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ScienceDirect
Metabolism Clinical and Experimental 56 (2007) 910–914
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

Effect of body mass index on apolipoprotein A-I kinetics in middle-aged men and postmenopausal women

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Received 21 August 2006; accepted 2 January 2007

Abstract

The effect of body mass index (BMI) and obesity on apolipoprotein (apo) A-I levels and kinetics was examined by gender. Apo A-I kinetics were determined with a primed, constant infusion of deuterated leucine in the fed state in 19 men and 13 postmenopausal women. Compared with nonobese men, nonobese women had a higher level of high-density lipoprotein cholesterol (HDL-C) and apo A-I due to a 48% higher apo A-I production rate (PR) ($P = .05$). Obesity had no significant effects on apo A-I kinetics in women. In contrast, compared with nonobese men, obese men had a 9% lower apo A-I level due to a 64% higher fractional catabolic rate (FCR) partially offset by a 47% higher PR. Obese women had a 52% higher HDL-C than obese men (50 vs 33 mg/dL, respectively; $P = .012$), a finding related to the faster apo A-I FCR in obese men. BMI was directly correlated with apo A-I FCR ($r = 0.84$, $P < .001$) and PR ($r = 0.79$, $P < .001$) in men but not in women. Sixty-two percent of the variability in PR and 71% of the variability in FCR were due to BMI in men and only 3% and 23%, respectively, in women. In conclusion, BMI has a significant effect on apo A-I PR and FCR in men but not in women.

1. Introduction

High levels of high-density lipoprotein cholesterol (HDL-C) have been associated with lower rates of coronary heart disease in epidemiologic studies [1]. The plasma level of apolipoprotein (apo) A-I, the major protein of atheroprotective HDL, is higher in both pre- and postmenopausal women compared with men [2]. The reasons for this are not entirely clear. A prior meta-analysis of 13 stable isotope studies examined the effect of obesity on apo A-I kinetics but did not report results by sex [3]. Two prior studies, using stable isotopes, have reported on sex differences in kinetics of apo A-I but did not have a large enough sample size to examine the effect of obesity by sex on kinetics [4,5]. Using stable isotopes in the current study, we added obese subjects to the prior 2 studies and used multicompartmental modeling to examine the effect of body mass index (BMI) and obesity on the apo A-I fractional catabolic rate (FCR) and production rate (PR) in obese and nonobese middle-aged men and women.

2. Methods

Subjects for these studies were 19 men and 13 postmenopausal women stratified in relation to obesity as defined by a BMI of 30 kg/m^2 or greater. We added 2 obese men, 3 obese women, and 4 nonobese women to the previously published subjects [4,5]. All subjects received a primed, constant infusion of [$^2H_3$]leucine intravenously at 10 μmol/kg per hour for 15 hours while consuming small hourly meals, as previously described [4-8]. Lipoproteins were isolated by sequential density ultracentrifugation: very low-density lipoprotein (VLDL) at d less than 1.006 and HDL at d greater than 1.063 but less than 1.21. After separation of VLDL apo B-100 and HDL apo A-I by sodium dodecyl sulfate–polyacrylamide gel electrophoresis, the apolipoprotein bands were cut from the gels, hydrolyzed, and derivatized, and the isotopic enrichment of the leucine was measured by gas chromatography–mass spectrometry [4-8]. Plasma lipids were measured in the fasting state by standardized enzymatic methods [6]. Plasma apo A-I was measured by an immunoturbidimetric assay [9]. Using the plateau enrichment of VLDL apoB-100 as the forcing function [8], we determined FCR of apo A-I as the rate

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doi:10.1016/j.metabol.2007.01.022

Table 1
Baseline characteristics

	Men			Postmenopausal women			*P* (nonobese men vs nonobese postmenopausal women)	*P* (obese men vs obese postmenopausal women)
	Nonobese (n = 15)	Obese (n = 4)	*P*	Nonobese (n = 7)	Obese (n = 6)	*P*		
Age (y)	57 ± 12	48 ± 7	.2	59 ± 8	61 ± 9	.67	.65	.05
BMI (kg/m^2)	25.7 ± 1.8	30.6 ± 0.8	<.001	24.7 ± 2.5	33.4 ± 3.4	.0002	.3	.15
TC (mg/dL)	225 ± 46	219 ± 50	.82	228 ± 37	251 ± 41	.31	.88	.3
TG (mg/dL)	118 ± 37	159 ± 12	.045	98 ± 37	170 ± 59	.02	.24	.73
LDL-C (mg/dL)	135 ± 28	148 ± 39	.45	144 ± 30	157 ± 49	.57	.5	.77
HDL-C (mg/dL)	43 ± 9	33 ± 4	.04	61 ± 20	50 ± 10	.23	.0064	.012

Values are mean ± SD. TC indicates total cholesterol; TG, triglyceride.

constant *k* (0,3) in the single-compartment model published previously using the SAAM II program (SAAM Institute, Seattle, WA) [7,10]. The PR is calculated as the FCR multiplied by the apo A-I pool size and divided by the body weight in kilograms.

Statistical analyses were carried out with the Instat2 program (GraphPad Software, San Diego, CA). Two-sided Student *t* tests and Pearson correlation coefficients were used to test for statistical significance ($P < .05$). All values are mean ± SD.

3. Results

The group averages of age, BMI, and lipid levels of the subjects are shown in Table 1. The obese men were an average of 13 years younger than the obese postmenopausal women ($P = .05$), but there was no significant difference in BMIs (31 vs 33 kg/m^2). Two sets of comparisons were performed. The first comparison was the effect of sex by obesity status (Table 2). Compared with nonobese men, nonobese women had a 42% higher level of HDL-C (43 ± 9 vs 61 ± 20 mg/dL, respectively; $P = .006$) (Table 1) and a 19% higher level of apo A-I (121±15 vs 144±24 mg/dL, respectively; $P = .012$) (Table 2) due to a 48% higher PR of apo A-I ($P = .05$) partially offset by a nonsignificant 18% higher FCR ($P = .15$).

Compared with obese men, obese women had a 52% higher level of HDL-C (33 ± 4 vs 50 ± 10 mg/dL, respectively; $P = .012$) (Table 1) and a 20% higher level of apo A-I (110 ± 5 vs 132 ± 21 mg/dL, respectively; $P = .07$) (Table 2) due primarily to a trend toward a 21% lower apo A-I FCR ($P = .11$). Therefore, both obese and nonobese postmenopausal women had higher levels of HDL-C and apo A-I than men, but the mechanisms differed.

The second comparison was the effect of obesity within the same sex (Table 3). Compared with nonobese men, obese men had a 24% lower level of HDL-C (43 ± 9 vs 33 ± 4 mg/dL, $P = .04$), 35% higher level of triglyceride ($P = .045$) (Table 1), and a 9% lower apo A-I level ($P = .17$) (Table 3) due to a 64% higher apo A-I FCR ($P = .0001$), partially offset by a 47% higher PR ($P = .013$) (Table 3). Compared with nonobese women, obese women had an 18% lower level of HDL-C (61 ± 20 vs 50 ± 10 mg/dL, $P = .23$), 74% higher level of triglyceride ($P = .02$) (Table 1), and an 8% lower level of apo A-I ($P = .36$) (Table 3) due primarily to a 10% increase in FCR offset by a 2.5% increase in PR; however, these differences were not significant.

When BMI was treated as a continuous variable, sex differences were more striking, with significant relationships between BMI and apo A-I PR and FCR in men but not in women. A strong positive correlation was found between BMI and apo A-I PR in men ($r = 0.79$, $P < .0001$), but no correlation was observed in women (Fig. 1). Sixty-two percent of the variability in PR was due to BMI in men and only 3% in women. Fig. 2 shows the correlations between BMI and apo A-I FCR. A strong positive correlation is evident for men ($r = 0.84$, $P < .0001$) but not for women ($r = 0.48$, $P = .098$). Seventy-one percent of the variability in FCR is due to BMI in men but only 23% in women. When a correction was made for the effect of age and body weight on plasma volume [11], the slope of the plot of BMI vs apo A-I production rate did not change significantly (*r* value decreased from 0.79 to 0.73).

Table 2
Effect of sex by obesity status on apo A-I kinetic constants

	Nonobese				Obese			
	Men (n = 15)	Women (n = 7)	% Difference	*P*	Men (n = 4)	Women (n = 6)	% Difference	*P*
Apo A-I (mg/dL)	121 ± 15	144 ± 25	↑ 19%	.012	110 ± 5	132 ± 21	↑ 20%	.07
Apo A-I FCR (pools per day)	0.139 ± 0.030	0.164 ± 0.050	↑ 18%	.15	0.228 ± 0.042	0.181 ± 0.040	↓ 21%	.11
Apo A-I PR (mg/kg per day)	6.71 ± 1.62	9.95 ± 3.57	↑ 48%	.05	11.3 ± 1.85	10.2 ± 2.66	↓ 10%	.50

Values shown are means ± SD.

Table 3
Effect of obesity on Apo A-I kinetic constants by sex

	Men				Postmenopausal women			
	Nonobese (n = 15)	Obese (n = 4)	% Difference	*P*	Nonobese (n = 7)	Obese (n = 6)	% Difference	*P*
Apo A-I (mg/dL)	121 ± 15	110 ± 5	↓ 9%	.17	144 ± 25	132 ± 21	↓ 8%	.36
Apo A-I FCR (pools per day)	0.139 ± 0.030	0.228 ± 0.042	↑ 64%	.0001	0.164 ± 0.050	0.181 ± 0.040	↑ 10%	.51
Apo A-I PR (mg/kg per day)	6.71 ± 1.62	11.3 ± 1.85	↑ 47%	.0013	9.95 ± 3.57	10.2 ± 2.66	↑ 2.5%	.89

Values shown are means ± SD.

Table 4 indicates the correlations between apo A-I kinetics and fasting plasma TG, apo A-I, and HDL-C levels. The apo A-I level was correlated with its PR ($r = 0.62$, $P = .024$) in women but not in men. A trend for an inverse correlation between apo A-I levels and apo A-I FCR was observed ($r = -0.42$, $P = .07$) in men but not in women. HDL-C was negatively correlated with apo A-I FCR in men and positively correlated with apo A-I PR in women.

4. Discussion

In the current study, nonobese women had a higher HDL-C level than nonobese men due to a 48% higher apo A-I PR. Because these women were postmenopausal, this sex difference cannot be attributed to higher estrogen levels but is more likely due to the presence of testosterone in men, which has been shown to lower HDL-C because of decreased production of apo A-I at puberty [12].

When we examined the effect of obesity on HDL-C levels and apo A-I kinetics, we found that compared with nonobese men, obese men had a 9% lower apo A-I level and lower HDL-C levels due to a 47% higher apo A-I PR and a 64% faster apo A-I FCR. In contrast, there were no significant differences in HDL-C levels or apo A-I kinetics in obese and nonobese women. A likely explanation for the higher apo A-I PR in obese men is conversion of testosterone to estrogen in peripheral adipose tissue. Estrogen is known to increase apo A-I PR [13,14].

A possible explanation for the sex difference in effect of obesity on apo A-I FCR could lie in sex differences in body fat distribution. Central adiposity relates inversely with HDL-C levels and positively with apo A-I FCR [15,16]. Increased intra-abdominal (visceral) fat has been shown to selectively lower apo A-I by increasing its FCR [17,18]. In general, obese men have more visceral fat than women, who have more peripheral fat [19,20]; therefore, one would predict that men would have lower HDL-C levels than women due to a higher FCR, the finding that we observed in the current study. Although we did not quantitate visceral fat, it is likely that this was increased in our obese male subjects. Verges et al [21] have shown that adiponectin is a determinant of apo A-I catabolism, suggesting an additional explanation for sex differences related to differences in body fat distribution. Although Verges et al did not find an effect of BMI on apo A-I kinetics, the number of subjects in their study may have been too small to detect an effect.

When BMI was treated as a continuous variable, sex differences were even more striking, with significant relationships between BMI and both apo A-I PR and apo A-I FCR in men but not in women. In fact, 62% of the variability in PR was due to BMI in men but only 3% in women, and 71% of the variability in FCR was due to BMI in men but only 23% in women.

A second major finding in the current study is that although both nonobese and obese women had higher HDL-C and apo A-I levels compared with nonobese and

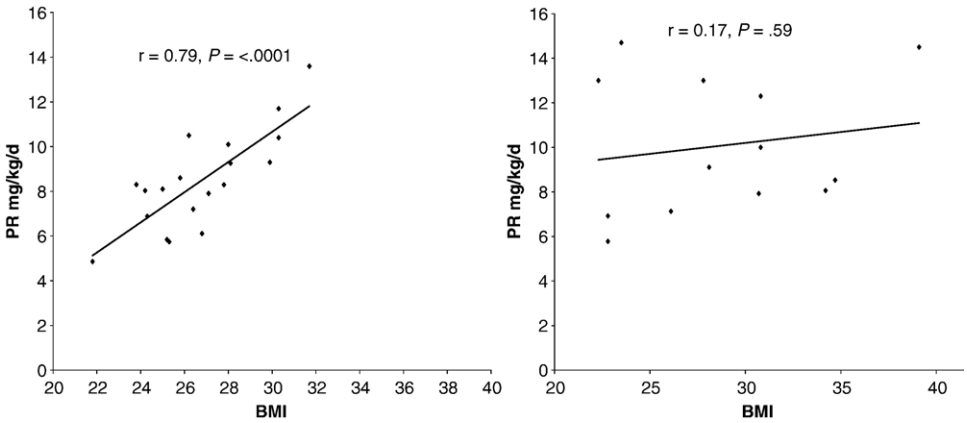

Fig. 1. Association of BMI with apo A-I PR in men (left) and postmenopausal women (right).

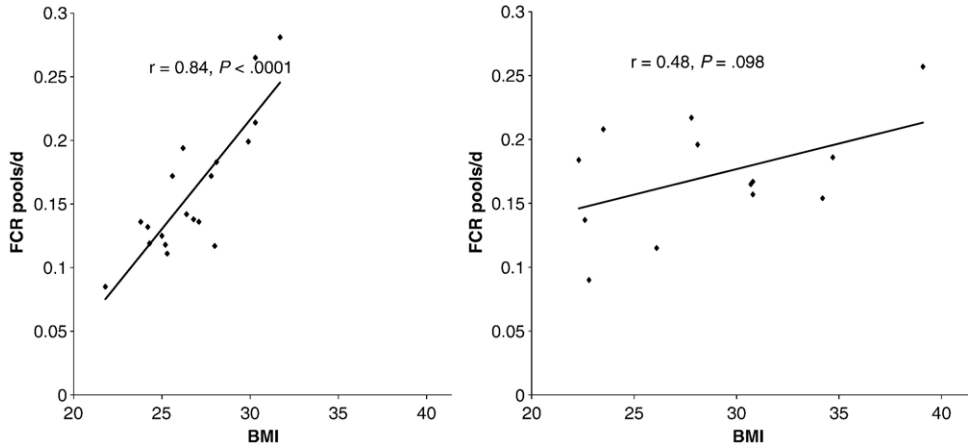

Fig. 2. Association of BMI with apo A-I FCR in men (left) and postmenopausal women (right).

obese men, respectively, the mechanisms differed. Nonobese women had a higher level of apo A-I due to a higher PR compared with nonobese men. In contrast, compared with obese men, obese postmenopausal women had a higher apo A-I level because obesity was associated with a higher FCR in men. In support of these findings, apo A-I levels were correlated with FCR in men and PR in women in the current study.

The obese men in the present study were significantly younger than obese women. Verges et al [21] showed no effect of age on apo A-I FCR. If there is an effect of age on apo A-I FCR, one would predict a decline; therefore, because our obese men are younger than the obese women, an age effect should increase the difference seen between men and women rather than attenuate it.

No prior studies have examined the effect of BMI on apo A-I kinetics by sex. In a meta-analysis that pooled data from 13 studies of apo A-I kinetics, using stable isotopes in a total of 147 lean and overweight men and postmenopausal women, BMI was significantly correlated with both FCR ($r = 0.61$, $P < .001$) and PR ($r = 0.34$, $P = .013$) of apo A-I [3]. The authors concluded that compared with lean individuals, overweight and obese individuals had significantly higher FCRs and PRs of apo A-I, but they did not examine kinetics by sex. The results of the present study suggest that this conclusion applies to men but not women.

In conclusion, we found that obesity, as judged by the BMI, is associated with an increase in both FCR and PR of apo A-I in obese men but not in obese women. Therefore, when making sex comparisons of apo A-I kinetics, it's critical to consider BMI and obesity. We also found that obese and nonobese women have higher HDL-C levels than men because of different mechanisms and that apo A-I levels are correlated with FCR in men and PR in women. Future research should explore reasons for these differential effects.

Acknowledgments

This study was supported by grants HL 39326 (E.J.S.) and HL56895 (F.K.W.) and contract 53-3KO6-5-10 from the US Department of Agricultural Research Service (E.J.S.).

We are extremely grateful to the study subjects for participating in the kinetics studies.

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Table 4
Pearson correlations between plasma levels of TG, apo A-I, HDL-C and Apo A-I FCR and PR by sex

	Apo A-I FCR			Apo A-I PR		
	TG	Apo A-I	HDL-C	TG	Apo A-I	HDL-C
Men	0.44 (.11)	−0.42 (.07)	−0.56 (.01)	0.27 (.34)	0.10 (.67)	−0.21 (.37)
Women	0.39 (.18)	0.12 (.69)	0.08 (.79)	−0.04 (.90)	0.62 (.024)	0.57 (.044)

Values shown are Pearson r values; P values are in parentheses.

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