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Altered Composition of High Density Lipoproteins in Women with the Polycystic Ovary Syndrome*

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ABSTRACT

Women with polycystic ovary syndrome (PCOS) appear at increased cardiovascular risk due in part to a dyslipidemia characterized by increased plasma triglyceride and reduced high density lipoprotein (HDL) cholesterol levels. This is a detailed exploratory study of HDL composition in 35 obese [body mass index (BMI), >27] and 22 nonobese subjects with PCOS and in 14 healthy obese and 18 nonobese women.

Although we found reduced levels of total and HDL_2 cholesterol in obese women with PCOS, HDL composition was modified by depletion of lipid relative to protein, with reduced ratios of HDL total cholesterol and HDL phospholipids to apolipoprotein A-I (apoA-I) compared to those in obese controls ($P = 0.008$ and $P = 0.012$, respectively). This was explained by reduced cholesterol ($P = 0.004$) and phospholipid (although not significant, $P = 0.07$) in HDL with no change in the content of apoA-I, its major protein.

Obesity, insulin resistance, and hyperandrogenemia are features of PCOS and potentially affect lipid metabolism. Insulin sensitivity was assessed by the reduction in endogenous glucose concentration after exogenous insulin; the insulin, glucose, and fatty acid responses to oral glucose; and the fasting insulin concentration. When age, BMI, free androgen index, insulin sensitivity determined by all methods, and the presence of PCOS were subjected to stepwise multivariate regression analysis, the presence of PCOS was the most consistent predictor of lipid-depleted HDL (HDL total cholesterol/apoA-I and HDL phospholipids/apoA-I). We speculate that altered activity of hepatic lipase or lipid transfer protein could explain this aspect of the dyslipidemia.

Obesity has an important influence on the lipid profile. Obese PCOS and control subjects had higher levels of cholesterol, triglyceride, apoB, and fatty acids than their lean counterparts, and BMI proved the best predictor of blood levels on multiple regression analysis. In contrast, lean PCOS patients had normal sensitivity to insulin and lipid profiles similar to those of the lean controls and did not manifest the HDL abnormalities. Although in PCOS, correlations were obtained between the free androgen index and cholesterol, triglyceride, and apoB levels and between the integrated glucose and insulin responses after oral glucose and fasting fatty acid and triglyceride levels, when age and adiposity were included as covariates only fatty acids and the integrated glucose response remained significantly correlated. Among the controls, total, low density lipoprotein cholesterol, triglycerides, and apoB were related to aspects of insulin sensitivity independent of age and BMI.

Lipid metabolism in PCOS is dependent on several related factors, but subjects with PCOS who are obese show a specific reduction in HDL lipid, suggesting a reduced capacity for cholesterol removal from tissues with diminished antiatherogenic potential. Efforts should be directed toward reducing obesity in PCOS to improve the metabolic disturbance in addition to ameliorating the presenting symptoms. (*J Clin Endocrinol Metab* **82:** 3389–3394, 1997)

THE POLYCYSTIC ovary syndrome (PCOS) is a common disorder, with estimates of the prevalence lying between 3.5–7.5% of women (1). In women, cardiovascular disease is the most common cause of death (2), and those with PCOS have a 7.4-fold relative risk for myocardial infarction calculated by risk factor analysis (3) due to the prevalence of glucose intolerance, hypertension, insulin resistance (4–6), central obesity (7), and dyslipidemia. The latter is characterized by low HDL cholesterol and raised triglycerides (8, 9) and may explain their cardiovascular risk (10), particularly as low high density lipoprotein (HDL) cholesterol appears to be the most important lipoprotein predictor of CHD in women (11).

Cholesterol is only one component of HDL, a particle with continuously changing composition *in vivo* as unesterified cholesterol is taken from tissues, esterified, and exchanged for triglyceride with other lipoprotein species. Consequently, measurement of a single constituent in a particle involved in a dynamic process gives an incomplete picture. It is not known whether HDL composition is normal in PCOS, as previous reports have quantified HDL by measurement of its cholesterol concentration only, and the quantitatively more important phospholipid (PL) and apolipoprotein (apo) components have not been measured. We aimed to perform a detailed study of HDL composition to help understand the processes leading to the reduced concentrations previously reported in PCOS.

Materials and Methods

The diagnosis of PCOS was based on finding polycystic ovaries on transvaginal sonography (12) together with oligomenorrhea (intermenstrual interval of >35 days) and/or hirsutism (Ferriman Gallwey score >7) in the presence of raised serum testosterone, androstenedione, or both. Fifty-seven women with PCOS attending the endocrine and fertility clinics participated in the study. Local ethical committee approval was given, and informed consent was obtained from all subjects and controls. Thirty-two normal ovulatory women served as controls. A body mass index [BMI; weight (kilograms)/height $(meters)^2$] greater than 27 was used to classify subjects as obese. A more conventional BMI cut-off of 25 was used to investigate the effects of obesity *per se*. These numbered 35 in the PCOS group and 14 in the control group.

All investigations were carried out within 7 days of menstruation in both subjects and controls who were, therefore, in the early follicular

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phase. The absence of luteinization, and by implication recent ovulation, was confirmed by progesterone measurements in the 13 patients with 3 or more months of amenorrhea. None of the subjects had been taking any medication for at least 3 months before the investigations. Serum LH, FSH, testosterone, androstenedione, sex hormone-binding globulin (SHBG), estradiol, PRL, and progesterone were measured by methods previously described (13). Ovulation was confirmed in the controls by a midluteal serum progesterone level of 30 nmol/L or more. The free testosterone index (FTI) was calculated by the equation: FTI = testosterone $\times$ (6.11 $-$ 2.38 $\times$ $\log_{10}$ SHBG) (14).

Ovarian morphology was examined by transvaginal ultrasound scanning; polycystic ovaries were diagnosed by the presence of 10 or more follicles tending to distribute peripherally in an echo-dense stroma. Late-onset 21-hydroxylase deficiency was excluded by serial measurements of 17α-hydroxyprogesterone and cortisol after ACTH stimulation.

Insulin sensitivity was assessed by 1) levels of insulin in fasting blood, 2) the rate of fall of endogenous blood glucose per min calculated by linear regression between 3–15 min after iv insulin (0.1 U/kg BW; IVITT); samples were taken at $-$15, 0, 3, 6, 9, 12, and 15 min, as described previously (13); 3 and 4) the area under the curve of glucose (AUC-glu) and insulin (AUC-ins) concentrations against time after a 75-g oral glucose load (after a 14-h fast, blood glucose and insulin were measured at 0, 30, 60, 90, and 120 min); and 5) the percent suppression of nonesterified fatty acids (NEFA) by oral glucose, as described above, with NEFA levels measured at 0 and 60 min.

Laboratory methods

Blood glucose was measured by the glucose oxidase method; the interassay coefficient of variation (CV) was 4%. Insulin was determined by a double antibody RIA method; the interassay CV was 12%, and the intraassay CV was 2.4% at 15 mIU/L and 5.1% at 50 mIU/L. Fasting serum levels of triglycerides, PL, and total (TC) and free cholesterol were measured by commercial enzymatic methods (Boehringer Mannheim, Lewes, UK). Supernatants containing total HDLs or the HDL_3 subfraction were obtained by precipitation of the other lipoproteins with buffered polyethylene glycol (Quantolip, Immuno Ag, Vienna, Austria). The lipid determinations were made on the supernatants, but increased assay sensitivity was achieved by increasing the sample volume and adding tribromohydroxybenzoic acid to a concentration of 0.5 g/L in the assay reagent (15). All lipid analyses were controlled using commercial quality control serum (Lyotrol N, BioMerieux, France; Pathonorm H, Nycomed, Norway); all analyses gave interassay CVs below 4%, except for HDL free cholesterol and triglyceride, which were 11% and 9%, respectively, due to the low levels being measured. NEFA were measured in serum by a coupled enzymatic method (Randox Laboratories, Antrim, UK); the interassay CV was 6%. Apolipoproteins A-I (apoA-I) and B (apoB) were measured by rate immunonephelometry (Beckman Instruments, Fullerton, CA); the interassay CV was 5%. Lipoprotein(a) was measured by enzyme linked immunoassay (Biopool AB, Umea, Sweden).

Data analysis

Statistical analysis was performed using the NCSS package (J. Hintzee, Kaysville, UT). As the data did not fit a normal distribution, nonparametric tests were used throughout, and the results were described by the median, range, and interquartile range. Numerical variables were compared between groups using the Mann-Whitney U test. Correlations were performed using Spearman's rank coefficient of correlation, and partial correlations were calculated. The coefficients were adjusted for the effects of age and BMI by including these as covariates. Multiple regression analysis was used to determine whether age, BMI, PCOS, free testosterone index, and insulin sensitivities were predictive of the various lipid parameters.

Results

The PCOS and control groups were well matched for BMI and age (Table 1). All 57 patients had polycystic ovaries on transvaginal ultrasound, and 53 patients met the criteria for PCOS bilaterally. All PCOS had oligomenorrhea; hirsutism was present in at least 60% of lean and 80% of obese PCOS patients, but in none of the controls. Normal ovarian morphology was confirmed in all controls by transvaginal sonography.

Sex hormones (table 1)

Both obese and nonobese PCOS had significantly higher testosterone (P = 0.0001), free testosterone index (P = 0.0001), and androstenedione (P = 0.0002) levels than their respective controls (Table 1). The SHBG level was lower in the obese PCOS than in either obese controls (P = 0.018) or nonobese PCOS (P = 0.0007). Consequently, FTI was higher in obese than in nonobese PCOS (P = 0.018).

Insulin sensitivity (Table 1)

As reported previously in our subjects (13), obese PCOS had reduced insulin sensitivity determined by IVITT compared to both obese controls (P = 0.0007) and nonobese PCOS (P = 0.0003). Fasting insulin levels were higher in obese PCOS than in obese controls (P = 0.035) and nonobese PCOS

TABLE 1. The clinical features and serum androgen levels in the four groups

	PCOS		Controls	
	Obese (n = 35)	Nonobese (n = 22)	Obese (n = 14)	Nonobese (n = 18)
Age (yr)	26 (18–35)	27 (15–34)	32 (24–39)	31 (19–36)
BMI (kg/m^2)	35 (27–48)	23 (19–27)	35 (27–48)	23 (17–26)
Fasting insulin (μU/mL)	19.8 (7.6–86.4)[a,b]	10.5 (4.7–14.6)	11.0 (2.2–44.2)	7.7 (2.1–19.3)
Postinsulin %/min fall in glucose	3.0 (1.4–4.7)[a,b]	4.4 (2.1–6.1)	4.3 (3.3–7.4)	4.6 (1.1–6.3)
AUC-glucose (mmol/L·min)	70.1 (20.2)[a]	57.9 (7.03)	63.5 (13.2)[c]	58.1 (8.6)
AUC-insulin (μU/mL·min)	835.2 (999.6)[a,b]	299.5 (141.9)	565.0 (477.4)[c]	279.0 (186.9)
FFA (% suppression)	68.4 (57.9)[b]	74.5 (31.1)	83.9 (29.3)	83.6 (32)
Testosterone (nmol/L)	3.0 (1.3–6.2)[b]	3.1 (1.4–6.1)[d]	2.0 (1.1–2.8)	1.8 (0.6–3.1)
Andro'dione (nmol/L)	12.0 (8–23)[b]	12.8 (8–19)[d]	7.1 (5–11)	8.1 (4–16)
SHBG (nmol/L)	22 (9–60)[a,b]	39 (21–64)	29 (11–76)	47 (16–88)
FTI	9.0 (4.3–20.5)[a,b]	6.2 (3.3–17.5)[d]	4.6 (2.9–7.9)	3.6 (0.6–7.5)

Results are medians (interquartile range or actual range is in parentheses). There were significant differences in insulin sensitivity and hormone measurements at $P < 0.05$, see text for absolute values.

[a] PCOS (obese *vs.* nonobese).

[b] Controls (obese *vs.* nonobese).

[c] Nonobese (PCOS *vs.* controls).

[d] Obese (PCOS *vs.* controls).

($P < 0.0001$). The AUC-glu was significantly greater in obese PCOS than in their lean counterparts ($P < 0.0001$), but differences between obese PCOS and obese controls and between obese and lean controls fell short of statistical significance ($P = 0.07$ and $P = 0.06$, respectively). The AUC-ins was greater for obese PCOS ($P = 0.0001$) and controls ($P = 0.025$), but in this case the obese PCOS were more hyperinsulinemic than the obese controls ($P = 0.016$). Obese PCOS patients had significantly higher fasting fatty acid levels than the nonobese PCOS patients ($P = 0.017$), and although fasting fatty acids were not higher than the obese control values, there was less suppression of the levels after glucose administration ($P = 0.05$). Lean PCOS had comparable insulin sensitivity to the controls (shown in Fig. 1 by the IVITT results). This shows that insulin sensitivity does not differ significantly from the control value until the BMI rises above 29 by IVITT. The other assessments of insulin sensitivity gave similar results.

Lipid and lipoprotein profiles (Tables 2 and 3)

There were no significant differences in lipid measurements between the obese and nonobese PCOS patients, except FFA levels, which were higher in obese subjects ($P = 0.017$; Table 2). The obese controls had significantly higher levels of cholesterol ($P = 0.002$), PL ($P = 0.028$), and apoB ($P = 0.028$) than their lean counterparts. The ratio of total to HDL cholesterol, a widely used index of cardiovascular risk (16), was significantly greater in obese PCOS than in nonobese PCOS ($P = 0.023$) or obese controls ($P = 0.029$), but this was not reflected in the ratio of apoB to apoAI. The lipid profiles in the nonobese PCOS and weight-matched controls showed no significant differences.

Obese PCOS compared to the obese controls had lower HDL TC ($P = 0.004$) due to a reduction in both HDL_3 TC ($P = 0.015$) and HDL_2 TC ($P = 0.024$; Table 3). HDL PL was lower, particularly HDL_3 PL, but this fell short of statistical significance ($P = 0.066$) using the BMI cut-off of 27 kg/m^2, but became so if this was reduced to 25 ($P = 0.011$). As there was

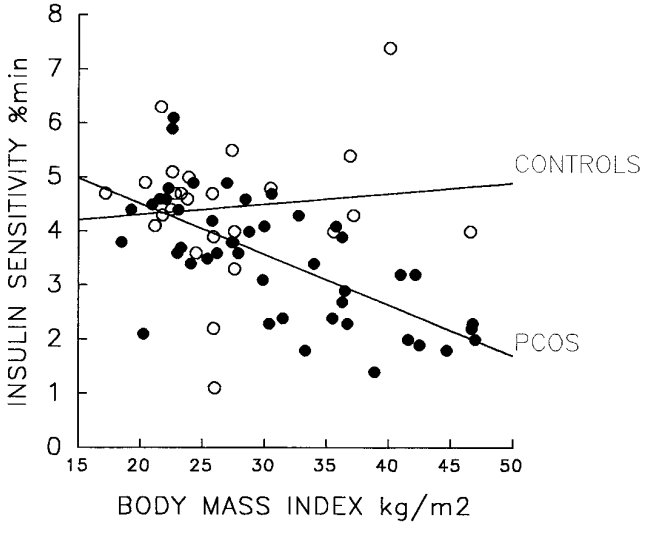

FIG. 1. Relationship between insulin sensitivity assessed by IVITT and BMI for PCOS patients (●) and control subjects (○).

TABLE 2. The free fatty acid, lipid, and lipoprotein profiles in the four groups

	PCOS		Controls	
	Obese (n = 35)	Nonobese (n = 22)	Obese (n = 14)	Nonobese (n = 18)
FFA (0 min)	0.5 (0.4)[a]	0.3 (0.2)	0.43 (0.4)	0.3 (0.5)
FFA (60 min)	0.15 (0.2)	0.10 (0.9)	0.10 (0.15)	0.06 (0.1)
TG	1.2 (0.7)	0.9 (0.4)	1.0 (0.9)	1.0 (0.6)
TC	4.6 (1.2)	4.5 (1.2)	4.8 (1.1)[b]	4.2 (0.8)
PL	2.8 (0.7)	2.5 (0.6)	2.7 (0.5)[b]	2.5 (0.5)
HDL	0.6 (0.5)[c]	0.8 (0.4)	0.8 (0.6)	0.7 (0.3)
TC/HDL	8.33[a,c] (6.01)	5.78 (2.72)	5.87 (4.04)	6.0 (2.0)
ApoB (g/L)	1.1 (0.4)	0.9 (0.4)	1.0 (0.2)[b]	0.8 (0.3)
ApoB/A-I	0.50 (0.40)	0.47 (0.34)	0.64 (0.15)[b]	0.52 (0.23)

Results are expressed as the median (millimoles per L) and interquartile range. Significance differences at $P < 0.05$; see text for absolute levels.

[a] PCOS (obese *vs.* nonobese).
[b] Controls (obese *vs.* nonobese).
[c] Obese (PCOS *vs.* controls).
[d] Nonobese (PCOS *vs.* controls).

TABLE 3. High density lipoprotein composition in PCOS and controls

	Obese PCOS (n = 35)	Nonobese PCOS (n = 22)	Obese controls (n = 14)	Nonobese controls (n = 18)
HDL-TC	0.63 (0.48)[a]	0.84 (0.42)	0.78 (0.6)	0.71 (0.27)
HDL-PL	0.90 (0.33)	1.05 (0.27)	0.99 (0.24)	1.08 (0.36)
HDL-FC	0.09 (0.12)	0.15 (0.12)	0.09 (0.15)	0.12 (0.09)
HDL-TG	0.11 (0.18)	0.11 (0.15)	0.18 (0.15)	0.12 (0.18)
HDL_3-TC	0.42 (0.33)[a]	0.57 (0.30)	0.66 (0.48)	0.45 (0.42)
HDL_3-PL	0.78 (0.33)	0.84 (0.21)	0.92 (0.33)	0.93 (0.33)
HDL_3-FC	0.06 (0.08)	0.09 (0.06)	0.08 (0.06)	0.06 (0.09)
HDL_3-TG	0.06 (0.09)	0.02 (0.09)	0.12 (0.09)	0.09 (0.15)
HDL_2-TC	0.12 (0.18)[a]	0.18 (0.24)	0.24 (0.18)	0.21 (0.32)
HDL_2-PL	0.12 (0.12)	0.11 (0.15)	0.15 (0.15)	0.15 (0.18)
HDL_2-FC	0.03 (0.05)	0.04 (0.06)	0.04 (0.05)	0.03 (0.04)
HDL_2-TG	0.03 (0.11)	0.06 (0.09)	0.03 (0.12)	0.02 (0.09)
ApoA-I (g/L)	1.9 (0.4)	1.9 (0.4)	1.6 (0.5)	1.9 (0.6)
HDLTC/A-I	0.34 (0.25)[a]	0.45 (0.34)	0.46 (0.40)	0.40 (0.17)
HDLPL/A-I	0.50 (0.25)[a]	0.56 (0.23)	0.65 (0.16)	0.60 (0.28)

Results are expressed as the median (millimoles per L) and interquartile range.

[a] $P < 0.05$ for obese (PCOS *vs.* controls).

no difference in apoA-I concentration between the groups, the HDL PL/apoA-I and HDL TC/apoA-I ratios, reflecting the lipid content of HDL, were lower in obese PCOS than in obese controls ($P = 0.012$ and $P = 0.008$, respectively). The lean PCOS did not show any differences in HDL composition compared to the lean controls.

Correlation among lipids, androgens, insulin sensitivity, and adiposity (Tables 4 and 5)

The relationship among lipids, insulin sensitivity, free androgen index, and adiposity were examined by calculating correlation and regression coefficients against BMI (Table 4). Insulin sensitivity and androgenicity were strongly related to BMI in the PCOS patients, but there was no relationship between BMI and either the lipid or protein components of total HDL, its subfractions, or the HDL lipid to protein ratios. Triglycerides were correlated to BMI in both PCOS and controls, as were TC, total PL, and apoB in the controls (Table 4).

TABLE 4. Regression and correlation coefficients between lipid measurements and body mass index in PCOS and control subjects

	PCOS			Controls		
	Slope	*P*	r_s	Slope	*P*	r_s
IVITT	−0.094	<0.0001	−0.664	0.020	NS	−0.178
AUC-ins	71.2	<0.0001	0.745	15.40	0.007	0.357
AUC-glu	1.060	<0.0001	0.695	0.405	0.031	0.394
Fasting ins	1.36	<0.0001	0.653	0.263	NS	0.219
FFA supp %	−0.733	NS	−0.149	−0.482	NS	0.002
fTI	0.210	0.002	0.412	0.178	0.041	0.247
Apo B	−0.011	0.017	0.296	0.008	0.056	0.491
TC	−0.027	0.070	0.227	0.430	0.19	0.584
TG	0.026	0.001	0.430	0.026	0.006	0.419
FFA	9.96	0.040	0.333	8.23	NS	0.257
FFA, 60 min	3.6	NS	0.180	8.05	0.050	0.129
PL	0.011	NS	0.245	0.014	0.05	0.409
HDL-TC	0.069	NS	−0.200	0.004	NS	0.183
HDL-PL	−0.000	NS	−0.054	0.000	NS	0.064
Apo A-I	−0.008	NS	−0.171	−0.010	NS	−0.254
HDL-PL apo A-I	−0.012	NS	0.014	0.003	NS	0.209
HDL TC Apo A-I	−0.002	NS	−0.145	0.005	NS	0.259
LDL	0.021	NS	0.224	0.260	NS	0.362

TABLE 5. Correlation analysis

	Spearman's	Partial
PCOS		
FTI *vs.* TC	$r = 0.312$, $P = 0.033$	P = NS
FTI *vs.* TG	$r = 0.355$, $P = 0.015$	P = NS
FTI *vs.* LDL	$r = 0.331$, $P = 0.023$	P = NS
FTI *vs.* apo B	$r = 0.349$, $P = 0.016$	P = NS
FTI *vs.* PL	$r = 0.340$, $P = 0.019$	P = NS
Ins sen *vs.* apo B	$r = 0.289$, $P = 0.05$	P = NS
Ins sen *vs.* FFA	$r = -0.334$, $P = 0.04$	P = NS
AUC-glu *vs.* FFA	$r = 0.505$, $P = 0.0007$	$r = 0.450$, $P = 0.003$
AUC-glu *vs.* TG	$r = 0.395$, $P = 0.012$	P = NS
AUC-ins *vs.* FFA	$r = 0.319$, $P = 0.010$	P = NS
AUC-ins *vs.* TG	$r = 0.330$, $P = 0.032$	P = NS
Controls		
Ins sen *vs.* LDL	$r = -0.499$, $P = 0.005$	$r = 0.463$, $P = 0.013$
AUC-glu *vs.* apo B	$r = 0.458$, $P = 0.005$	$r = 0.468$, $P = 0.012$
AUC-glu *vs.* TC	$r = 0.626$, $P = 0.0001$	$r = 0.586$, $P = 0.001$
AUC-glu *vs.* TG	$r = 0.602$, $P = 0.0001$	$r = 0.66$, $P = 0.0001$
AUC-ins *vs.* apo B	$r = 0.347$, $P = 0.035$	P = NS
AUC-ins *vs.* TC	$r = 0.566$, $P = 0.0002$	$r = 0.554$, $P = 0.002$
AUC-ins *vs.* TG	$r = 0.311$, $P = 0.05$	$r = 0.337$, $P = 0.06$

Spearman's rank coefficient of correlation and partial correlation, taking age and BMI into account, are shown in the PCOS (obese and nonobese) and controls (obese and nonobese).

The relationships between lipoprotein composition and insulin sensitivity or hyperandrogenicity were examined initially by calculating ranked (Spearman's) correlation coefficients (Table 5). Then, to compensate for the effects of age and adiposity, partial coefficients were calculated with age and BMI as covariates. Although there were several significant correlations between free testosterone index and insulin sensitivity with lipids in both PCOS and control groups after allowing for age and BMI, residual statistical significance in the PCOS patients remained between AUC-glu and fasting fatty acid levels. In the controls, the correlation between AUC-glu and AUC-ins to TC, LDL cholesterol, triglycerides, and apoB largely persisted after allowing for age and adiposity.

To establish whether PCOS had an effect on HDL composition after allowing for insulin sensitivity, androgenicity, age, and body mass, these factors were allowed to compete in a stepwise multiple regression analysis. PCOS was the single most consistent factor in determining the lipid enrichment of HDL. When AUC-glu, AUC-ins, and fasting insulin were included, PCOS exerted an effect on HDL PL/apoA-I (all $P = 0.005$) and on HDL TC/apoA-I (all $P = 0.027$). When insulin sensitivity was expressed as fatty acid suppression by glucose, PCOS remained significant ($P = 0.0041$ and $P = 0.020$, respectively), but this was reduced to $P = 0.028$ and $P = 0.14$, respectively, when insulin sensitivity expressed by IVITT was included.

Adiposity was the strongest independent predictor of TC ($P = 0.017$), apoB ($P = 0.007$), and triglyceride ($P < 0.0001$) when the other factors were included. Despite the strong influence of obesity on blood lipids there were only a few significant differences between the obese and lean subjects in either PCOS or control groups. This was surprising, so we reduced the BMI cut-off between lean and obese subjects from 27 to 25 kg/m^2. In this case obese subjects in both PCOS and control groups had significantly higher serum triglyc-

eride, LDL, PL, TC, FFA, and apoB levels compared to the nonobese subjects, confirming the trend seen in the correlation analyses.

Discussion

This study confirms reports of raised triglyceride and reduced HDL cholesterol levels in women with PCOS (10, 17–19), but our new finding is of lipid-depleted HDL. *In vivo*, HDL composition changes continuously with lipid flux from tissues and between lipoproteins. As the number of apoA-I molecules in each lipoprotein particle is relatively constant, apoA-I levels are a guide to particle numbers. In obese PCOS patients, we found that the HDL content of cholesterol and PL was reduced in both subfractions, with no change in its main protein, apoA-I, giving rise to reduced HDL lipid/apoA-I ratios.

In this cross-sectional study, stepwise multiple regression analyses suggested that PCOS selectively reduced HDL lipid. As hepatic lipase and PL transfer protein remove lipid from HDL (20, 21) and are induced by insulin resistance (21, 22), hyperandrogenemia (23), and obesity (24, 25), we speculate that increased activity in PCOS could explain the lipid-depleted HDL, but further definitive studies in PCOS and similar disorders are required.

In nonobese PCOS, HDL was not reduced, probably because the full metabolic disturbance is not manifest in the absence of obesity, as we see, for example, with insulin sensitivity. Low HDL was not a feature in our obese controls, but this is often the case in adult females (26, 27), particularly if plasma triglyceride levels are not raised (28). HDL cholesterol levels were lower in this study than usually found in premenopausal women, probably due to analytical factors, although our method for HDL determination has a high degree of correlation with the reference method of analytical ultracentrifugation (29). It is possible that small differences between the groups are undetected or correlations are not significant due to the imprecision of the methods employed.

In this study, blood levels of TC, apoB, and triglycerides correlated with adiposity, and BMI proved the strongest independent predictor on multivariate analysis. The absence of dyslipidemia in the lean PCOS subjects further supports the conclusion of the majority of other studies on the importance of obesity (17, 18, 30–32). Interestingly, after allowing for BMI, the level of the insulin and glucose response to oral glucose among the controls remained correlated to blood levels of cholesterol, triglycerides, and apoB, but insulin sensitivity assessed by IVITT was not. This may be due to these parameters reflecting different aspects of insulin sensitivity. Although the IVITT and fatty acid suppression by glucose reflect aspects of insulin sensitivity in peripheral tissues, the glucose and insulin responses to a glucose challenge may relate to hepatic lipid synthesis.

HDL levels markedly predict coronary risk in women (11); consequently, the 30% reduction in obese PCOS is important, as risk increases by 3.2% and mortality by 3.7–4.7% for each 0.026 mmol/L reduction in HDL cholesterol (33). As HDL removes cholesterol from tissues and its PL component functions as the cholesterol acceptor, this process and, therefore, the antiatherogenic role of HDL may be compromised when PL levels are low. Interestingly, both reduced HDL PL and lipid depletion of HDL relative to protein have been shown to increase cardiovascular risk (34, 35).

Weight loss, particularly from upper body fat stores, improves hormonal (36) and metabolic (37) profiles, decreasing cardiovascular risk. Consequently, efforts should be directed to preventing obesity, particularly in patients in whom several mild abnormalities coexist that significantly increase cardiovascular risk.

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