Obesity, Lipoproteins, and Heart Disease

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Obesity is a poorly understood disorder that undoubtedly has multiple etiologies. Although it has many health complications (1), there is considerable debate concerning its influence in cardiovascular disease. One possibility for divergent observations of associations between obesity and cardiovascular disease (CVD) may be that its effect differs in different populations. For example, among Caucasians there is clear evidence that obesity is a risk factor for CVD (2). On the other hand, there appeared to be no relationship between body mass index and 20-year CVD mortality in black men or women (3). Of importance in understanding the effect of obesity on cardiovascular disease is the definition of its association with CVD risk factors such as plasma lipoproteins. An examination of the influence of obesity on plasma lipoproteins, however, is difficult because of both the heterogeneity of the disorder and the confounding effects when comparing obese subjects with nonobese controls. For these reasons, we have focused our efforts on a thorough examination of the effects of obesity on lipoproteins in the Pima Indians. This a genetically homogenous group with a high prevalence of obesity (4). By comparing obese and lean subjects within this population, we have more clearly defined the associations of obesity with plasma lipoproteins and investigated the metabolic determinants of the effects of obesity on lipoprotein concentrations.

Lipids and Lipoproteins in Obesity

Plasma lipoprotein cholesterol and triglyceride concentrations were measured in a population based sample of 1400 Pima Indians greater than 15 years of age (5). In both younger and older Pimas of both sexes, obesity was associated with high concentrations of total and very low density lipoprotein (VLDL) triglycerides and low concentrations of high density lipoprotein (HDL) cholesterol (Table I). When all of the data from the population were analyzed using Duncan's multiple range test adjusted for age, the effect of obesity was significant in men on total and VLDL triglyceride and HDL cholesterol. In women, obesity had a significant effect on total and VLDL triglyceride and HDL cholesterol. In a multivariate analysis adjusted for age, smoking, alcohol consumption, and plasma glucose, obesity was significantly positively associated with total and VLDL triglyceride and inversely associated with HDL cholesterol in both men and women (Table II). On the other hand, obesity had less relationship with total or low density lipoprotein (LDL) cholesterol.

Metabolism of Lipoproteins in Obesity

Metabolic studies of VLDL and LDL metabolism were performed to examine mechanisms for the differences in lipoproteins (Table II) (6). There was a greatly increased rate of production of VLDL apoB in the obese subjects and the difference was significant even when data were expressed per kilogram of fat free mass. The fractional catabolic rate for VLDL was marginally elevated in obese subjects. Production of VLDL triglyceride also was increased in obese subjects expressed as absolute flux and when adjusted per kilogram of fat free mass. When production rates of VLDL apoB and VLDL triglyceride were compared, the increases in rates were the same. Likewise, the ratios of triglycerides to apoB and cholesterol to apoB and the VLDL of obese subjects were unchanged compared with lean subjects. These findings suggested that the increased production of VLDL in obese subjects consisted of secretion of particles of normal composition.

When the metabolism of LDL was compared in obese and lean subjects, the absolute rates of LDL production were elevated in obese subjects compared with those in lean subjects, but this difference was not sustained when data were normalized per kilogram of fat free mass. On the other hand, obese subjects had a significant increase in the fractional catabolic rate for LDL (Table III). When the interconversion of VLDL to LDL was elevated, obese subjects had much greater proportion of VLDL removed from the circulation without conversion to LDL, even when data were expressed per kilogram of lean body mass.

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Table I. Plasma Lipids and Lipoproteins in Lean (BMI < 27) versus Obese (BMI > 35) Pima Indians[a]

Measurement	15–24 Years of age		>35 Years of age	
	Lean	Obese	Lean	Obese
Male subjects				
n	70	64	36	79
Total cholesterol	4.3 ± 0.1	180 ± 3[b]	184 ± 5	180 ± 8
LDL cholesterol	2.8 ± 0.1	124 ± 3[b]	120 ± 5	123 ± 7
HDL cholesterol	1.2 ± 0.0	39 ± 1[c]	50 ± 2	40 ± 2[c]
Total triglyceride	2.4 ± 0.2	147 ± 8[c]	111 ± 8	151 ± 16[b]
VLDL triglyceride	0.62 ± 0.06	93 ± 7[c]	58 ± 6	1 ± 12[b]
Female subjects				
n	118	125	26	70
Total cholesterol	4.2 ± 0.1	164 ± 2	180 ± 7	168 ± 4
LDL cholesterol	2.6 ± 0.0	109 ± 2[d]	116 ± 6	112 ± 4
HDL cholesterol	0.0 ± 0.0	42 ± 1[c]	47 ± 3	42 ± 1[d]
Total triglyceride	0.1 ± 0.04	120 ± 4[c]	128 ± 13	118 ± 7
VLDL triglyceride	0.51 ± 0.03	67 ± 3[c]	70 ± 9	61 ± 5

[a] Data are mean ± SE. BMI, body mass index.
[b,c,d] $P < 0.05$, $P < 0.01$, and $P < 0.001$ by Student's *t* test. When all the data from the population were examined by Duncan's multiple range test adjusting for age, the effect of obesity was significant in male subjects on total and VLDL triglyceride and HDL cholesterol. In female subjects, obesity had a significant effect on total and VLDL triglyceride and HDL cholesterol.

Table II. Correlation Coefficient between Obesity[a] and Plasma Lipoproteins in Nondiabetic Pimas

	Men (n = 392)		Women (n = 507)	
	r (P)	Partial r^b (P)	r (P)	Partial r^b (P)
Total cholesterol	—	—	—	—
LDL cholesterol	—	—	—	—
HDL cholesterol	−0.25 (0.0001)	−0.22 (0.0001)	−0.27 (0.0001)	−0.33 (0.0001)
Total triglyceride	−0.17 (0.002)	—	−0.17 (0.0002)	—
VLDL triglyceride	0.19 (0.0007)	0.19 (0.0007)	0.11 (0.01)	0.06 (NS)

[a] As measured by body mass index (kg/m^2).
[b] Controlled for age, smoking, alcohol consumption, and plasma glucose.

Table III. Effect of Obesity on the Metabolism of VLDL and LDL

	Obese (n = 9)	Nonobese (n = 7)
VLDL		
Triglyceride (mg/dl)	114 ± 21	81 ± 19
apoB (mg/dl)	10.1 ± 1.3	7.9 ± 1.2
Triglyceride/apoB	11.0 ± 1.1	10.1 ± 1.2
LDL		
Cholesterol (mg/dl)	77 ± 7	72 ± 7
apoB (mg/dl)	60 ± 4	63 ± 7
apoB/cholesterol	0.80 ± 0.05	0.86 ± 0.02
VLDL apoB		
Fractional catabolic rate (d^{-1})	5.6 ± 0.7	5.5 ± 0.8
prod (mg/day)	2,241 ± 215	1,133 ± 72[a]
prod (mg/kg FFM-day)	27.8 ± 2.1	21.1 ± 1.2[b]
% → LDL	47 ± 3	41 ± 3[b]
VLDL triglyceride		
Fractional catabolic rate (d^{-1})	12.2 ± 2.3	11.4 ± 1.5
prod (mg/day)	48,672 ± 9,734	26,200 ± 7,300[b]
prod (mg/kg FFM-day)	618 ± 110	480 ± 121
LDL apoB		
Fractional catabolic rate (d^{-1})	0.48 ± 0.02	0.41 ± 0.02[b]
prod (mg/day)	1,224 ± 87	802 ± 83[c]
prod (mg/kg FFM-day)	15.2 ± 0.6	15.3 ± 1.6

[a] $P < 0.001$.
[b] $P < 0.05$.
[c] $P < 0.01$.

Thus, the data suggest that the major abnormality of lipoprotein metabolism in obese subjects is a greatly increased output of VLDL. One possible cause of the elevated VLDL production might be increased total body cholesterol synthesis, which has also been shown to be elevated in obese Pimas (7). In most cases, there is overproduction of all components, so that VLDL composition is unchanged. Furthermore, the increased production of VLDL appears to induce a sequence of metabolic changes, including removal of a greater proportion of VLDL before conversion of LDL and an increase in the fractional clearance of LDL. This, in most subjects, results in normal LDL concentrations. Finally, obesity is associated with a greater flux of LDL particles, as shown by both increased production and fractional clearance of LDL.

HDL Composition, Lipase Activities, and Steroid Hormones in Obesity

In order to understand why low HDL concentrations are observed in obese individuals, HDL compo-

Table IV. HDL Composition, Lipase Activities, and Steroid Hormones[a]

	Men		Women	
	Obese	Lean	Obese	Lean
HDL_2 (mg/dl)				
Cholesterol	11 ± 1	13 ± 2	15 ± 1	25 ± 2
Phospholipid	18 ± 1	25 ± 5	29 ± 3	55 ± 5
Triglyceride	4 ± 0	4 ± 0	5 ± 1	8 ± 1
apoA1	15 ± 3	19 ± 7	25 ± 4	55 ± 4
HDL_3 (mg/dl)				
Cholesterol	24 ± 1	27 ± 1	22 ± 1	25 ± 1
Phospholipid	43 ± 3	51 ± 3	42 ± 2	50 ± 3
Triglyceride	6 ± 0	7 ± 1	7 ± 1	7 ± 0
apoA1	83 ± 5	93 ± 4	77 ± 5	80 ± 3
Adipose LPL (μmol/g/hr)	1.2 ± 0.2	0.8 ± 0.2	1.5 ± 0.3	2.2 ± 0.3
Hepatic lipase (μmol/ml/hr)	30 ± 2	30 ± 3	22 ± 3	13 ± 1
Estradiol (pmol/liter)	125 ± 1	133 ± 7	176 ± 29	634 ± 108
Testosterone (pmol/liter)	22 ± 2	29 ± 2	3 ± 0	3 ± 0
Steroid-binding globulin (nmol/liter)	20 ± 3	23 ± 3	28 ± 5	59 ± 16

[a] LDL cholesterol in both lean and obese men was significantly higher than in lean women with Duncan's multiple range test. HDL cholesterol was significantly higher in lean women than in the other three groups with this test. Total A1 was significantly higher in lean women compared with obese men or women with this test. When this test was used for subfraction data, HDL_2 cholesterol, phospholipid, triglyceride, and A1 were significantly higher in lean women than in the other three groups. HDL_2 phospholipid was also significantly higher in obese women compared with obese men. HDL_3 cholesterol and A1 were significantly higher in lean men compared with obese women.
By Duncan's multiple range test, testosterone was higher in the groups of lean men compared with obese men, and higher in both groups of men compared with both groups of women. Steroid-binding globulin and estradiol were signifciantly higher in lean women compared with the other three groups.
By Duncan's multiple range test, hepatic lipase was lower in lean women compared with all three groups, and also lower in obese women compared with lean men. Adipose lipoprotein lipase was significantly higher in lean women than in lean men.

sition, lipase activities, and steroid hormone concentrations have been compared (Table IV) (8). Lean women had higher concentrations of HDL and HDL_2 than did either obese women or lean or obese men. Lean women had significantly lower hepatic lipase activities and significantly higher concentrations of estradiol compared with obese women. Obese women had altered HDL_2 composition as indicated by the molar ratio of HDL_2 cholesterol to apoA1. Significant negative correlations between HDL and obesity measured by body mass index or percentage of body fat, were observed in both sexes, but the slope of the relationship was steeper in women. Significant negative associations were observed between HDL or HDL_2 concentrations and hepatic lipase in both sexes. There were significant positive associations between HDL_2 and plasma estradiol in women. The data suggest that obesity in this population has a stronger negative effect on HDL concentrations in women, possibly through changes in estradiol and hepatic lipase activities.

Obesity and Cardiovascular Disease

Although body mass index is a strong risk factor for diabetes among the Pimas, it does not appear to be associated with increased mortality rates. When age-adjusted mortality rates were examined for Pimas classified by body mass index, there was a slight inverse relationship for mortality for men and women up to a body mass index of 40 (9). A preliminary report of deaths from fatal coronary heart disease in Pima Indians examined deaths between 1975 and 1984 (10). Only 28 deaths were attributed to coronary heart disease, and all of these occurred among diabetic persons. Incidence of fatal coronary heart disease was associated with age and duration of diabetes, male sex, proteinuria, medial arterial calcification, diabetic retinopathy, insulin therapy, and an abnormal electrocardiogram. However, there was no independent association with obesity as measured by body mass index. Although these observations await extension to a larger number of subjects, they suggest that obesity among the diabetic members of this group may not be associated with increased cardiovascular disease.

Summary and Conclusions

Studies of lipoproteins in this homogenous study population indicate clear and consistent associations between obesity and abnormalities in lipoproteins. These include both increases in VLDL and lower HDL, which were observed in both men and women. A high production of total body cholesterol in obese subjects, probably associated with increased flux of glucose and free fatty acids, leads to a greater production of VLDL. This, in turn, creates a greater flux of metabolic products of VLDL either back to the liver or through LDL. Obesity induces an increase in hepatic lipase, perhaps in women because of lower estrogen levels, which is associated with lower HDL concentrations, and altered HDL composition. Several of these observed changes, such as the greater proportion of VLDL remnants, the

greater flux of particles through the LDL compartment, and the altered HDL composition, may be associated with increased atherosclerosis. However, preliminary data do not show a relationship between obesity and death from coronary heart disease in this population. More studies are needed to resolve this apparent conflict.

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