mmol/L)</td>
<td>0.21±0.04</td>
<td>0.23±0.04</td>
<td>0.025</td>
</tr>
<tr>
<td>HDL cholesterol esters (mmol/L)</td>
<td>1.05±0.07</td>
<td>0.81±0.08</td>
<td>0.030</td>
</tr>
<tr>
<td>HDL phospholipids (mmol/L)</td>
<td>1.20±0.36</td>
<td>1.46±0.24</td>
<td>0.015</td>
</tr>
<tr>
<td>HDL apoA-I (g/l)</td>
<td>1.34±0.08</td>
<td>0.94±0.11</td>
<td>0.001</td>
</tr>
<tr>
<td>HDL apoA-II (g/l)</td>
<td>0.24±0.02</td>
<td>0.22±0.02</td>
<td>NS</td>
</tr>
<tr>
<td>HDL apoE (g/l)</td>
<td>0.011±0.005</td>
<td>0.016±0.011</td>
<td>0.007</td>
</tr>
<tr>
<td>HDL residual protein (g/l)</td>
<td>0.089±0.066</td>
<td>0.30±0.010</td>
<td>0.007</td>
</tr>
</tbody>
</table>

*The values of glucose and insulin were based on the mean of two consecutive oral glucose tolerance tests used for the diagnosis of impaired glucose tolerance. The diet of patients was based on two 2-h post-glucose values between 7.8 and 11.1 mmol/L, according to the World Health Organization guidelines. Abbreviations: VLDL – very low density lipoproteins; HDL – high density lipoproteins; CETP – cholesteryl ester transfer protein.

†NS – not significant (p>0.05).

Log-transformed value.

Mean lipoprotein mass composition: the mass percentage of each lipid and protein constituent from the total HDL mass (15).

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stored in cryovials at -80 °C. Plasma insulin and proinsulin were determined by specific enzyme immunoassay (BioSource, Ratingen, Germany; within-day precision <3.8%, between-day precision <6.5%; no cross reaction with human proinsulin and insulin, respectively). Cholesteryl ester transfer protein activity was measured as published elsewhere, with some modifications (4). In brief, HDL-like particles containing 0.1 μmol/mL of the fluorescent cholesteryl ester analog N-(7-Nitrobenz-2-oxa-1,3-diazole)-23,24-dinor-5-cholen-22-amine-3β-ol (NBD-CE, WAK Medical, Bad Soden, Germany) were used as donor particles and VLDL isolated from pooled normal fasting plasma were used as acceptor particles. The fluorescent cholesteryl linoleate is present in a self-quenched state when contained within the core of the donor particle. The cholesteryl ester transfer is determined by an increase in fluorescence intensity (excitation at 465 nm, and emission at 535 nm) as the cholesteryl linoleate is removed from the donor particle and transferred to the acceptor particle in the presence of a cholesteryl ester transfer protein-containing sample. The reaction was linear and the amount of cholesteryl ester transferred was derived from a standard curve by use of different concentrations of NBD-CE. The within-day and between-day precision of the assay was <6.0% and <7.8%, respectively. The use of VLDL- and LDL-free plasma samples substantially eliminates the influence of the endogenous VLDDL and LDL pools on the cholesteryl ester transfer activity measurement ex vivo. Cholesteryl ester transfer protein activity is expressed as nmol/mL×h⁻¹ (4). Accordingly, in this assay, cholesteryl ester transfer protein activity was only influenced by the cholesteryl ester transfer protein concentration, therefore reflecting likely the cholesteryl ester transfer protein mass.

Statistical Analysis

We used SPSS 11.0.1 software package (SPSS Inc., Chicago, Ill., USA) for all statistical analyses. Descriptive data were expressed as arithmetic means ± standard deviations (SD). The distribution of values was assessed by Kolmogorov-Smirnov test for homogeneity of variances and parameters were transformed logarithmically if necessary. Metabolic variables of two study groups were compared by t-test. For correlation analyses within the total study population, Spearman’s rank correlation coefficient (r) was used. Additionally, we calculated partial correlation coefficients within the study groups using sex, age, and body mass index as covariates.

Results

Biochemical Characteristics

Subjects with impaired glucose tolerance and their controls were well-matched for age, sex, and body mass index (Table 1). The concentration of glycated hemoglobin (HbA1c) was below 6% in both groups. Fasting values for plasma glucose, free fatty acids, insulin, and proinsulin, and 2-hour post-challenge values (after 75 g oral glucose load) for glucose, free fatty acids, insulin, and proinsulin were significantly increased in subjects with impaired glucose tolerance (Table 1). These values were considered as highly indicative for an insulin resistant/hyperinsulinemic state of the subjects with impaired glucose tolerance. In subjects with impaired glucose tolerance, plasma triglycerides were higher by 77% (p<0.05), apoB-100 concentrations by 56% (p<0.05), and apoE concentrations by 39% (p<0.05), compared with control group. However, all these parameters were still in the upper normal range. VLDL triglycerides were higher by 88% (p<0.05) in subjects with impaired glucose tolerance. The plasma levels of total cholesterol showed no differences between subjects with impaired glucose tolerance and controls.

Cholesteryl Ester Transfer Protein Activity

The rate of cholesteryl linoleate transfer from HDL particles to VLDL was significantly higher (47%) in the impaired glucose tolerance group than in the control group.

HDL Composition

Plasma apoA-I and HDL cholesterol concentrations were 32% and 35% lower, respectively, in subjects with impaired glucose tolerance (Table 1). Among HDL constituents, concentrations of HDL apoA-I and HDL cholesteryl esters were significantly lower, whereas concentrations of HDL triglycerides and HDL phospholipids were significantly higher in
subjects with impaired glucose tolerance. The concentrations of free cholesterol, apoA-II, and apoE in HDL did not differ between the two groups. Furthermore, HDL particle composition, expressed as the mass percentage of each lipid and protein constituent from the total HDL mass, was substantially altered in subjects with impaired glucose tolerance (Table 1). This compositional misbalance consequently led to HDL particles that were significantly enriched with triglycerides and phospholipids, but depleted in their cholesterol ester and apoA-I content.

**Correlation Analysis**

In the total study population of 86 participants, cholesteryl ester transfer protein activity correlated directly with plasma triglycerides ($r = 0.675; p < 0.05$), HDL triglycerides ($r = 0.818; p < 0.01$), HDL triglyceride content ($r = 0.927; p < 0.001$; Fig. 1), HDL phospholipid content ($r = 0.655; p < 0.05$), as well as with 2-h-post glucose ($r = 0.651; p < 0.001$; Fig. 2), fasting insulin ($r = 0.724; p < 0.001$; Fig. 3), 2-h-post insulin ($r = 0.802; p < 0.001$; Fig. 4), and 2-h-post proinsulin ($r = 0.651; p < 0.001$; Fig. 5). An inverse association was found between the cholesteryl ester transfer protein activity and HDL cholesteryl esters ($r = -0.688; p < 0.05$) and HDL cholesteryl ester content ($r = -0.849; p < 0.001$; Fig. 6). To compensate for possible effects of age, body mass index, and sex, partial correlation coefficients were calculated for both

**Figure 3.** Relationship between cholesteryl ester transfer protein (CETP) activity and fasting insulin in 86 subjects with impaired glucose tolerance (squares) or normal glucose tolerance (triangles).

**Figure 4.** Relationship between cholesteryl ester transfer protein (CETP) activity and 2-h-post insulin in 86 subjects with impaired glucose tolerance (squares) or normal glucose tolerance (triangles).

**Figure 5.** Relationship between cholesteryl ester transfer protein (CETP) activity and 2-h-post proinsulin in 86 subjects with impaired glucose tolerance (squares) or normal glucose tolerance (triangles).

**Figure 6.** Relationship between cholesteryl ester transfer protein (CETP) activity and HDL cholesteryl ester (%) in 86 subjects with impaired glucose tolerance (squares) or normal glucose tolerance (triangles).
groups separately, with these parameters used as covariates. In subjects with impaired glucose tolerance, differences remained statistically significant for correlation between cholesteryl ester transfer protein activity and plasma triglycerides, HDL triglycerides, HDL triglyceride content, HDL cholesteryl ester content, HDL phospholipid content, 2-h-post glucose, fasting insulin, 2-h-post insulin, and 2-h-post proinsulin (Table 2). In contrast, only the HDL triglyceride and cholesteryl ester content, as well as the 2-h-post proinsulin levels remained associated with choles-

tery ester transfer protein activity in controls (Table 2).

Discussion

This study showed that fasting cholesteryl ester transfer protein activity, measured by a new fluorescent spectrophotometric method, was significantly increased in normoglycemic and mildly hyperglycemic subjects with impaired glucose tolerance. The assay measured cholesteryl ester transfer protein activity as the specific cholesteryl linoleate transfer from HDL (donor) particles to VLDL (accep-
tor) particles. By using this method and VLDL- and LDL-depleted plasma as the cholesteryl ester transfer protein source, we avoided the influence of endo-
geneous lipoproteins. Thus, the cholesteryl ester transfer protein activity reflected the cholesteryl ester transfer protein mass. Observations regarding choles-
teryl ester transfer protein activity may differ depend-
ing on the assays used (6). However, the increased cholesteryl ester transfer protein activity we showed is in agreement with our previous data and partly with the results of several recent studies in which a similar assay system to measure cholesteryl ester transfer protein activity was used (4, 12, 17, 18).

The activity of cholesteryl ester transfer protein was directly associated with parameters highly indicative for an insulin resistant/hyperinsulinemic condition (19-21). Among these, fasting insulin, 2-h-post in-
sulin, and 2-h-post proinsulin showed the highest sta-
tistical power. On the other hand, no association be-
tween free fatty acids and cholesteryl ester transfer protein activity could be found. This is of special in-
terest, because there is experimental and clinical evi-
dence that free fatty acids may exert direct effects on cholesteryl ester transfer protein concentrations and also modulate cholesteryl ester transfer rates through alterations in the concentration and composition of plasma lipoprotein substrates (6, 7, 11, 22).

Furthermore, we found cholesteryl ester transfer protein activity to be directly associated with parameters of HDL particle composition, particularly with the HDL triglyceride and cholesteryl ester content. In this context, the use of very fast ultracentrifugation technique was essential for the present analysis, be-
cause it provided albumin-free HDL particles, which allowed the exact calculation of HDL particle composi-
tion. In addition, there was a strong relationship be-
tween HDL phospholipid content and cholesteryl es-
ter transfer protein activity. This seems to reflect the specific phospholipid transfer activity of cholesteryl ester transfer protein (6).

When the study groups were analyzed sepa-
rately, most of the associations found persisted in sub-
jects with impaired glucose tolerance, taking into ac-
to account sex, age, and body mass index. In contrast, only the HDL triglyceride and cholesteryl ester content, as well as the 2-h-post proinsulin concentrations re-
ained associated with cholesteryl ester transfer protein activity in controls. There was no correlation be-
tween VLDL triglycerides and cholesteryl ester transfer protein activity in either group, confirming the re-
sults of other studies (9). The correlations discussed above suggest that cholesteryl ester transfer protein is likely to be an important modulator of HDL particle composition under both normal and insulin resistant conditions, even when triglyceride concentrations are normal or mildly increased.

Data in this study substantially support our previ-
ous findings on increased in vivo catabolism of HDL apoA-I in subjects with impaired glucose tolerance (4). Those former kinetic data suggested that confor-
mational changes in the HDL particles due to their in-
creased triglyceride and phospholipid content as well as decreased cholesteryl ester content favored their direct catabolism. Hypothetically, the enrichment with triglycerides in particular could make the HDL a favored substrate of the hepatic lipase (7, 23). Hepatic lipase hydrolyzes HDL triglycerides and subse-
quently the HDL particle size decreases. ApoA-I is weakly bound to these small, cholesteryl ester-de-
ppleted HDL particles and, consequently, the apoA-I pool is easily dissociable and more rapidly catabo-
lized. This is in accordance with the current hypothe-
theses on the metabolic reason of the preponderance of small, dense LDL under diabetic and prediabetic conditions (24-26). Ambrosch and colleagues (18) found increased cholesteryl ester transfer protein activity in insulin resistant persons who were identified among young, clinically healthy subjects by the clamp tech-
nique. They reported a strong association of increased cholesteryl ester transfer protein activity with decreasing LDL particle diameter in these subjects (18).

The association between cholesteryl ester transfer protein and phospholipid content in HDL is sus-
pected to be an indicator of the known intrinsic phospholipid transfer activity of cholesteryl ester transfer protein (7). However, we did not investigate the impact of another lipid transfer protein – the phos-
pholipid transfer protein – on the metabolism of HDL.
There is experimental and clinical evidence that phospholipid transfer protein activity is altered in insulin-resistant states, with further consequences for HDL composition (27).

In conclusion, our observations suggest that neutral lipid transfer mediated by cholesteryl ester transfer protein is crucial for the modification of HDL composition in subjects with impaired glucose tolerance. Under insulin resistant/hyperinsulinemic conditions, increased cholesteryl ester transfer protein activity modulates HDL metabolism more drastically than in normoglycemic conditions. This modulation may be explained by the increased availability of triglyceride-rich lipoproteins for neutral lipid exchange in subjects with impaired glucose tolerance. As a consequence, HDL cholesterol is decreased in impaired glucose tolerance conditions. Low HDL is an integral part of the atherogenic lipoprotein phenotype in diabetic and prediabetic states (1, 4). However, the mechanisms by which cholesteryl ester transfer protein is regulated in its activity or synthesis, particularly in insulin-resistant subjects, have to be further elucidated. We suggest that insulin has a direct influence on the cholesteryl ester transfer protein in vivo, but under insulin resistant conditions this specific insulin action can be diminished. This would be in agreement with clinical and experimental evidence that the higher the plasma insulin concentration (more insulin resistant), the greater the fractional catabolic rate of HDL and the lower the plasma HDL cholesterol concentrations in diabetic and prediabetic states (4, 28, 29). Additional work, including experimental and clinical use of recently developed cholesteryl ester transfer protein inhibitors (30), is needed to further understand the consequences of increased cholesteryl ester transfer for the development of the atherogenic lipoprotein phenotype in diabetic and prediabetic states.

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