Postprandial Reduction in High-Density Lipoprotein Cholesterol Concentrations in Postmenopausal Women: Improvement by 17β-Estradiol

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The aim of the study was to characterize postprandial high-density lipoprotein (HDL) cholesterol metabolism in postmenopausal women and to evaluate the effect of replacement therapy with 17β-estradiol. Sixteen healthy normolipidemic (plasma cholesterol, 5.39 ± 0.68 mmol/L; plasma triglycerides [TGs], 1.24 ± 0.55 mmol/L) postmenopausal women received an oral vitamin A fat tolerance test (50 g fat with 60,000 IU vitamin A/m^2 body surface area). Venous blood samples were taken before the test, at hourly intervals up to 8 hours, and 24 hours after ingestion of the fat load for determination of HDL cholesterol, HDL TG, and HDL apolipoprotein (apo) A-I concentrations. TG and vitamin A concentrations were also measured. A subgroup of six women were treated with 2 mg micronized 17β-estradiol orally each day for 6 weeks, after which the oral vitamin A fat tolerance test was repeated. A reduction in plasma HDL cholesterol concentrations was observed 3 to 8 hours after ingestion of the fat load, and the minimal postprandial HDL cholesterol concentration was, on average, 31.7% (P = .04) lower than the fasting HDL cholesterol concentration. HDL cholesterol had returned to the initial value 24 hours after the fat load. The decrease in postprandial HDL cholesterol concentrations was attenuated by treatment with 17β-estradiol. The area under the curve (AUC) for the postprandial reduction in HDL cholesterol improved substantially by 66% during 17β-estradiol (−2.4 ± 2.6 mmol · h · L^{-1} before 17β-estradiol and −1.1 ± 1.2 mmol · h · L^{-1} during 17β-estradiol, P = .038). In conclusion, HDL cholesterol concentrations decreased by 32% in the postprandial state in normolipidemic postmenopausal women, indicating that HDL cholesterol must be measured in the fasting state. Replacement therapy with 17β-estradiol reduced the postprandial decrease in HDL cholesterol by 66%. This effect of 17β-estradiol can be beneficial in reducing the risk of coronary artery disease.

EPIDEMIOLOGIC evidence shows that the plasma concentration of high-density lipoprotein (HDL) cholesterol is the major independent lipid factor associated with protection against coronary artery disease in women.[1,2] Plasma HDL cholesterol concentrations are higher in women than in men, supposedly due to lower catabolic rates of apolipoprotein (apo) A-I, the major protein constituent of HDL.[3]

In women, plasma HDL cholesterol concentrations do not change[4] or change only marginally with age, puberty, and menopause.[5,6] Exogenous estrogens increase HDL cholesterol concentrations by increasing apo A-I production.[7] The protective effect of HDL is attributed to its function in reverse cholesterol transport[8] and its ability to prevent oxidation of low-density lipoprotein particles[9] and to protect the endothelium against cytotoxic agents derived from triglyceride (TG)-rich lipoprotein remnants.[10] Moreover, HDL cholesterol is considered a good marker of the metabolism of atherogenic remnants of TG-rich lipoproteins,[11-13] but this has only been demonstrated in men. In reverse cholesterol transport,[8] free cholesterol is taken up from peripheral tissues and esterified by lecithin: cholesterol acyltransferase into HDL particles that contain predominantly apo A-I.[14] Subsequently, HDL particles are transported to the liver for catabolism, mediated in part by the enzyme hepatic lipase. During reverse cholesterol transport, cholesterol ester is transferred from HDL to atherogenic remnants of TG-rich lipoproteins by the cholesterol ester transfer protein and, vice versa, TG is transferred from TG-rich lipoprotein remnants to HDL particles.[8] In the postprandial state, the concentration of TG-rich lipoproteins is elevated, and as a consequence, the transfer of cholesterol esters from HDL to remnants is increased, resulting in decreased plasma HDL cholesterol concentrations.[13,15] The transfer of TG to HDL leads to the formation of TG-enriched HDL_2 particles, which are an excellent substrate for hepatic lipase,[16] contributing further to the postprandial reduction in HDL cholesterol.

These changes in HDL cholesterol metabolism turn the postprandial state into a potentially more atherogenic condition in men, but no data are available in women. Since humans exist predominantly in the postprandial state, there is a distinct possibility that the postprandial HDL cholesterol response also defines the risk of coronary artery disease. The magnitude of postprandial lipemia has already been reported as a useful indicator of the risk of coronary artery disease.[17] A postprandial reduction in plasma HDL cholesterol has been reported in healthy young (21 to 27 years) men[13] and in a group of men and women of different ages.[15] No data are available on the relationship between alimentary lipemia and postprandial metabolism of HDL in postmenopausal women, a group with an increased risk of coronary artery disease. Expansion of the knowledge on postprandial HDL cholesterol metabolism is necessary because HDL cholesterol is the major protective factor in women.[1,2] We therefore characterized postprandial HDL cholesterol and HDL-associated apo A-I concentrations in postmenopausal women and evaluated the effect of hormone replacement therapy with 17β-estradiol.

SUBJECTS AND METHODS

Subjects and Study Design

The objective of the study was to characterize postprandial HDL metabolism in postmenopausal women, a group at risk for coronary

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artery disease, and to evaluate the effect of hormonal replacement therapy on postprandial HDL metabolism. The 16 women who participated provided written informed consent; all were in good health, euthyroid, and nonsmokers, and did not use alcohol. Sixteen normolipidemic postmenopausal women received an oral fat load. The first six postmenopausal women who entered the study were treated with 2 mg micronized 17β-estradiol (Estrofem; NOVO Nordisk, Copenhagen, Denmark) orally each day before bedtime. After 6 weeks of treatment, the oral fat-loading test with investigation of postprandial lipid metabolism was repeated. After completion of the study, progestagens were added to the regimens of women with an intact uterus. The study protocol was approved by the Ethics Committee of the University Hospital Utrecht.

Oral Retinyl Palmitate Fat-Loading Test

Cream, a 40% (wt/vol) fat emulsion with a polyunsaturated to saturated fat ratio of 0.06 containing 0.001% (wt/vol) cholesterol and 2.8% (wt/vol) carbohydrates, was used as a fat source. Retinyl palmitate (RP), which is incorporated into newly synthesized chylomicrons,[13] was added to the cream. After an overnight fast of 12 hours, the subjects ingested the fresh cream in a dose of 50 g fat/m^2 body surface area, with 60,000 IU RP/m^2 body surface area. During the following 24 hours, the women were allowed to drink only water. Peripheral venous blood samples were collected before the meal, at hourly intervals up to 8 hours, and 24 hours after the meal. The samples were collected in tubes containing sodium EDTA (2 mg/mL), and the tubes were protected against light by aluminum foil. The tubes were centrifuged immediately for 15 minutes at 3,000 rpm at 4°C. The plasma obtained was subjected to a rapid ultracentrifugation procedure, as described previously,[13,18] to separate plasma into the fraction with a Svedberg flotation unit (Sf) value greater than 1,000, containing chylomicrons and large chylomicron remnants, and the infranatant fraction (Sf < 1,000), containing small chylomicron remnant particles, very-low-density lipoproteins (VLDL), low-density lipoproteins, HDL, and plasma proteins. Aliquots were stored at −20°C until assayed. Individual variability in the response to the oral fat load, measured in our laboratory in individuals before and after placebo, is 8.7% with RP and 22% with TG, calculated from the areas under the curve (AUCs), respectively.[19] The RP level was measured by high-performance liquid chromatography using retinyl acetate as an internal standard.[13]

Analytical Methods

Precipitation of apo B–containing lipoproteins in the Sf < 1,000 fraction using phosphotungstic acid and magnesium chloride[13] yielded a fraction that contained HDL particles, free apo A-I, and plasma proteins. These HDL-containing fractions, which are equivalent to the density gradient ultracentrifugation fraction, d > 1.063 g/mL, were prepared on the same day the fat-loading test was performed. Cholesterol, TG, and apo A-I levels were measured in these HDL fractions. TG and cholesterol levels were measured in duplicate with a commercial colorimetric assay (GPO-PAP Kit no. 701912 and Monotest Cholesterol CHOD-PAP Kit no. 237574, respectively; Boehringer, Mannheim, Germany). Plasma apo A-I and apo B were determined using the Behring immunonephelometer 100 (Behringwerke, Marburg, Germany) with assigned values according to the International Federation of Clinical Chemistry. Interassay variabilities for apo A-I and apo B were 4% and 7%, respectively. Postheparin (50 IU/kg body weight) plasma lipoprotein lipase and hepatic lipase activities were determined as described by Hüttünen et al.[20] Postheparin enzyme activities were determined in the fasting state 1 week after the oral fat load, to avoid interference of ingested fat with lipase activity and, vice versa, to avoid effects of lipase activity on the elimination of TG-rich lipoproteins and the measurement of the postprandial lipid response. Lipolytic activity is expressed as nanomoles of free fatty acids per minute per milliliter of plasma. Normal values for women are greater than 70 mU/mL for lipoprotein lipase and greater than 360 mU/mL for hepatic lipase.

Hormone Measurements

Serum estrone (E1) and estradiol (E2) concentrations were measured using commercial competitive radioimmunoassays (Amersham, Little Chalfont, UK). The coefficient of variation was 2.0% for E1 and 2.8% for E2. In postmenopausal women, normal values are 40 to 200 pmol/L for E1 and 10 to 50 pmol/L for E2. Serum follicle-stimulating hormone (FSH) level was measured with a noncompetitive enzyme immunoassay (Enzymun FSH; Boehringer). The coefficient of variation for the FSH assay was 3.1%. The normal value for serum FSH in postmenopausal women is greater than 20 IU/L.

Statistical Analysis

Values are expressed as the mean ± SD. Student's *t* tests for matched pairs and for independent samples were used in the SPSS.PC 6.0 program (SPSS, Chicago, IL). Wilcoxon's matched-pairs signed-rank test was applied to evaluate data that were not distributed normally, ie, decremental 8-hour postprandial HDL cholesterol AUCs. Pearson's correlation coefficients with two-tailed significance were calculated. Two-tailed *P* values less than .05 were considered significant.

RESULTS

Clinical characteristics of the 16 women studied are shown in Table 1. Each woman was postmenopausal as assessed by amenorrhea over 1 year and serum FSH concentrations greater than 20 IU/L. Each subject was normolipidemic; plasma concentrations are presented in Table 1.

Subjects Treated With 17β-Estradiol

A subgroup of six postmenopausal women were treated with 2 mg 17β-estradiol for 6 weeks. Pretreatment values for fasting and postprandial parameters of lipid and lipoprotein metabolism, plasma steroid hormone concentrations, body mass index (BMI), and waist to hip ratio (WHR) were not significantly different between this subgroup of six postmenopausal women and the entire group of 16 postmenopausal women (*t* tests for independent samples).

The subgroup had a mean age of 55.5 ± 4.0 years, a BMI

Table 1. Clinical Characteristics and Fasting Lipids in 16 Normolipidemic Postmenopausal Women

Parameter	Mean ± SD
Age (yr)	59 ± 6.3
BMI (kg/m^2)	25.3 ± 2.9
WHR	0.80 ± 0.06
FSH (IU/L)	72 ± 29
E1 (pmol/L)	140 ± 51
E2 (pmol/L)	57 ± 40
Cholesterol (mmol/L)	5.39 ± 0.68
TG (mmol/L)	1.24 ± 0.55
HDL cholesterol (mmol/L)	0.96 ± 0.38
Plasma apo A-I (mg/dL)	142 ± 25

of 27.0 ± 4.6 kg/m^2, and a WHR of 0.8 ± 0.1. After treatment with 17β-estradiol, plasma FSH decreased from 89 ± 36 to 39 ± 15 IU/L (P = .01), plasma E1 increased from 123 ± 39 to 1,925 ± 667 pmol/L (P = .001), and plasma E2 increased from 50 ± 31 to 336 ± 124 pmol/L (P = .002).

Fasting plasma cholesterol was 5.63 ± 0.83 mmol/L, TG 1.47 ± 0.69 mmol/L, and HDL cholesterol 1.15 ± 0.56 mmol/L, none of which changed significantly after 17β-estradiol treatment. By contrast, replacement therapy with 17β-estradiol significantly increased fasting apo A-I in total plasma from 146 ± 23 to 159 ± 26 mg/dL (P = .03), whereas apo A-I in the HDL-containing fractions remained unchanged (129 ± 29 mg/dL before and 130 ± 40 mg/dL after 17β-estradiol). Hepatic lipase activity was significantly reduced from 417 ± 84 to 284 ± 71 mU/mL by 17β-estradiol, whereas lipoprotein lipase activity was not affected (138 ± 40 mU/mL).

Fasting and Postprandial HDL Cholesterol, HDL TG, and HDL-Associated Apo A-I

Postprandial HDL cholesterol concentrations were significantly lower than fasting values (Student's paired t tests) 3 to 8 hours after ingestion of the fat load. The minimal postprandial HDL cholesterol concentration was 0.62 ± 0.16 mmol/L, which represented a 31.7% decrease from the fasting HDL cholesterol concentration of 0.96 ± 0.38 mmol/L (P = .002, paired t test). The 8-hour AUC for the postprandial reduction in HDL cholesterol was −1.7 ± 2.7 mmol · h · L^{-1}. HDL TG concentrations decreased significantly at 1 to 3 hours after the fat load. The minimal postprandial HDL TG concentration was 0.15 ± 0.04 mmol/L, which is 31.8% lower than the fasting HDL TG of 0.22 ± 0.04 mmol/L (P < .001, paired t test). Apo A-I in HDL-containing fractions also decreased in the postprandial state; this decrease reached significance after 3 and 6 hours. Fasting HDL apo A-I level was 108 ± 42 mg/dL, and the minimal postprandial HDL apo A-I concentration was reduced by 23.1% to 83 ± 17 mg/dL (P = .022, paired t test). HDL cholesterol, HDL TG, and HDL apo A-I concentrations had returned to the initial fasting values after 24 hours. Plasma apo A-I was 147 ± 26 mg/dL in the fasting state, and decreased significantly at 5 hours (140 ± 27 mg/dL, P = .017) and 6 hours (139 ± 25 mg/dL, P = .001) after the fat load (Fig 1).

Effects of 17β-estradiol. Hormone replacement therapy with 17β-estradiol significantly reduced the AUC for the postprandial decrease in HDL cholesterol by 66% from −2.4 ± 2.6 to −1.1 ± 1.2 mmol · h · L^{-1} (P = .038, Wilcoxon signed-rank test; Table 3), although fasting HDL cholesterol concentrations had not changed. Postprandial HDL TG and HDL apo A-I did not change significantly after 17β-estradiol.

Postprandial RP and TG Metabolism

The postprandial plasma TG response, expressed as AUC at 8 hours for TG, was 14.2 ± 6.3 mmol · h · L^{-1} and significantly correlated with fasting plasma TG concentration (1.24 ± 0.55 mmol/L, r = .97, P < .001), BMI

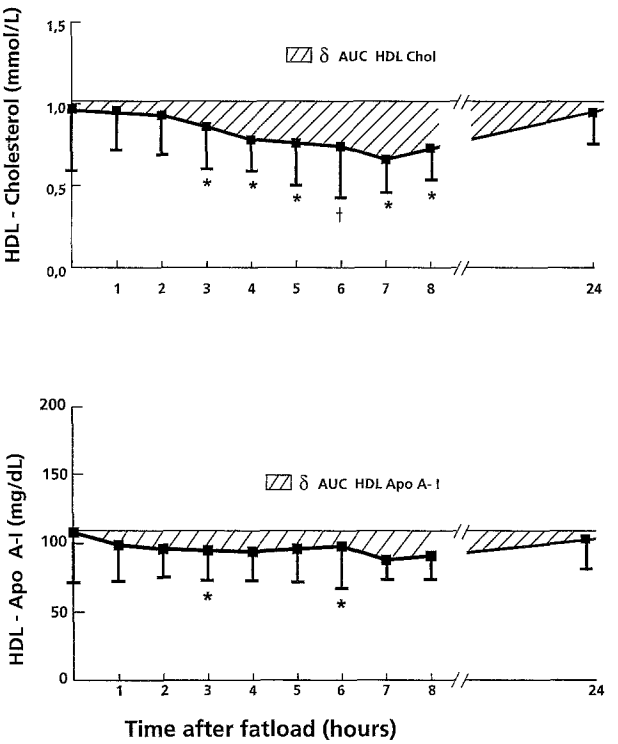

Fig 1. Postprandial HDL metabolism in 16 normolipidemic postmenopausal women. HDL cholesterol and HDL-associated apo A-I concentrations at 0 to 8 hours and 24 hours after ingestion of an oral fat load (50 g fat/m^2 body surface area) are shown for 16 normolipidemic postmenopausal women. Postprandial values (1 to 8 hours) were compared with fasting values using paired t tests. *P < .05, †P < .01. δ AUC HDL Chol (mmol · h · L^{-1}), decremental 8-hour postprandial AUC for HDL cholesterol. δ AUC HDL Apo A-I (mg · h · dL^{-1}), decremental 8-hour postprandial AUC for HDL apo A-I.

(25.3 ± 2.9 kg/m^2, r = .62, P = .01), and WHR (0.80 ± 0.06, r = .83, P < .001), but not with fasting lipoprotein lipase activity (Table 2).

Effects of 17β-estradiol. The total postprandial mass of chylomicrons and chylomicron remnants, expressed as the 8-hour AUC of RP in plasma, decreased from 27.1 ± 15.9 to 16.6 ± 13.2 mg · h · L^{-1} (P = .01), and the amount of large chylomicron remnants, expressed as the 8-hour AUC of RP in the Sf > 1,000 fraction, decreased from 11.5 ± 9.0 to 7.0 · 9.8 mg · h · L^{-1} (P = .005) after treatment with 17β-estradiol.

Correlations Between Fasting and Postprandial HDL Cholesterol and TG Metabolism

The fasting HDL cholesterol concentration correlated inversely with the 8-hour AUC for the decrease in HDL cholesterol (r = −.92, P < .001). The interpretation is that fasting HDL cholesterol concentration predicted the magni-

Table 2. Postprandial RP and TG Concentrations in 16 Normolipidemic Postmenopausal Women

	Plasma	Sf > 1,000	Sf < 1,000
RP 8-hour AUC (mg · h · L^{-1})	42.5 ± 24.6	19.2 ± 12.9	19.4 ± 10.2
TG 8-hour AUC (mmol · h · L^{-1})	14.2 ± 6.3	2.6 ± 1.3	11.3 ± 5.1

tude of the reduction in postprandial HDL cholesterol concentration. However, neither the fasting HDL cholesterol concentration nor the 8-hour AUC of postprandial HDL cholesterol correlated with fasting or postprandial TG and RP concentrations in total plasma, Sf < 1,000 fractions, or Sf > 1,000 fractions.

Effects of 17β-estradiol. The 17β-estradiol–induced improvement of the postprandial reduction in HDL cholesterol, calculated as the decremental AUC of HDL cholesterol (Table 3), correlated with 17β-estradiol–induced changes in the corrected AUC of plasma TG, calculated as plasma AUC of TG divided by fasting plasma TG concentration ($r = .93, P = .008$; Fig 2).

DISCUSSION

The present data show that in normolipidemic postmenopausal women, HDL cholesterol concentrations decrease by 32% in the postprandial state. This decrease is similar to the 35% reduction in postprandial HDL cholesterol observed in young normolipidemic men,[13] indicating that a postprandial reduction in HDL cholesterol occurs to the same extent in young men and postmenopausal women. It should therefore be recognized that the postprandial reduction in HDL cholesterol is a physiological response to an oral fat load that is transient in nature. HDL cholesterol and apo A-I returned to initial values 24 hours after the oral fat load in the present study in women and in men. The greater than 30% difference between fasting and minimal postprandial HDL cholesterol concentrations also supports the conclusion that HDL cholesterol concentrations should be measured in the fasting state, as recommended by the National Institutes of Health,[21] and that only fasting HDL cholesterol values can be used for interindividual comparison and intraindividual follow-up evaluation. In postmenopausal women, fasting HDL cholesterol concentrations correlate inversely with the postprandial reduction in HDL cholesterol, but this relation is absent in men.[13] The reason for this interesting discrepancy is not clear. An inverse association between fasting HDL cholesterol concentrations, particularly HDL_2 cholesterol,[16] and postprandial lipemia has previously been reported in men[12] and in combined groups of men, premenopausal women, and postmenopausal women,[15,16] but was not found in the present study. Fasting and postprandial HDL cholesterol concentrations did not correlate with either fasting TG levels or the postprandial 8-hour TG AUC. This suggests that in normolipidemic postmenopausal women, fasting HDL cholesterol concentrations do not reflect the efficiency of postprandial TG metabolism. Our results show that in postmenopausal women, fasting HDL cholesterol concentrations predict postprandial HDL cholesterol metabolism in response to an oral fat load. An explanation for the absence of a clear correlation between HDL cholesterol and TG metabolism is that in normolipidemic women the metabolism of TG-rich lipoproteins and HDL particles is less interrelated than in men, due to more efficient clearance of TG-rich lipoproteins,[22] reduced catabolism of HDL,[3] and higher de novo hepatic HDL and apo A-I production.[7] Epidemiological studies strongly suggest that hormone replacement therapy can protect postmenopausal women against coronary artery disease.[23] This protective effect is partly attributed to changes in fasting lipids, including an increase in HDL cholesterol concentrations. In the postprandial state, TG concentrations are elevated and HDL cholesterol concentrations are reduced. The atherogenicity of such a high-TG/low-HDL lipid profile in the fasting state has been established in large prospective trials in men,[24,25] but not yet in women.

Hormone replacement therapy with oral 17β-estradiol did not change fasting HDL cholesterol and TG concentrations, but significantly attenuated the postprandial reduction in HDL cholesterol concentrations. This suggested that more HDL cholesterol remained involved in reverse cholesterol transport, one of the important functions of HDL particles. The clinical relevance of the 17β-estradiol–induced attenuation of postprandial HDL cholesterol reductions in postmenopausal women remains to be determined. However, protection against coronary artery disease may be

Table 3. Postprandial Reduction in HDL Cholesterol Before and After 6 Weeks of Treatment With 2 mg 17β-Estradiol in Six Normolipidemic Postmenopausal Women

	δ-AUC HDL Cholesterol (mmol · h · L^{-1})	
Subject No.	Before 17β-Estradiol	After 17β-Estradiol (% improved)
1	−2.47	−0.65 (74)
2	−0.29	−0.25 (12)
3	−2.59	−1.10 (58)
4	−1.27	−1.00 (21)
5	−0.35	+0.29 (183)
6	−7.40	−3.71 (50)
Mean ± SD	−2.40 ± 2.64	−1.07 ± 1.17 (66%; range, 12%-183%)*

*$P = .028$ by Wilcoxon signed-rank test.

Abbreviation: δ-AUC HDL cholesterol, decremental 8-hour postprandial AUC for HDL cholesterol.

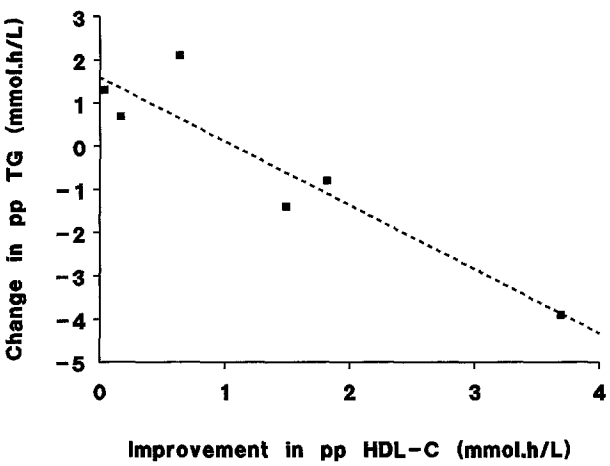

Fig 2. Line plot of correlation between 17β-estradiol–induced changes in postprandial HDL cholesterol and TG metabolism. The 17β-estradiol–induced improvement in postprandial (pp) HDL cholesterol, calculated as the decremental AUC for HDL cholesterol, is plotted against changes in pp TG calculated as AUC for TG divided by fasting TG concentration.[12,18] ($r = .93, P = .008$, Pearson's correlation coefficient with two-tailed significance).

expected, since HDL cholesterol is a powerful protective lipid factor in women.[1,2]

Fasting plasma apo A-I concentrations were significantly increased by 17β-estradiol treatment, which is in accordance with previous reports on increased production rates of apo A-I after oral estrogens.[7] Furthermore, we found a reduction in the activity of hepatic lipase, the enzyme that reduces HDL cholesterol concentration by promoting hepatic cholesterol uptake from HDL particles. The decrease in hepatic lipase is also a known estrogen effect.[26] In addition, estrogens improve the clearance of chylomicron remnant particles,[22] which may result in reduced transfer of cholesterol ester from HDL to remnants of TG-rich lipoproteins. Each of the above-mentioned 17β-estradiol effects can, in theory, contribute to the observed improvement of the postprandial reduction in HDL cholesterol. But each effect separately did not correlate with the 17β-estradiol–induced changes in postprandial HDL cholesterol metabolism. This finding suggests that the mechanism of the improvement of postprandial HDL metabolism after 17β-estradiol therapy is complex, and probably the net result of influences on several aspects of HDL metabolism or TG metabolism. The most conspicuous association was found between 17β-estradiol–induced changes in the corrected AUC for plasma TG[12,18] and in the decremental AUC for HDL cholesterol ($r = .93$, $P = .008$), indicating that the improvement in postprandial HDL cholesterol metabolism with 17β-estradiol was at least partly related to changes in TG metabolism. We cannot conclude whether the changes in the corrected AUC for plasma TG reflect alterations in elimination,[22] secretion of VLDL or chylomicrons, or a combination of both.

Treatment with 17β-estradiol increased fasting apo A-I concentrations in total plasma, but apo A-I in HDL fractions remained unchanged. This increase in non-HDL apo A-I could reflect an increase in VLDL-associated apo A-I via a 17β-estradiol–induced increased production of VLDL particles[27]; it could also represent apo A-I in surface fragments released from VLDL or chylomicron particles during hydrolysis.[28]

In conclusion, postprandial HDL cholesterol concentrations were 32% lower than fasting HDL cholesterol concentrations in postmenopausal women, and in view of the marked decrease in postprandial HDL cholesterol, the data strongly support a recommendation that HDL cholesterol be determined in the fasting state. In postmenopausal women, fasting HDL cholesterol accurately predicted the postprandial reduction in HDL cholesterol. Hormone replacement therapy with 17β-estradiol improved the postprandial decrease in HDL cholesterol, rendering the postprandial state potentially less atherogenic.

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