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Effect of Body Mass Index on Apolipoprotein A-I Kinetics in Middle-Aged Men and Postmenopausal Women

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Abstract

The effect of body mass index (BMI) and obesity on apo A-I levels and kinetics was examined by gender. ApoA-I kinetics were determined with a primed-constant infusion of deuterated leucine in the fed state in 19 men and 13 postmenopausal women. Compared to nonobese men, nonobese women had a higher HDL-C and apoA-I level due to a 48% higher apoA-I PR ($p=0.05$). Obesity had no significant effects on apoA-I kinetics in women. In contrast, compared to non-obese men, obese men had a 9% lower apoA-I level due to a 64% higher FCR partially offset by a 47% higher PR. Obese women had a 52% higher HDL-C than obese men (50 mg/dL vs 33 mg/dL, respectively, $p=0.012$), a finding related to the faster apoA-I FCR in obese men. BMI was directly correlated with apoA-I FCR ($r = 0.84$, $p < 0.001$) and PR ($r = 0.79$, $p < 0.001$) in men but not women. 62% 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 apoA-I PR and FCR in men but not in women.

Keywords

Stable isotopes; apolipoprotein A-I; high density lipoprotein cholesterol; metabolism; kinetic studies; postmenopausal women; gender differences

High levels of high density lipoprotein-cholesterol (HDL-C) have been associated with lower rates of coronary heart disease (CHD) in epidemiological 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 to 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 apoA-I kinetics but did not report results by gender (3). Two prior studies have reported on gender differences in kinetics of apoA-I using stable isotopes but did not have a large enough sample size to examine the effect of obesity by gender on kinetics (4,5). In the current study, we added obese subjects to the prior two studies and used multicompartmental modeling to examine the effect of body mass index (BMI) and obesity on the apoA-I fractional catabolic rate (FCR)

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and production rate (PR) in obese and nonobese middle-aged men and women using stable isotopes.

METHODS

Subjects for these studies were 19 men and 13 postmenopausal women stratified in relation to obesity as defined by a BMI = 30. We added 2 obese men, 3 obese women and 4 non-obese women to the previously published subjects (4,5). All subjects received a primed constant infusion of $^2\text{H}_3$ -leucine at 10 micromoles/kg/hr intravenously for 15 hr while consuming small hourly meals, as previously described (4–8). Lipoproteins were isolated by sequential density ultracentrifugation- VLDL at $d < 1.006$ and HDL at $d > 1.063 < 1.21$. After separation of VLDL apo B-100 and HDL apo A-I by SDS-PAGE, the apolipoprotein bands were cut from the gels, hydrolyzed, derivatized, and the isotopic enrichment of the leucine measured by GC-MS (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), the FCR of apo A-I was determined as the rate 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 kg.

Statistical analyses were carried out with the InStat2 program (GraphPad Software, San Diego, CA). Two-sided Student t tests and Pearson correlation coefficients were employed to test for statistical significance ($P < 0.05$). All values are means $\pm$ the standard deviation.

RESULTS

The group averages of age, BMIs 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 ($P = 0.05$), but there was no significant difference in BMIs (31 vs 33). Two sets of comparisons were performed. The first comparison was the effect of gender by obesity status (Table 2). Compared to non-obese men, non-obese women had a 42% higher level of HDL-C (43 ± 9 vs 61 ± 20 mg/dL, respectively, $p=0.006$) (Table 1) and a 19% higher level of apoA-I (121 ± 15 vs 144 ± 24 mg/dL, respectively, $p=0.012$) (Table 2) due to a 48% higher PR of apoA-I ($p=0.05$) partially offset by a non-significant 18% higher FCR ($p=0.15$).

Compared to obese men, obese women had a 52% higher level of HDL-C (33 ± 4 vs 50 ± 10 mg/dL, respectively, $p=0.012$) (Table 1) and a 20% higher level of apoA-I (110 ± 5 vs 132 ± 21 mg/dL, respectively, $p=0.07$) (Table 2) due primarily to a trend toward a 21% lower apoA-I FCR ($p=0.11$). Therefore, both obese and nonobese postmenopausal women had higher levels of HDL-C and apoA-I than men, but the mechanisms differed.

The second comparison was the effect of obesity within the same gender (Table 3). Compared to non-obese men, obese men had a 24% lower level of HDL-C (43 ± 9 vs 33 ± 4 mg/dL, $p=0.04$), 35% higher level of triglyceride ($p=0.045$) (Table 1), and a 9% lower apoA-I level ($p=0.17$) (Table 3) due to a 64% higher apoA-I FCR ($p=0.0001$), partially offset by a 47% higher PR ($p=0.013$) (Table 3). Compared to non-obese women, obese women had an 18% lower level of HDL-C (61 ± 20 vs 50 ± 10 mg/dL, $p=0.23$), 74% higher level of triglyceride ($p=0.02$) (Table 1) and an 8% lower level of apo A-I ($p=0.36$) (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, gender differences were more striking, with significant relationships between BMI and apoA-I PR and FCR in men but not in women. A strong positive correlation was found between BMI and apoA-I PR in men ($r = 0.79$, $p <$

0.0001), but no correlation was observed in women (Figure 1). 62% of the variability in PR was due to BMI in men and only 3% in women. Figure 2 shows the correlations between BMI and apoA-I FCR. A strong positive correlation is evident for men ($r = 0.84$, $p < 0.0001$) but not for women ($r = 0.48$, $p = 0.098$). 71% 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 versus apoA-I production rate did not change significantly (r value decreased from 0.79 to 0.73).

Table 4 indicates the correlations between apoA-I kinetics and fasting plasma TG, apoA-I and HDL-C levels. The apoA-I level was correlated with its PR ($r=0.62$, $p=0.024$) in women but not in men. A trend for an inverse correlation between apo A-I levels and apo A-I FCR was observed ($r=-0.42$, $p = 0.07$) in men but not in women. HDL-C was negatively correlated with apoA-I FCR in men and positively correlated with apoA-I PR in women.

DISCUSSION

In the current study, nonobese women had a higher HDL-C level than nonobese men due to a 48% higher apoA-I PR. Since these women were postmenopausal, this gender 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 due to decreased production of apoA-I at puberty (12).

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

A possible explanation for the gender difference in effect of obesity on apoA-I FCR could lie in gender differences in body fat distribution. Central adiposity relates inversely with HDL-C levels and positively with apoA-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 gender differences related to differences in body fat distribution. Although Verges et al (21) 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, gender differences were even more striking with significant relationships between BMI and both apoA-I PR and apoA-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 non-obese and obese women had higher HDL-C and apo A-I levels compared to non-obese and obese men, respectively, the mechanisms differed. Non-obese women had a higher level of apo A-I due to a higher PR compared to non-obese men. In contrast, compared to obese men, obese postmenopausal women had a higher apoA-I level because obesity was associated with a higher FCR in men. In support of these findings, apoA-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 apoA-I FCR. If there is an effect of age on apoA-I FCR, one would predict a decline; therefore, since 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 apoA-I kinetics by gender. In a meta-analysis which 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 ($r=0.61$, $p < 0.001$) and PR ($r=0.34$, $p = 0.013$) of apo A-I (3). The authors concluded that compared to lean individuals, overweight and obese individuals had significantly higher FCRs and PRs of apo A-I, but they did not examine kinetics by gender. 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 gender comparisons of apoA-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 due to different mechanisms and that apoA-I levels are correlated with FCR in men and PR in women. Future research should explore reasons for these differential effects.

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

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

Table 1

Baseline Characteristics

	Men		Post-menopausal women					
	Non-obese (n = 15)	Obese (n = 4)	p-value	Non-obese (n = 7)	Obese (n = 6)	p-value	p-value (Non-obese men vs non-obese post-menopausal women)	p-value (Obese men vs obese post-menopausal women)
Age (yr)	57 ± 12	48 ± 7	0.2	59 ± 8	61 ± 9	0.67	0.65	0.05
BMI (kg/m ²)	25.7 ± 1.8	30.6 ± 0.8	<0.001	24.7 ± 2.5	33.4 ± 3.4	0.0002	0.3	0.15
TC (mg/dl)	225 ± 46	219 ± 50	0.82	228 ± 37	251 ± 41	0.31	0.88	0.3
TG (mg/dl)	118 ± 37	159 ± 12	0.045	98 ± 37	170 ± 59	0.02	0.24	0.73
LDL-C (mg/dl)	135 ± 28	148 ± 39	0.45	144 ± 30	157 ± 49	0.57	0.5	0.77
HDL-C (mg/dl)	43 ± 9	33 ± 4	0.04	61 ± 20	50 ± 10	0.23	0.0064	0.012

Values are mean ± SD

Table 2
Effect of Gender on Apo A-I Kinetic Constants by Obesity Status

	Nonobese				Obese			
	Men (n = 15)	Women (n = 7)	% difference	p-value	Men (n = 4)	Women (n = 6)	% difference	p-value
Apo A-I (mg/dl)	121 ± 15	144 ± 25	↑ 19%	0.012	110 ± 5	132 ± 21	↑ 20%	0.07
Apo A-I FCR (pools/day)	0.139 ± 0.030	0.164 ± 0.050	↑ 18%	0.15	0.228 ± 0.042	0.181 ± 0.040	↓ 21%	0.11
Apo A-I PR (mg/kg/day)	6.71 ± 1.62	9.95 ± 3.57	↑ 48%	0.05	11.3 ± 1.85	10.2 ± 2.66	↓ 10%	0.50

Values shown are means ± SD

Table 3

Effect of Obesity on Apo A-I Kinetic Constants by Gender

	Men				Postmenopausal women			
	Non-obese (n = 15)	Obese (n = 4)	% difference	p-value	Non-obese (n = 7)	Obese (n = 6)	% difference	p-value
Apo A-I (mg/dl)	121 ± 15	110 ± 5	↓ 9%	0.17	144 ± 25	132 ± 21	↓ 8%	0.36
Apo A-I FCR (pools/day)	0.139 ± 0.030	0.228 ± 0.042	↑ 64%	0.0001	0.164 ± 0.050	0.181 ± 0.040	↑ 10%	0.51
Apo A-I PR (mg/kg/day)	6.71 ± 1.62	11.3 ± 1.85	↑ 47%	0.0013	9.95 ± 3.57	10.2 ± 2.66	↑ 2.5%	0.89

Values shown are means ± SD

Table 4
Pearson Correlations Between Plasma Levels of TG, Apo A-I, HDL-C and Apo A-I FCR and PR by Gender

	Apo A-I FCR			Apo A-I PR		
	TG	Apo A-I	HDL-C	TG	Apo A-I	HDL-C
Men	0.44 (0.11)	-0.42 (0.07)	-0.56 (0.01)	0.27 (0.34)	0.10 (0.67)	-0.21 (0.37)
Women	0.39 (0.18)	0.12 (0.69)	0.08 (0.79)	-0.04 (0.90)	0.62 (0.024)	0.57 (0.044)

Values shown are Pearson r values; p-values are in parentheses.