Plasma Apolipoprotein CI and CIII Levels Are Associated With Increased Plasma Triglyceride Levels and Decreased Fat Mass in Men With the Metabolic Syndrome

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OBJECTIVE — To determine whether, in accordance with observations in mouse models, high concentrations of the lipoprotein lipase inhibitors apolipoprotein (Apo) CI and ApoCIII are associated with increased triglyceride concentrations and decreased fat mass in men with the metabolic syndrome.

RESEARCH DESIGN AND METHODS — Plasma ApoCI, ApoCIII, and triglyceride concentrations were measured in the postabsorptive state in 98 men with the metabolic syndrome. Subcutaneous and visceral fat areas were measured by 3T-magnetic resonance imaging.

RESULTS — Triglyceride concentrations were 49% higher, and the average visceral fat area was 26% lower (both $P < 0.001$), in subjects with high ApoCI and ApoCIII compared with low ApoCI and ApoCIII. Subjects with either high ApoCI or ApoCIII had 16% ($P < 0.05$) and 18% ($P < 0.01$) decreased visceral fat area, respectively.

CONCLUSIONS — High concentrations of ApoCI and ApoCIII are associated with increased triglycerides and decreased visceral fat mass in men with the metabolic syndrome. These findings translate mouse studies into human pathophysiology.

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Apolipoprotein (Apo) CI and ApoCIII are present on HDL and triglyceride (TG)-rich lipoproteins (1) and mainly affect plasma lipid metabolism by inhibition of lipoprotein lipase (LPL) (2). This enzyme hydrolyzes TG in VLDL and chylomicrons, releasing fatty acids for storage by adipocytes or for energy metabolism in muscles (2,3). Overexpression of human ApoCI in mice increases VLDL-associated TG plasma levels in combination with decreased body fat (4). The effect of ApoCIII overexpression is unknown, but ApoCIII deficiency in mice led to lower VLDL-associated TG levels and increased diet-induced obesity (5). Because it has recently been shown that LPL activity is higher in visceral adipose tissue (VAT) compared with subcutaneous adipose tissue (SAT) (6), LPL inhibitors such as ApoCI and ApoCIII may differentially affect VAT compared with SAT. The objective of this study was to determine whether, like in mouse models, high ApoCI and ApoCIII concentrations are associated with increased TG concentrations and decreased fat mass (VAT vs. SAT) in men with the metabolic syndrome.

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RESEARCH DESIGN AND METHODS

— We studied 98 male subjects aged 50–70 years with the metabolic syndrome (defined using International Diabetes Federation criteria [7]). Exclusion criteria were the presence of type 2 diabetes, overt cardiovascular disease, use of statins or fibrates, and a BMI >40 kg/m^2. The study protocol was approved by the local ethics committee. Blood samples were collected after a 12-h overnight fast. Plasma concentrations of ApoCI and ApoCIII were determined using sandwich enzyme-linked immunosorbent assays specific for human ApoCI and ApoCIII (8).

Magnetic resonance imaging (MRI), measuring SAT and VAT area at the level of the intervertebral disk level between the fourth and fifth lumbar vertebra, was performed on a 3T scanner (Philips; Achieva, Best, the Netherlands) as described previously (9).

To address the question whether high ApoCI, high ApoCIII, and the combination of high ApoCI and ApoCIII are associated with increased TG concentrations and decreased VAT and SAT area, the study subjects were divided into groups according to median ApoCI concentration (6.38 mg/dl; skewed distribution) and mean ApoCIII concentration (10.2 mg/dl; normal distribution).

Statistical analyses were performed using SPSS version 14.0 for Windows. The level of significance was set at 0.05. Differences in clinical and laboratory parameters and SAT and VAT area were assessed by independent *t* test or one-way ANOVA, with post hoc least significant difference testing, if appropriate. Mann-Whitney tests or Kruskall-Wallis tests (followed by Mann-Whitney tests, *P* values were multiplied by three to correct for multiple testing) were performed for parameters that were not normally distributed. Smoking frequency was assessed by Pearson χ^2 tests. Correlations were calculated using Spearman's ρ.

RESULTS

— Clinical and laboratory parameters, including waist circumfer-

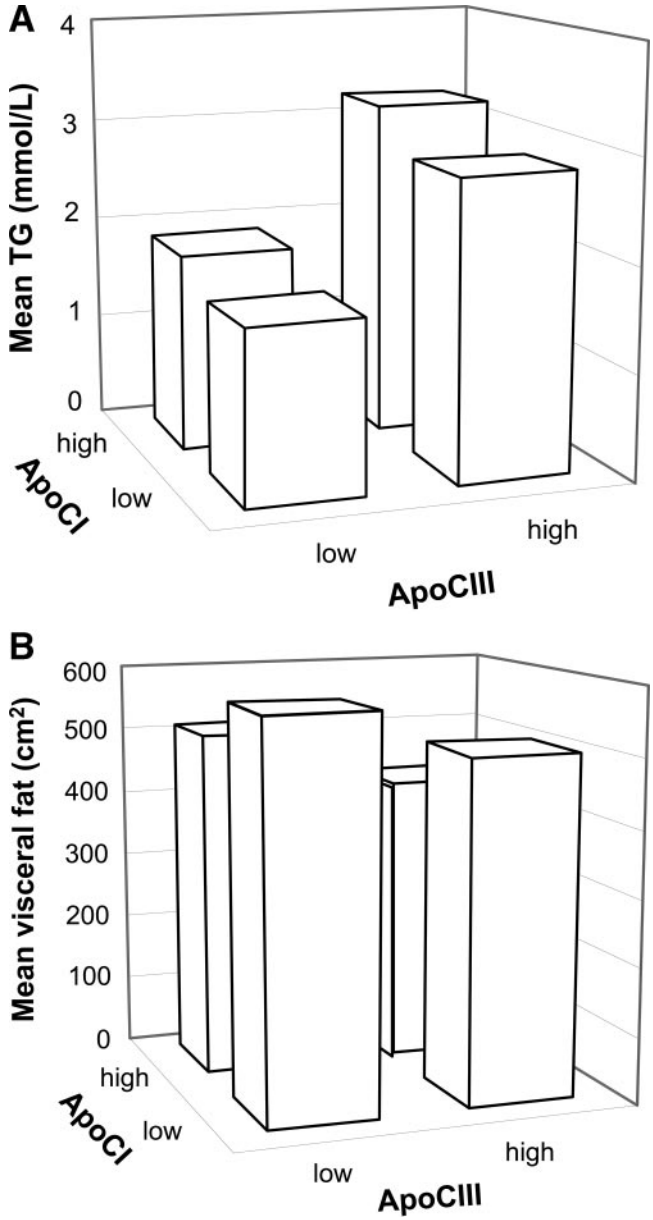

Figure 1—*Illustration of the inverse relationship of ApoCI and ApoCIII concentrations with plasma triglyceride concentration (positive,* A*) and with visceral adipose tissue area (negative,* B*). ApoCI/ApoCIII < median/mean = low, ApoCI/ApoCIII > median/mean = high. Groups: 1: low ApoCI and ApoCIII* (n = *35); 2: high ApoCI/low ApoCIII* (n = *21); 3: low ApoCI/high ApoCIII* (n = *14); 4: high ApoCI and ApoCIII* (n = *28). Triglyceride concentration: 1 vs. 3, 1 vs. 4, and 2 vs. 4: P < 0.001. 2 vs. 3:* P < *0.01. Visceral adipose tissue area: low ApoCI and ApoCIII vs. high ApoCI and ApoCIII:* P < *0.001.*

ence and homeostasis model assessment, were not different between the four groups, apart from HDL cholesterol, total cholesterol, and smoking (see Table A1a in the online appendix available at http://dx.doi.org/10.2337/dc08-1330). There were more smokers in the group with high ApoCIII compared with low ApoCIII (33 and 7%, respectively; $P < 0.01$).

ApoCI and ApoCIII levels were positively correlated ($\rho = 0.405$, $P < 0.001$). TG concentrations were 49% higher in subjects with both high ApoCI and ApoCIII compared with subjects with low ApoCI and ApoCIII ($P < 0.001$) (Fig. 1*A*). Subjects with both high ApoCI and ApoCIII had 26% decreased VAT area ($P < 0.001$) and 7% lower SAT area (not significant) compared with subjects with both low ApoCI and ApoCIII levels (Fig. 1*B*). Subjects with ApoCI above the median had 16% lower VAT area ($P < 0.05$) and 3% higher SAT area (not significant). Subjects with ApoCIII above the median had 18% lower VAT area ($P < 0.01$) and 14% lower SAT area (not significant).

To exclude the difference in smoking frequency as a possible confounder, the analysis was repeated after exclusion of smokers. TG levels were slightly lower, but for both TG and VAT area, the results remained highly significant (online appendix Table A1b).

CONCLUSIONS — High ApoCI and ApoCIII concentrations are associated with increased TG concentrations and decreased VAT area in men with the metabolic syndrome. The phenotypic appearances caused by modulation of ApoCI and ApoCIII may be very relevant for human subjects with the metabolic syndrome, since visceral obesity and increased TG levels are two of its main characteristics (7). In addition, intra-abdominal fat is presumed to be an important determinant of metabolic dysregulation (10,11). The data presented in this study are in line with experimental data and indicate that the mechanisms uncovered by these experimental studies can be translated to the human situation. To be more precise, these data suggest that the known inhibition of LPL by ApoCI and ApoCIII contributes to higher TG and lower VAT area in human subjects. Furthermore, the difference in effect of ApoCI and ApoCIII on TG concentrations observed in this study underlines the stronger inhibition of LPL by ApoCIII compared with ApoCI, as shown in experimental studies (2).

ApoCI and ApoCIII levels were mainly related to the VAT compartment. This can be related to a higher expression of LPL in VAT versus SAT, as evident from experimental studies in mice (6). Alternatively, LPL may be differently regulated in various fat depositions (e.g., VAT vs. SAT). This adds to the discussion relating LPL to fat deposition, since studies comparing LPL mass, activity, and mRNA expression between subcutaneous and visceral fat have shown contradictory results (10,12,13). The difference in smoking frequency has not confounded our results, because when the analysis was repeated after exclusion of smokers, almost identical results were obtained.

The current observations are restricted to male, abdominally obese subjects, aged 50–70 years, without type 2 diabetes or cardiovascular disease. Nevertheless, this study shows that in men with

the metabolic syndrome, high ApoCI and ApoCIII levels are associated with increased TG levels and decreased visceral fat mass, which is in line with in vivo data from mouse models. This study is the first to address the effect of LPL regulation on adipose tissue deposition in humans and necessitates further studies on the effect of LPL, the LPL coactivator ApoCII, and their polymorphisms on adipose tissue mass.

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