Postprandial Changes in the Distribution of Apolipoprotein AIV Between Apolipoprotein B- and Non–Apolipoprotein B-Containing Lipoproteins in Obese Women

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Plasma apolipoprotein AIV (apo AIV) level has been shown to be a good marker of triglyceride changes after a high-fat diet. However, the distribution of apo AIV between apo B- and non–apo B-containing lipoproteins (Lp) during the postprandial state has not been described as well as the influence of obesity on this distribution. Our aim was to study the influence of parameters related to obesity and insulin resistance on the postprandial changes in apo AIV-containing Lp after a high-fat meal in obese women. Twenty-three overweight or obese women (body mass index [BMI] ranging from 29.1 and 64.0 kg · m^{-2}), for whom blood samples were taken after fasting overnight, participated in the study. Thirteen of these obese women were given a fatty meal and, in this case, blood samples were taken at fast and 30 minutes, 1, 2, 4, and 6 hours after ingestion of the fat meal. Apo AIV-containing particle families, Lp B:AIVf (family [f] of particles containing at least apo B and apo AIV) and Lp AIV non-Bf (family [f] of particles containing apo AIV, but free of apo B) were quantified by sandwich enzyme-linked immunosorbent assay (ELISA). When fasting, Lp B:AIVf and Lp AIV non-Bf did not correlate with any of the parameters related to obesity and insulin resistance, if one excepts a positive correlation between HDL-cholesterol (HDL-C) and Lp AIV non-Bf. Postprandial lipemia was associated with a trend towards an increase in the plasma levels of apo AIV-containing Lp 6 hours after fat ingestion. The postprandial peak of Lp B:AIVf and Lp AIV non-Bf occurred 2 hours after the triglyceride peak. The distribution between apo B- and non–apo B-containing Lp did not change after ingestion of the fat meal, if one excepts a tendancy towards a lower ratio of bound and nonbound forms at 8 hours. Fasting plasma Lp B:AIVf concentration correlated with the area under the curve (AUC) of plasma triglycerides (β = 0.11, P < .02). In a multivariate analysis, BMI (β = 51.85, P < .001), fasting triglycerides (β = 431.08, P < .01), and low-density lipoprotein-cholesterol (LDL-C) (β = 2638.57, P < .005) were independent and positive determinants of the AUC of Lp AIV non-Bf, while waist circumference (β = -23.94, P < .001), cholesterol (β = -1655.02, P < .01), and systolic blood pressure (β = -6.34, P < .05) were negative and independent determinants of this AUC. Fasting Lp B:AIVf may represent a good marker of the postprandial triglyceride increase in obese women. Changes in apo AIV concentrations in apo B- and non–apo B-containing Lp after a fat meal depend mainly on the degree of obesity rather than on insulin resistance. This effect is more obvious for Lp AIV non-Bf than for Lp B:AIVf.

HUMAN APOLIPOPROTEIN (apo) AIV, a 46-kd protein, is exclusively synthesized in the small intestine.[1-3] Although its precise function remains unclear, apo AIV has been suggested to play a role in the metabolism of both triglyceride-rich lipoproteins (TRL) and high-density lipoprotein (HDL). It may also be a signal for satiety in the central nervous system).[4,5] It has been reported that apo AIV binds to bovine aortic endothelial cells[6] and hepatic tissues.[7,8] Apo AIV is implicated in several key points of reverse cholesterol transport, such as cholesterol efflux,[9,10] lecithin:cholesterol acyltransferase activity,[11-13] and the HDL processing mediated by cholesteryl ester transfer protein.[14,15] In addition, apo AIV modulates the activation of lipoprotein lipase (LPL) in the presence of apo CII, suggesting a role of apo AIV in the metabolism of TRL.[16]

Several studies have shown that apo AIV can be found associated mainly with HDL, but also with TRL,[3,17-23] 2 species of plasma lipoproteins (Lp) that can be distinguished by either the absence (Lp non-B) or the presence of apo B (Lp B). Therefore, we recently developed a methodology allowing the measurement of apo AIV associated with apo B-containing lipoprotein family (Lp B:AIVf) and of apo AIV nonassociated with apo B-containing lipoprotein family (Lp AIV non-Bf).[24] Apo AIV levels are increased in hypertriglyceridemic patients[19,25-26] due to an increase in apo AIV associated with apo B-containing Lp.[24]

Very little is known about the relationship between apo AIV-containing Lp and postprandial lipemia. So far, only a few studies have reported,[2,26-30] while it was shown that apo AIV synthesis increases after consumption of a fat-rich meal.[30-32] In addition, Vergès et al[32] have shown that fasting apo AIV could be a good marker of triglyceride response after a high-fat meal in obese subjects. These postprandial TRL levels seem to be involved in the development of atherosclerosis.[33] In obese subjects, altered postprandial lipemia could explain, at least in part, the greater development of cardiovascular disease in this population.[34,35]

The present study was set up to evaluate the influence of obesity on postprandial changes in apo AIV-containing Lp after high-fat meal ingestion.

MATERIALS AND METHODS

Subjects and Sampling

Twenty-three Caucasian obese women volunteers were included in the study. Apart from obesity, all subjects were in good health. None of the volunteers were engaged in any type of exercise program or were excessively sedentary. None were suffering from any infection as assessed by clinical examination and blood cell count. Subjects taking

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medications known to affect plasma lipid levels were excluded. For each subjects, waist (WC) and hip circumferences, systolic (SBP), and diastolic (DBP) blood pressures were measured. Body mass index [BMI = weight (kg)/height^2 (m^2)] and waist-to-hip ratio (WHR) were calculated.

Diet and Sample Collection

A weight maintenance diet was prescribed for all patients for 1 week before the study to ensure uniformity. At approximately 8 AM after an overnight fast (at least 12 hours), 13 obese women among the 23 women included were given a fatty breakfast. The fatty meal (54.13% fat, 17.20% carbohydrates, 28.07% protein) contained 1,420 kilocalories. This breakfast was ingested within 15 minutes. After the meal, the subjects remained fasted for 6 hours, but were allowed to drink water ad libitum.

Blood samples were taken at baseline and 30 minutes, 1, 2, 4, and 6 hours after the fat-rich meal. They were centrifuged, and serum was divided into aliquots and kept at −80°C before analysis. The 10 subjects who did not accept the high-fat meal were sampled after an overnight fast only (at least 12 hours).

Analytical Methods

Plasma levels of glucose, cholesterol, triglycerides, and HDL-cholesterol (HDL-C) were assayed enzymatically using a multiparametric analyzer (Hitachi 747; Roche Molecular Biochemicals, Meylan, France). LDL-cholesterol was calculated by the Friedewald formula.[36] Serum insulin concentrations were measured using commercial radioimmunoassay (RIA) kits (Bi-Insulin IRMA; ERIA Pasteur, Paris, France). Insulin sensitivity was calculated using the homeostasis model assessment (HOMA = [glucose (mmol/L) × insulin (UI/L)]/22.5), a mathematical estimate of insulin sensitivity based on fasting glucose and insulin concentrations.[37]

To measure total apo AIV [AIV Lp] and apo AIV associated with apo B [Lp B:AIVf], we used a noncompetitive enzyme-linked immunosorbent assay (ELISA) (sandwich ELISA) as previously described.[25] Apo AIV nonassociated with apo B [Lp AIV non-Bf] was calculated by subtracting Lp B:AIVf from apo AIV Lp levels. Triglycerides and apo AIV-containing particle levels were measured at baseline, and 30 minutes, 1, 2, 4, and 6 hours after the meal ingestion.

Table 1. Clinical and Biochemical Parameters, Lipids, and Apo AIV-Containing Lipoprotein Particle Concentrations in Studied Subjects

	Means	Min	Max
BMI (kg/m^2)	39.7 ± 8.34	29.1	64.0
WC (cm)	108 ± 14.6	85	140
WHR	0.89 ± 0.09	0.70	1.04
HOMA*	3.21 ± 2.70	1.06	12.8
Glucose (mmol/L)	4.91 ± 0.49	4.2	6.1
Insulin* (mU/L)	14.2 ± 10.3	5.7	47.2
Cholesterol (g/L)	2.24 ± 0.28	1.79	2.82
Triglycerides (g/L)	1.33 ± 0.31	0.83	1.84
HDL-cholesterol (g/L)	0.46 ± 0.09	0.32	0.74
LDL-cholesterol (g/L)	1.52 ± 0.28	1.05	2.12
SBP* (mm Hg)	126 ± 12.0	90	140
DBP* (mm Hg)	73.9 ± 10.3	50	90
Lp B:AIV (mg/L)	39.6 ± 5.64	27.6	53.0
Lp AIV non-Bf (mg/L)	92.9 ± 46.8	15.8	203
AIV Lp (mg/L)	132 ± 48.4	59.9	248

Abbreviations: BMI, body mass index; WC, waist circumference; WHR, waist to hip ratio: HOMA, insulin sensitivity index (glucose × insulin/22.5); SBP, systolic blood pressure; DBP, diastolic blood pressure.

*Variables log transformed because of absence of normality.

Table 2. Relationships Between Various Clinical and Biological Parameters Related to Obesity and Insulin Resistance and Apo AIV-Containing Lipoprotein Concentrations as Assessed by a Simple Regression Model

	Lp B:AIVf (mg/L)		Lp AIV non-Bf (mg/L)	
	β	P	β	P
BMI (kg/m^2)	−0.25	.09	−0.77	.54
WC (cm)	−0.14	.11	−0.60	.41
WHR	−8.15	.56	−124	.27
HOMA	−0.36	.44	−0.13	.97
Glucose (mmol/L)	−1.76	.50	1.81	.93
Insulin (mU/L)	−0.09	.46	−0.26	.80
Cholesterol (g/L)	−0.21	.97	−14.8	.71
Triglycerides (g/L)	0.19	.96	19.9	.55
HDL-cholesterol (g/L)	13.7	.31	317	.001
LDL-cholesterol (g/L)	−2.12	.66	−61.7	.11

Statistical Analysis

Data are means ± SD. The areas under the time concentrations curves (area under the curves [AUCs]) were calculated by the trapezoidal method.[38] Incremental AUC was evaluated after subtracting the initial individual value (T0) from all respective postprandial measurements, yielding the net postprandial change.

Results were analyzed using the SAS statistical software (SAS, Cary, NC). Differences between sampling times in the oral fat load test were assessed by analysis of variance (ANOVA). Linear regression models were used to look at relationships between variables. A multiple regression procedure, including all parameters correlated with the explained variables with a P value less than .25 in the univariate analysis, was performed to identify significant independent predictors of apo AIV-containing Lp postprandial changes.

RESULTS

Characteristics of the Studied Population

Clinical and biological characteristics of the obese fasting subjects are shown in Table 1. Obesity ranged from net overweight to morbid obesity. On the basis of HOMA, it may be considered that the population included noninsulin-resistant as well as severe insulin resistant women (HOMA was above 2.5 for 25% of the subjects).

Relationships Between Apo AIV-Containing Lp Levels and Parameters Related to Obesity and Insulin Resistance

Table 2 shows the regression coefficients (β) between apo AIV-containing Lp levels and some of the clinical and biological parameters related to obesity and insulin resistance.

No significant correlation was found for Lp B:AIVf, except a trend towards a negative correlation with BMI and WC. Lp AIV non-Bf level was significantly and positively correlated with HDL-C.

Changes in Apo AIV-Containing Lp Levels After the Oral Fat Meal

Figure 1 shows means of triglycerides (Fig 1A), Lp B:AIVf (Fig 1B), and Lp AIV non-Bf (Fig 1C) before and after the oral fat meal.

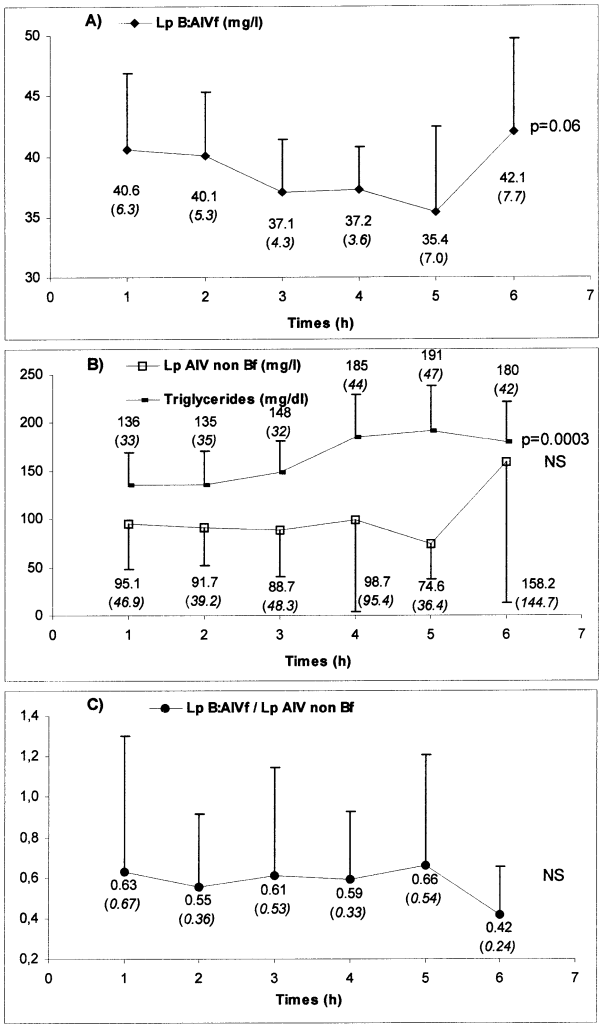

Fig 1. Means (SD) of (A) plasma Lp B:AIVf, (B) triglycerides and Lp AIV non-Bf levels, and (C) the ratio between bound and nonbound forms during the high-fat diet in the whole population studied.

Mean plasma triglyceride levels increased progressively to reach a peak (+ 40%) 4 hours after the ingestion of the fat-rich meal. This was followed by a slow decrease, which was not sufficient enough to return at baseline.

Mean Lp B:AIVf concentration tended to decrease progressively up to 4 hours after the meal ingestion and increased thereafter. However, these variations were not significant.

Mean Lp AIV non-Bf concentrations remained fairly stable up to 4 hours and tended to increase 6 hours after the meal. These changes were not significant.

The distribution between apo B- and non–apo B-containing Lp did not change after ingestion of the fat meal, if one excepts a tendancy towards a lower ratio of bound and nonbound forms at 8 hours.

Relationships Between Postprandial Changes in Triglycerides or Apo AIV-Containing Lp Levels and Parameters Related to Obesity and Insulin Resistance

Relationships between AUC of triglycerides or apo AIV-containing Lp and clinical and fasting biological parameters related to obesity or insulin resistance are presented in Table 3.

In univariate analysis, AUCs of plasma triglycerides were positively correlated with fasting Lp B:AIVf levels. AUCs of Lp B:AIVf were positively correlated with BMI and tended to be correlated with WC. AUCs of Lp AIV non-Bf were positively correlated with BMI and fasting LDL-C levels and negatively correlated with fasting triglyceride levels.

A multiple regression model, including parameters related to the AUCs of apo AIV-containing Lp with a *P* value less than .25 in the univariate model, was run to assess their independent contribution to the postprandial changes in apo AIV-containing Lp (Table 4). Postprandial Lp B:AIVf variations were not significantly explained by any of the parameters introduced in the model (BMI and WC). Lp AIV non-Bf postprandial AUCs were positively and independently influenced by BMI, fasting levels of LDL-C, and triglycerides and negatively and significantly influenced by WC, cholesterol, and SBP.

Table 3. Relationships Between Various Clinical and Biological Parameters Related to Obesity and Insulin Resistance and the Area Under the Curve of Triglycerides and Apo AIV-Containing Lipoproteins as Assessed by a Simple Regression Model

	Lp B: AIVf (mg/L · h)		Lp AIV non-Bf (mg/L · h)		Triglycerides (g/L · h)	
	β	*P*	β	*P*	β	*P*
BMI	3.00	.02	19.5	.03	−0.02	.73
WC	1.35	.06	7.41	.17	0.01	.65
WHR	37.4	.65	60.3	.92	2.68	.40
HOMA	1.97	.67	54.0	.08	−0.24	.16
Glucose (mmol/L)	23.2	.32	154.8	.35	0.69	.44
Insulin (mU/L)	0.27	.81	12.1	.10	−0.06	.15
Cholesterol (g/L)	20.9	.47	324	.09	0.45	.68
Triglycerides (g/L)	−8.05	.76	−336	.05	−0.08	.94
HDL-cholesterol (g/L)	−27.6	.83	−275	.75	2.14	.65
LDL-cholesterol (g/L)	23.5	.42	418	.02	0.33	.77
SBP (mm Hg)	0.51	.42	6.29	.14	0.01	.74
DBP (mm Hg)	0.19	.82	4.72	.41	0.03	.33
Lp B:AIVf (mg/L)	—	—	—	—	0.11	.02

Table 4. Independent Contribution of Various Clinical and Biological Parameters Related to Obesity and Insulin Resistance and the Area Under the Curve of Apo AIV-Containing Lipoproteins as Assessed by a Multiple Regression Model

	Lp B:AIVf (mg/L · h)		Lp AIV non-Bf (mg/L · h)	
	β	P	β	P
BMI	2.77	.16	51.8	.0008
WC	0.16	.88	−23.9	.0015
HOMA	—	—	130	.1279
Insulin (mU/L)	—	—	−36.8	.0870
Cholesterol (g/L)	—	—	−1655	.0064
Triglycerides (g/L)	—	—	431	.0109
LDL-cholesterol (g/L)	—	—	2638	.0027
SBP (mm Hg)	—	—	−6.34	.0218

NOTE. Multiple regression model includes all parameters correlated with the apo AIV-containing lipoprotein particles at a P value $< .25$ in univariate analysis.

DISCUSSION

The aims of the present study in obese women were (1) to determine how the severity of obesity and the factors associated with insulin resistance affect the distribution of apo AIV between apo B- and non apo B-containing Lp, (2) to examine the influence of a high-fat meal on this distribution, and (3) to determine how the degree of obesity and the factors associated with insulin resistance affect the postprandial changes in apo AIV associated with apo B- and non–apo B-containing Lp.

Special attention has recently been put on apo AIV because of its potentially important role in Lp metabolism. We recently developped a new ELISA method[25] allowing the measurement of apo AIV associated with apo B-containing Lp and the calculation of apo AIV associated with non–apo B-containing Lp. Lp B:AIVf represents the minor fraction of apo AIV-containing Lp, and it was suggested that the presence of apo AIV in this subfraction reflects its transfer from HDL towards TRL when those accumulate.[19,26,39] In addition, it should be kept in mind that our antibody against apo B recognizes apo B48 as well as apo B100. Therefore, in the postprandial state, Lp B:AIVf represents a mixture of chylomicron and very-low-density lipoprotein (VLDL) remnants containing apo AIV. However, it was shown recently[29] that no correlation exists between apo AIV and apo B48 catabolism. During the postprandial state, apo AIV seems to be able to recirculate between TRL and HDL.[29] In our previous work realized in a general population sample,[24] Lp B:AIVf concentration was shown to be positively correlated with triglycerides. Therefore, the absence of correlation between these 2 parameters in our obese population was surprising. This lack of correlation cannot be explained by a negative effect of insulin resistance on Lp B:AIVf, because none of the factors related to this pathophysiologic condition, particularly HOMA and the fat distribution as determined by WHR, was correlated with Lp B:AIVf concentration. The only trend observed is a negative effect of obesity itself, as suggested by the correlation coefficient between BMI and Lp B:AIV concentration, which was found close to significance ($P = .09$). One hypothesis would be that obesity leads to a decrease in apo AIV in HDL and/or in its free form, which would represent a reservoir for Lp B:AIVf. As a matter of fact, while our method cannot distinguish between free apo AIV and HDL apo AIV, the positive correlation between HDL-C and Lp AIV non-Bf suggests that the latter reflects mainly HDL apo AIV. Consequently, in obesity, the increase in Lp B:AIVf related to the accumulation of TRL could be counteracted by the decrease in the HDL pool, generally observed in this situation.

Plasma apo AIV, which is synthesized predominantly in the small intestine, is known to increase in the postprandial state.[28,40] In the present study, we have shown that plasma apo AIV-containing Lp levels increase moderately although not significantly after fat ingestion. The increase in Lp AIV non-Bf levels reached 66% of the fasting baseline value and peaked at 6 hours after the meal. Lp B:AIVf levels decreased up to 4 hours and increased thereafter by 19% and peaked at 6 hours. In most postprandial studies,[28,32] apo AIV-containing Lp increase 2 hours after the triglyceride peak, occurring between 2 hours and 3 hours.[27,28,40] Therefore, our subjects have an apparent delay in the increase of TRL and apo AIV after fat load. However, it was previously reported that normolipidemic obese subjects had altered postprandial lipemia with a significantly greater AUC of triglycerides and a peak of triglycerides around 4 hours after the fat-rich meal.[32] Our results seem to fit with this previous study. Nevertheless, the 6-hour observation time represents a limitation of our study. Further investigation should be performed using longer sampling times, of 8 to 10 hours. Vergès et al[32] have shown that fasting plasma apo AIV was highly correlated with the AUC of plasma triglycerides in obese subjects, suggesting that fasting apo AIV level could predict the postprandial triglyceride levels. Our results suggest that the level of fasting Lp B:AIVf could be a better predictor of the triglyceride increase after a high-fat meal than total apo AIV.

The postprandial change in Lp B:AIVf concentration seems to depend exclusively on the degree of obesity as suggested by the significant correlation between BMI and the corresponding AUC. However, this relationship seems to be rather weak, because it disappears in the multiple regression study. Interestingly, none of the parameters related to insulin resistance, particularly HOMA and the fat distribution as determined by WHR, seems to be correlated with the postprandial change in Lp B:AIVf. In contrast, changes in Lp AIV non-Bf are related to several of these parameters. Interestingly, in the multiple regression study, the positive correlation between BMI, triglycerides, LDL-C, and Lp AIV non-Bf AUC, contrasting with the negative correlation with WC, insulin, and SBP could suggest a dual effect of insulin resistance or the so-called metabolic syndrome and obesity itself. Further studies, including comparison between obese and non-obese subjects, as well as well-defined insulin-resistant subjects, are needed to confirm this hypothesis.

In summary, this report shows that fasting Lp B:AIVf level may represent a good predictor of postprandial triglycerides in obese women. Changes in apo AIV concentrations in apo B and non-apo B-containing Lp after a fat meal depend mainly on the degree of obesity rather than on insulin resistance. This effect is more obvious for Lp AIV non-Bf than for Lp B:AIVf. The specific effect of insulin resistance in itself on these parameters should be further studied.

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