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Running title: Postprandial apoA-V in type 2 diabetes

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Postprandial lipaemia is a distinct feature of diabetic dyslipidemia and may partly explain the atherogeneity of the lipid profile in type 2 diabetes (1). Several genetic factors contribute to the elevation of triglyceride-rich lipoproteins (TRLs). The role of apoC-III as a regulator of TRL metabolism is well documented (2). Recently, ApoA-V has been identified as a novel regulator of TG metabolism. When human apoA5 gene was expressed in transgenic mice, plasma TG concentration was decreased by 70%, whereas apoA5 gene knockout mice had fourfold elevation of plasma TG levels (3). Inherited apoA-V deficiency results in severe hypertriglyceridemia in humans (4). A mutation in apoA5 gene causes hypertriglyceridemia due to decreased LPL mass and activity (5). Thus, previous studies have proposed that apoA-V decreases TG by stimulating lipolysis.

The present study focused on the response of apoA-V and apoC-III during postprandial lipemia and the associations between apoA-V and apoC-III and postheparin plasma LPL and hepatic lipase (HL) activities in type 2 diabetes.

**RESEARCH DESIGN AND METHODS**

The present study cohort comprised 39 men and 8 women with type 2 diabetes enrolled in the previously published nateglinide study with the same inclusion and exclusion criteria (6). Seventeen patients were treated with diet alone, 20 with sulphonylurea, and 11 with metformin. The study protocol was approved by the Ethical committee of the Helsinki University Hospital, and all patients gave their informed consent.

The test meal was served after an overnight 12-h fast and it contained 63 g fat (P/S ratio 0.08), 490 mg cholesterol, 25 g carbohydrate, and 35 g protein as previously described (6). Blood samples were drawn from a catheter placed in an antecubital vein before the meal and at 3 h, 4 h, 6 h, and 8 h. Concentrations of cholesterol, triglycerides, HDL cholesterol; and apoB-100 and apoB-48 concentrations in the plasma lipoprotein fractions isolated by density gradient ultracentrifugation were analyzed as previously described (7). Postheparin LPL and HL were analysed by an established method (8). ApoA-V was analyzed by enzyme-linked immunosorbent assay (ELISA) (9). ApoC-III was determined by using commercially available kit (10).

Data were analysed using SPSS 13.0 software (SPSS Inc., Chicago, Illinois). Postprandial responses over the 8-h period were calculated as incremental areas under the curve (IAUC) as previously described (11). The significance of the postprandial response of different variables was calculated by using ANOVA of repeated measurements. Spearman rank correlations were calculated to study the associations between variables and P value <0.05 (two-tailed) was considered statistically as significant.

**RESULTS**

The patients were middle-aged (62.8±8.5 yrs), overweight (BMI 28.4±3.4 kg/m2) and mildly dyslipidemic (cholesterol 5.3±0.7 mmol/L, triglyceride 1.8±0.6 mmol/L, and HDL 1.31±0.28 mmol/L). The mean HbA1c level averaged 7.6±1.0% and the mean fasting glucose level averaged 10.1±2.7 mmol/l. ApoA-V and apoAC-III concentrations averaged 268±98 ng/ml (range 119-557 ng/mL) and 3.91±1.8 mg/dL (range 1.0-9.7 ng/mL), respectively.

The responses of both apoA-V and apoC-III paralleled closely the postprandial TG response, particularly in VLDL1 fraction (Figure). The IAUC of apoA-V during oral fat load was positively associated with IAUCs of serum TG (r=+0.571, P>0.001), chylomicron TG (+0.520, P<0.001), VLDL1-TG (+0.691, P<0.001), chylomicron apoB-48 (+0.525,P<0.001) and VLDL1-apoB-100 (+0.558, P<0.001). Similarly, the IAUC of apoC-III showed significant positive correlations with these
lipoprotein parameters (data not shown). Importantly, the IAUC of apoA-V correlated significantly with that of apoC-III ($R=+0.562$, $P<0.001$). Postheparin plasma LPL activity correlated negatively with IAUCs of VLDL1 triglycerides, VLDL1-cholesterol, and VLDL1- apoB-100 (data not shown).

Fasting ApoA-V concentration did not correlate with postheparin plasma LPL, or HL activities. The concentration of apoC-III showed no relationship with LPL or HL activities. The baseline concentration of apoC-III correlated significantly with triglyceride in fasting plasma ($r=+0.866$, $P<0.001$), chylomicrons ($r=+0.769$, $P<0.001$), VLDL1 ($r=+0.888$, $P<0.001$) and VLDL2 ($r=+0.741$, $P<0.001$). No relationship existed between IAUC of apoA-V and postheparin plasma LPL or HL activity.

**CONCLUSION**

Despite the lack of a correlation between the fasting apoA-V and lipid parameters, the postprandial increase of apoA-V paralleled those of plasma and VLDL1 TG as well as apoC-III reaching its maximum at 4 hours after oral fat load. Since apoA-V is associated with VLDL and chylomicron particles (12), the increase of apoA-V may reflect the increase of VLDL particles during postprandial phase in analogy with apoC-III overproduction (2). Another potential explanation is that apoA-V production in the liver is increased as a regulatory mechanism to cover the increase need of postprandial lipolysis. These both hypothesis are consistent with the two recent reports showing elevated apoA-V concentrations in patients with severe hypertriglyceridemia (13-14).

Although apoA-V has been reported to play an important role in lipolysis (3,15-16), we found no association between postprandial apoA-V values and LPL activity. This could be explained by the fact that ApoA-V is present in plasma at very low concentrations, which are far lower than other lipoprotein levels (14). In contrast, animal studies (3, 13) have used transgenic models manifesting higher concentrations of apoA-V than seen physiologically in plasma.

To summarize, apo A-V response to oral fat load closely parallels those of TRLs and apo CIII in people with Type 2 diabetes.

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REFERENCES


LEGENDS TO THE FIGURE

FIGURE. Postprandial response of  

A. VLDL1 triglycerides (VLDL1 TG);  

B. VLDL1-apoB-100;  

C. chylomicron triglycerides (Chylo-TG)  

D. chylomicron apo B-48 (Chylo-apoB-48)  

E. apoA-V; and  

F. apoC-III. The postprandial responses were calculated and presented as IAUCs the mean±SD. The significance of the postprandial change in each variable was calculated by using ANOVA of repeated measurements.