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Apolipoprotein A-II and adiponectin as determinants of very low-density lipoprotein apolipoprotein B-100 metabolism in nonobese men

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ABSTRACT

Data from cellular systems and transgenic animal models suggest a role of apolipoprotein (apo) A-II in the regulation of very low-density lipoprotein (VLDL) metabolism. However, the precise mechanism whereby apoA-II regulates VLDL metabolism remains to be elucidated in humans. In this study, we examined the associations between the kinetics of high-density lipoprotein (HDL)-apoA-II and VLDL-apoB-100 kinetics, and plasma adiponectin concentrations. The kinetics of HDL-apoA-II and VLDL-apoB-100 were measured in 37 nonobese men using stable isotope techniques. Plasma adiponectin concentration was measured using immunoassays. Total plasma apoA-II concentration was positively associated with HDL-apoA-II production rate (PR) ($r = 0.734$, $P < .01$); both were positively associated with plasma triglyceride concentration ($r = 0.360$ and 0.369, respectively) and VLDL-apoB-100 PR ($r = 0.406$ and 0.427, respectively), and inversely associated with plasma adiponectin concentration ($r = -0.449$ and -0.375, respectively). Plasma adiponectin was inversely associated with plasma triglyceride concentration ($r = -0.327$), VLDL-apoB-100 concentration ($r = -0.337$), and VLDL-apoB-100 PR ($r = -0.373$). In multiple regression models including waist circumference and plasma insulin, plasma adiponectin concentration was an independent determinant of total plasma apoA-II concentration (β-coefficient = –0.508, $P = .001$) and HDL-apoA-II PR (β-coefficient = –0.374, $P = .03$). Conversely, total plasma apoA-II concentration (β-coefficient = 0.348, $P = .047$) and HDL-apoA-II PR (β-coefficient = –0.350, $P = .035$) were both independent determinants of VLDL-apoB-100 PR. However, these associations were not independent of plasma adiponectin. Variation in HDL apoA-II production, and hence total plasma apoA-II concentration, may exert a major effect on VLDL-apoB-100 production. Plasma adiponectin may also contribute to the variation in VLDL-apoB-100 production partly by regulating apoA-II transport.

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1. Introduction

Dyslipidemia increases risk of cardiovascular disease (CVD) and is a feature of obesity, type 2 diabetes mellitus, and the metabolic syndrome [1]. Hypertriglyceridemia is the most consistent lipid abnormality and is chiefly a consequence of overproduction of triglyceride-rich very low-density lipoprotein (VLDL) particles [2]. The metabolism of VLDL involves regulatory processes governing the turnover of apolipoprotein (apo) B-100. However, the precise mechanisms involved are incompletely understood.

Apolipoprotein A-II is the second major apolipoprotein of high-density lipoprotein (HDL) and comprises 20% of the total HDL protein mass [3]. However, the functional properties of apoA-II in lipoprotein metabolism and atherosclerosis are less well established. Some, but not all, epidemiological studies demonstrate positive association with CVD in humans [4-7]. Whether apoA-II is proatherogenic or antiatherogenic remains unclear. Recent data from transgenic animal models suggest that apoA-II may have a direct effect on VLDL metabolism [8-12]. Boisfer et al [10] found that in transgenic mice expressing human apoA-II, hypertriglyceridemia was due to defective VLDL-triglyceride catabolism driven by reduced lipoprotein lipase (LPL) and hepatic lipase activities. Castellani et al [11] reported that overexpression of murine apoA-II in transgenic mice resulted in both impaired hydrolysis and overproduction of VLDL-triglycerides. Escola-Gil et al [12] further demonstrated that in cholesteryl ester transfer protein (CETP) transgenic mice fed a high-cholesterol high-fat diet, overexpression of apoA-II increased the plasma triglyceride concentration by increasing production and decreasing catabolism of VLDL-triglycerides. However, the precise role of apoA-II in control of VLDL-apoB-100 metabolism remains to be clarified in humans.

Adiponectin is a protein hormone secreted exclusively by adipocytes that has been shown to regulate the metabolism of lipids and glucose in animal studies [13]. Low plasma adiponectin levels have been shown in humans to be correlated with hypertriglyceridemia and low HDL cholesterol. We previously reported that plasma adiponectin concentration was significantly and positively associated with VLDL-apoB-100 fractional catabolic rate (FCR) and inversely associated with VLDL-apoB-100 production and HDL-apoA-I catabolism in men [14]. However, the association between plasma adiponectin and apoA-II metabolism has not been fully investigated. Whether the impact of adiponectin on VLDL metabolism is mediated by its effect on apoA-II metabolism also remains unclear.

To elucidate the potential regulatory effect of apoA-II on VLDL metabolism in humans, we set out, firstly, to examine the association between plasma apoA-II concentration and the kinetics of VLDL-apoB-100 and, secondly, to measure apoA-II kinetics and explore their relationship with VLDL-apoB-100 metabolism and adiponectin concentrations. To avoid other confounding factors such as obesity and insulin resistance on VLDL-apoB-100 metabolism, we conducted these association analyses in a group of healthy nonobese men.

2. Research design and methods

2.1. Subjects

We studied 37 white nonobese men with body mass index (BMI) ranging from 18 to 30 kg/m^2. All were nonsmokers and were consuming ad libitum weight maintenance diets. None of the subjects had diabetes, APOE2/E2 genotype, macroproteinuria, creatinemia (>120 μmol/L), hypothyroidism, or abnormal liver enzymes, or consumed more than 30 g alcohol per day. None reported a history of CVD, or was taking medication or other agents known to affect lipid metabolism. All subjects provided informed written consent, as approved by the Ethics Committee of the Royal Perth Hospital.

2.2. Study design and clinical protocols

All subjects were admitted to the metabolic ward in the morning after a 14-hour fast. They were studied in a semirecumbent position. Venous blood was collected for measurements of biochemical analytes. Plasma volume was determined by multiplying body weight by 0.045 L/kg. Arterial blood pressure was recorded after 3 minutes in the supine position using a Dinamap 1846 SX/P monitor (Critikon, Tampa, FL).

Details of infusion protocols have been described previously [15]. Briefly, an infusion of d_3-leucine was administered intravenously into an antecubital vein via a 21-gauge butterfly needle. Blood samples were taken at baseline and at 5, 10, 20, 30, and 40 minutes and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, and 10 hours after isotope injection. During this 10-hour period, all subjects were fasted and allowed to drink water only. Subjects were then given a snack and allowed to go home. Additional fasting blood samples were collected in the morning on the following 4 days of the same week (24, 48, 72, and 96 hours). Advice was given to maintain isocaloric dietary intake and physical activity during the study.

2.3. Isolation of apolipoproteins and measurements of leucine enrichments

Laboratory methods for isolation and measurement of isotopic enrichment have previously been detailed [15,16]. Briefly, apoB-containing lipoproteins were precipitated from 250 μL of plasma using heparin and $MnCl_2$. High-density lipoprotein was subsequently separated by ultracentrifugation, isolated using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and transferred to polyvinylidene difluoride membrane. The apoA-II band was excised from the membrane, hydrolyzed with 200 μL 6 mol/L HCl at 110°C for 16 hours, and dried for derivatization. For apoB isolation, VLDL were isolated from 3 mL of fresh plasma by ultracentrifugation at a density (d) of 1.006 g/mL. Apolipoprotein B-100 in the VLDL fraction was then precipitated by isopropanol, delipidated, hydrolyzed, and derivatized. Isotopic enrichment of apoA-II and apoB-100 was then determined by selected ion monitoring of derivatized samples using gas chromatography–mass spectrometry. Tracer to tracee ratio was derived from isotopic ratios for each sample.

2.4. Biochemical measurements

Plasma total cholesterol, HDL cholesterol, triglyceride, glucose, and free fatty acid (FFA) concentrations were determined by enzymatic methods. Total plasma apoA-I, apoA-II, and apoB-100 concentrations were determined by immunonephelometry (Dade Behring, Deerfield, IL). High-density lipoprotein apoA-II concentration was assumed to equal total plasma apoA-II because in the fasting state, more than 90% of apoA-II resides in the HDL fraction [3]. As described earlier, VLDL was isolated from 3 mL of fresh plasma by ultracentrifugation; and apoB-100 in the VLDL fraction was determined by a modified Lowry method. Plasma insulin was estimated by radioimmunoassay (DiaSorini, Saluggia, Italy). Insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR) score: fasting insulin (milliunits per liter) × fasting plasma glucose (millimoles per liter)/22.5 [17]. Plasma adiponectin concentration was determined using enzyme immunoassay kits (R&D Systems, Minneapolis, MN).

2.5. Model of HDL-apoA-II and VLDL-apoB-100 metabolism and calculation of kinetic parameters

Models of HDL-apoA-II and apoB-100 and calculation of kinetic parameters have previously been detailed [15,16]. Briefly, the apoA-II model includes a 4-compartment subsystem (compartments 1-4) that describes plasma leucine kinetics. This subsystem is connected to an intrahepatic delay compartment 5 that accounts for the time required for the synthesis and secretion of apoA-II into plasma. Compartments 6 and 7 describe the kinetics of apoA-II in the plasma HDL fraction and in a nonplasma compartment, respectively. The apoB-100 model includes a plasma leucine subsystem, intrahepatic delay compartment, and 5 compartments (4-compartment delipidation cascade and a single compartment for slowly turning over VLDL). The SAAM II program (SAAM Institute, Seattle, WA) was used to fit the model to the observed tracer data. The HDL-apoA-II and VLDL-apoB-100 metabolic parameters, including FCR and production rate (PR), were derived following a fit of the compartment model to the tracer-tracee ratio data.

2.6. Statistical analyses

All analyses were carried out using SPSS software version 15.0 (SPSS, Chicago, IL). Skewed variables were logarithmically transformed. Associations were examined by univariate regression and by multiple regression analyses. Significance was defined at the 5% level using a 2-tailed test.

3. Results

Table 1 shows the clinical and biochemical data relating to the 37 men studied. Twelve were lean (BMI <25 kg/m^2), and 25 were overweight (BMI between 25 and 30 kg/m^2). They were not dyslipidemic, hypertensive, diabetic, or insulin resistant. The kinetics of VLDL-apoB-100 and HDL-apoA-II were consistent with other reference populations [18-20].

Table 2 shows the Pearson correlation coefficients for the association of total plasma apoA-II concentration and kinetics with clinical and metabolic variables. Total plasma apoA-II concentration was significantly correlated with HDL-apoA-II PR (r = 0.563, P < .001), but not with HDL-apoA-II FCR. Both total apoA-II concentration and HDL-apoA-II PR were significantly and positively associated with waist circumference, plasma triglyceride, cholesterol, low-density lipoprotein (LDL) cholesterol, apoB-100 concentrations, and VLDL-apoB-100 PR. Fig. 1 shows the correlations of VLDL-apoB-100 PR with total plasma apoA-II concentration and HDL-apoA-II PR. The VLDL-apoB-100 concentration was significantly associated with HDL-apoA-II PR, but its association with total plasma apoA-II was of borderline statistical significance (P = .08). Plasma adiponectin concentration was also significantly (P < .05 in all) and inversely associated with plasma triglyceride (r = –0.327), VLDL-apoB-100 (r = –0.337), total apoA-II (r = –0.449), insulin (r = –0.366), HOMA score (r = –0.366), VLDL-apoB-100 PR (r = –0.373), and HDL-apoA-II PR (r = –0.349). Plasma apoC-III concentration was significantly (P < .05 in all) associated with plasma triglyceride concentration (r = 0.739), VLDL-apoB-100 concentration (r = 0.754), and VLDL-apoB-100 PR (r = 0.388). With the exception of VLDL-apoB-100 FCR, HDL-apoA-II FCR was not significantly correlated with any clinical characteristics, measures of insulin resistance, and plasma lipid and lipoprotein concentrations or with VLDL-apoB-100 PR. Fig. 2 shows the correlations of plasma adiponectin concentration with total plasma apoA-II concentration, HDL-apoA-II PR, and VLDL-apoB-100 PR.

Table 1 – Clinical and biochemical characteristics of the 37 nonobese subjects

Variables	Mean ± SD		Total
	Lean	Overweight	
Age, y	55 ± 14	51 ± 9	53 ± 10
BMI, kg/m^2	22 ± 2	28 ± 1	26 ± 4
Waist circumference, cm	85 ± 9	100 ± 5	95 ± 10
Systolic blood pressure, mm Hg	124 ± 17	132 ± 11	130 ± 14
Diastolic blood pressure, mm Hg	71 ± 10	86 ± 18	81 ± 17
Glucose, mmol/L	4.9 ± 0.5	5.3 ± 0.5	5.2 ± 0.5
Insulin, mU/L	15 ± 7	26 ± 9	22 ± 10
HOMA-IR score	3.3 ± 1.6	6.1 ± 2.5	5.2 ± 2.6
Adiponectin, mg/L	6.2 ± 1.8	5.2 ± 3.0	5.5 ± 2.7
FFAs, mmol/L	0.36 ± 0.15	0.32 ± 0.14	0.33 ± 0.14
Triglycerides, mmol/L	0.7 ± 0.2	1.4 (1.4)	1.0 (1.5)
Cholesterol, mmol/L	4.5 ± 0.6	5.7 ± 1.0	5.3 ± 1.1
HDL cholesterol, mmol/L	1.6 ± 0.5	1.1 ± 0.3	1.3 ± 0.4
LDL cholesterol, mmol/L	2.6 ± 0.1	3.7 ± 0.9	3.3 ± 0.9
ApoA-I, g/L	1.6 ± 0.4	1.2 ± 0.2	1.3 ± 0.3
ApoA-II, g/L	0.26 ± 0.09	0.30 ± 0.09	0.28 ± 0.08
ApoB-100, g/L	0.81 ± 0.1	1.1 ± 0.3	1.0 ± 0.3
ApoC-III, mg/L	98 ± 28	142 ± 46	128 ± 46
VLDL-apoB-100, mg/L	37 ± 21	75 (85)	55 (71)
VLDL-apoB-100 FCR, pools/d	8.3 ± 4.5	3.7 (2.8)	4.4 (3.9)
VLDL-apoB-100 PR, mg/(kg d)	11.3 ± 3.9	12.6 (7.0)	12.5 (6.8)
HDL-apoA-II FCR, pools/d	0.23 (0.10)	0.25 (0.05)	0.25 (0.06)
HDL-apoA-II PR, mg/(kg d)	3.2 ± 1.9	3.5 ± 1.2	3.4 ± 1.5

Data are means ± SEM or medians (interquartile range).

Table 2 – Correlation coefficients for the associations of total plasma apoA-II concentration and kinetics with clinical and metabolic variables

Variables	ApoA-II		
	Concentration	PR	FCR
Age, y	0.121	0.185	0.204
BMI, kg/m^2	0.164	0.151	–0.04
Waist circumference, cm	0.361 *	0.315 *	0.015
Glucose, mmol/L	–0.087	0.128	0.308
Insulin, mU/L	–0.027	0.120	0.182
HOMA-IR score	–0.022	0.120	0.182
Adiponectin, mg/L	–0.449 †	–0.375 *	–0.051
FFAs, mmol/L	0.185	0.024	–0.205
Triglycerides, mmol/L	0.360 *	0.369 *	0.038
Cholesterol, mmol/L	0.609 †	0.357 *	–0.159
HDL cholesterol, mmol/L	0.16	0.004	–0.02
LDL cholesterol, mmol/L	0.452 †	0.243	–0.181
ApoA-I, g/L	0.202	0.094	0.021
ApoA-II, g/L		0.734 †	–0.031
ApoB-100, g/L	0.570 †	0.364 *	–0.143
ApoC-III, mg/L	0.288	0.360 *	0.240
VLDL-apoB-100, mg/L	0.284	0.409 *	0.228
VLDL-apoB-100 FCR, pools/d	0.053	–0.162	–0.339 *
VLDL-apoB-100 PR, mg/(kg d)	0.406 *	0.427 †	0.093
HDL-apoA-II FCR, pools/d	–0.031	0.608 †	
HDL-apoA-II PR, mg/(kg d)	0.734 †		0.608 †

* $P < .05$.
† $P < .01$.

In multiple regression models including waist circumference and plasma insulin, plasma adiponectin concentration was independently associated with total plasma apoA-II concentration (β-coefficient = –0.508, $P = .001$) and HDL-apoA-II PR (β-coefficient = –0.374, $P = .03$). Likewise, total plasma apoA-II concentration (β-coefficient = 0.348, $P = .047$) and HDL-apoA-II PR (β-coefficient = –0.350, $P = .035$) were significantly associated with hepatic secretion of VLDL-apoB-100 after adjusting for waist circumference and plasma insulin concentration. However, the association between total plasma apoA-II concentration and HDL-apoA-II PR and VLDL-apoB-100 PR became nonsignificant after including plasma adiponectin in both these models (β-coefficient = 0.240 and 270, respectively; $P > .05$ in both).

4. Discussion

Our principal findings were that HDL-apoA-II PR and hence total plasma apoA-II concentration were significantly associated with VLDL-apoB-100 PR in nonobese men and that this was partially dependent on plasma adiponectin concentration; the latter was inversely associated with both HDL-apoA-II and VLDL-apoB-100 PRs.

Few studies have specifically examined the association of HDL-apoA-II with VLDL-apoB-100 metabolism in humans [21,22]. In an earlier radiokinetic study, Magill et al [21] reported that, in 17 subjects, HDL-apoA-II PR was positively associated with VLDL-apoB-100 PR. Another radiokinetic study by Fidge et al [22] found no significant relationship between HDL-apoA-II PR and VLDL-apoB-100 PR in 10 subjects. However, only a limited number of individuals have been examined in these studies; and the majority had various forms of hyperlipoproteinemia including primary hypercholesterolemia, primary hypertriglyceridemia, and LPL deficiency. Our present data extend previous studies by using a larger sample size, a nonradioactive label, and multicompartmental modeling of the kinetics of HDL-apoA-II and VLDL-apoB-100. We also examine the association between plasma adiponectin concentration and the kinetics of HDL-apoA-II and VLDL-apoB-100 in a group of apparently healthy nonobese subjects.

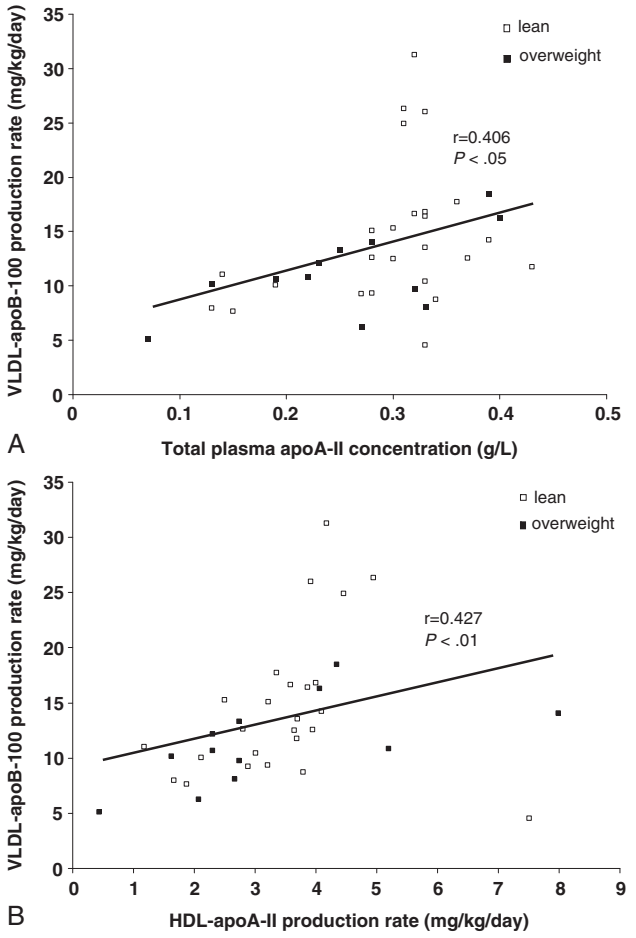

Fig. 1 – Associations of VLDL-apoB-100 PR with total plasma apoA-II concentration (A) and HDL-apoA-II PR (B).

Expansion of the VLDL-triglyceride pool enhances CETP-mediated exchange of neutral lipids with HDL and results in the formation of unstable triglyceride-enriched HDL particles that are rapidly removed from the plasma [2]. Consistent with this, we have previously found that, in nonobese men, variation in VLDL-apoB-100 production, and hence plasma triglyceride concentration, exerts a major effect on the catabolism of HDL-apoA-I [14]. Although HDL-apoA-I and apoA-II share similar metabolic pathways, we failed to observe any significant association between plasma triglyceride concentration (or VLDL-apoB-100 PR) and HDL-apoA-II FCR in these subjects. Instead, we found that total plasma apoA-II concentration and HDL-apoA-II PR were significantly associated with plasma triglyceride concentration and VLDL-apoB-100 PR. The mechanism linking plasma apoA-II and VLDL-apoB-100 PR remains unknown. There has been a suggestion

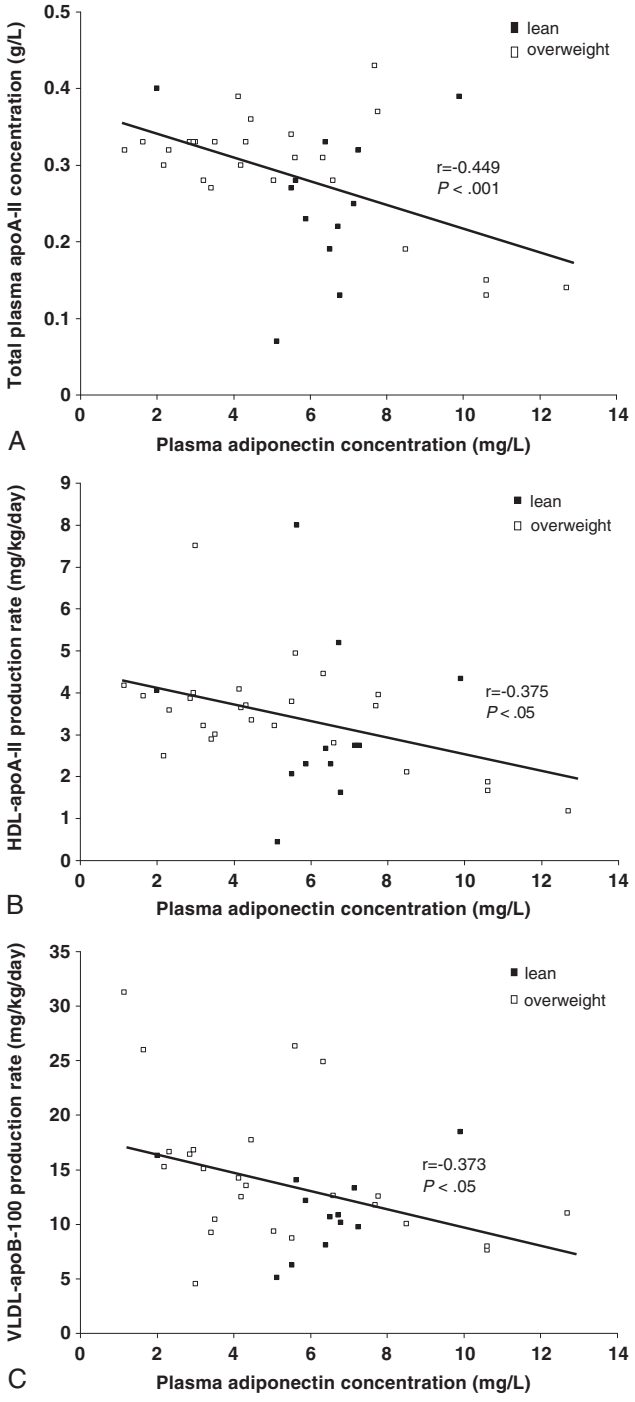

Fig. 2 – Associations of plasma adiponectin concentration with total plasma apoA-II concentration (A) and the PRs of HDL-apoA-II (B) and VLDL-apoB-100 (C).

that overproduction of apoA-II in insulin resistance can drive VLDL production by increasing hepatic lipogenesis and inhibiting fatty acid oxidation [11]. Although we did not find a significant association between total plasma apoA-II and plasma FFA concentration, measurement of FFA in plasma may not fully reflect the corresponding portal or hepatic FFA concentrations that regulate VLDL-apoB-100 metabolism in the liver. Although animal data have shown a direct role of apoA-II on VLDL-triglyceride clearance, our findings did not find a significant association between total plasma apoA-II and VLDL-apoB-100 clearance. Discrepancies could also be due to differences in experimental protocols; genetic-manipulated animal models do not strictly reflect the physiology of human lipid and lipoprotein metabolism. However, these observations may reflect that the apoB-100 and triglyceride components of VLDL are independently regulated. It is also likely that other plasma factors may play a more important role than apoA-II in regulating VLDL-apoB-100 FCR. Consistent with this speculation, we found that plasma apoC-III concentration is a highly significant determinant of VLDL-apoB-100 FCR [15].

We and others have previously shown that, in nonobese men, plasma adiponectin concentration was inversely associated with HDL-apoA-I FCR [14,23]. In this study, we demonstrate for the first time that plasma adiponectin concentration was associated with total plasma apoA-II and HDL-apoA-II PR independent of waist circumference and plasma insulin. This suggests that adiponectin may also have a direct role on HDL-apoA-II production. However, the mechanism linking plasma adiponectin and HDL-apoA-II production remains unknown. It has been shown that adiponectin may decrease gene expression of nuclear factor 4α in human hepatocytes [24]. Because hepatocyte nuclear factor 4α is found to be a direct regulator of apoA-II expression [25], it is conceivable that this mechanism could partly account for the effect of adiponectin on HDL-apoA-II production and hence total plasma apoA-II concentration. There is also direct evidence that adiponectin reduces apoB gene expression and secretion in human hepatocytes [24]. Accordingly, we reported that plasma adiponectin concentration was significantly and inversely associated with plasma triglyceride, VLDL-apoB-100, and VLDL-apoB-100 PR. These findings are generally in agreement with some, but not all, previous studies [14,26]. This discrepancy could be due to differences in study populations and sample sizes. In the present study, we also found that the association between total plasma apoA-II concentration and VLDL-apoB-100 PR was partially dependent on plasma adiponectin concentration. This suggests that the effect of apoA-II on VLDL-apoB-100 PR could in part be mediated by a direct action of adiponectin on the production of HDL-apoA-II and VLDL-apoB-100.

There are limitations to our study. Correlational analyses do not prove causality. However, in vitro data generally support the role of apoA-II on VLDL-apoB-100 metabolism. High-density lipoprotein particles are subjected to modifications by several lipase and lipid transfer proteins, particularly, lecithin cholesterol acyltransferase, LPL, hepatic lipase, and CETP. Measurements of their activities in plasma may help to formally corroborate our findings. We did not measure the concentration of apoA-II in VLDL and the kinetics of VLDL-triglyceride. These could otherwise provide new information on its association with VLDL-apoB-100 and HDL-apoA-II kinetics. We did not measure triglyceride content in HDL particles that could otherwise provide new information on its association with HDL-apoA-II and VLDL-apoB-100 kinetics. Further human studies are also needed to investigate the mechanism of action whereby apoA-II can impact triglyceride and FFA metabolism in both fasting and postprandial states.

Despite strong evidence supporting an inverse relationship between plasma apoA-I concentration and the risk of CVD, the association between apoA-II and CVD remains controversial

and hence poorly defined. Understanding the role of HDL-apoA-II on triglyceride-rich lipoprotein metabolism could be clinically important. Although the cellular and animal studies generally support the role of apoA-II in governing VLDL metabolism, direct evidence from human studies is relatively scarce. Our findings support a role of apoA-II in modulating VLDL-apoB-100 metabolism in men. Targeting apoA-II metabolism may therefore be an important therapeutic approach to managing dyslipidemia and CHD risk in metabolic syndrome. Whether or not apoA-II is antiatherogenic remains to be elucidated and must also be viewed in light of apoB-100 and apoA-I transport. Adiponectin has also been demonstrated to have several antiatherogenic functions, involving antiadhesive, antiproliferative, and antioxidant properties. Our kinetic study has shown that, in nonobese men, plasma adiponectin is associated with the plasma concentration and PR of HDL-apoA-II and VLDL-apoB-100. Whether our findings also apply to women and to patients with obesity and type 2 diabetes mellitus also merits investigation.

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