Postprandial Lipemia and Associated Metabolic Disturbances in Healthy and Hyperlipemic Postmenopausal Women

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The increased risk for coronary artery disease observed in postmenopausal women is partly explained by a more atherogenic fasting lipoprotein profile. Moreover, natural menopause has been associated with an altered postprandial lipid profile. To better characterize the interaction between fasting and postprandial lipid profile after menopause, we examined postprandial changes in several lipid parameters in three age-matched groups of postmenopausal women (16 affected by mixed hyperlipemia, 17 by common hypercholesterolemia, and 17 normolipemic), who underwent a standardized oral fat-loading test. The magnitude of postprandial lipemia, expressed as 8-hour triglyceride incremental area under the curve, was greater in women with mixed hyperlipemia (1,326 ± 372 mg · dL^{-1} · h^{-1}) than in normal (484 ± 384 mg · dL^{-1} · h^{-1}) and hypercholesterolemic (473 ± 223 mg · dL^{-1} · h^{-1}; both $P < .0001$) women, and the differences held after adjustment for body mass index and fasting insulin. Women with mixed hyperlipemia showed a significant postprandial decrease in high-density lipoprotein 2 (HDL_2) cholesterol, lipoprotein (a), and low-density lipoprotein (LDL) particle size. Both hypercholesterolemic and normolipemic women showed a significant postprandial decrease in HDL cholesterol and lipoprotein (a) levels but not in LDL size. In a multiple linear regression analysis, fasting triglyceride levels, insulin level, and waist-hip ratio were all independent predictors of the magnitude of postprandial lipemia. In conclusion, postmenopausal women with mixed hyperlipemia show a greater postprandial triglyceride increase and a more pronounced reduction in HDL cholesterol level and LDL size than hypercholesterolemic and normolipemic subjects. The presence of the features of insulin resistance syndrome could contribute to the deterioration of postprandial lipemic response in these subjects.

A RELATIONSHIP between postprandial lipemia and coronary artery disease (CAD) was initially observed in the 1950s and 1960s[1] and further investigated by Zilversmit, who proposed that atherogenesis was a postprandial phenomenon.[2] On the track of Zilversmit's hypothesis, several studies followed with the purpose to clarify the metabolic events occurring in the postprandial state and their association with cardiovascular disease.[3,4] In this regard, a cross-sectional study by Patsch et al[5] showed an association between plasma triglyceride levels measured late in the postprandial state and CAD in men with normal fasting triglyceridemia. Data on the postprandial lipid response as a CAD risk factor in normolipemic women are more conflicting.[6-8]

Postmenopausal estrogen deficiency has been associated with an adverse fasting[9] and postprandial[8] lipid profile, which may contribute to the increased CAD risk after menopause.[10,11] A transient postprandial reduction in high-density lipoprotein (HDL) cholesterol levels has been described in normolipemic postmenopausal women.[12] However, postprandial changes in several lipid parameters, including HDL cholesterol subfractions, lipoprotein (a) [Lp(a)], and low-density lipoprotein (LDL) particle size, have not been investigated so far in women with dyslipidemia. Thus, we investigated changes in these parameters after a standardized oral fat-loading test in postmenopausal women with hypercholesterolemia and mixed hyperlipemia and in a control group of normolipemic women.

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Submitted May 17, 2000; accepted August 28, 2000.

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0026-0495/01/5003-0030$35.00/0
doi:10.1053/meta.2001.20202

PATIENTS AND METHODS

Patients and Controls

Three age-matched groups of postmenopausal women were selected for the study. Seventeen women were affected by polygenic hypercholesterolemia, 16 by mixed hyperlipemia, and 17 normolipemic women served as control subjects. Secondary hyperlipemia was excluded in all subjects by appropriate thyroid, renal, and liver function tests. Menopausal status was defined by questionnaire as the absence of menses for at least 1 year. Women with uncertain menopausal status, as well as subjects in menopause for less than 1 year, were excluded from the study. All subjects with diabetes mellitus and history of CAD were excluded from the study. No subject was taking hormone-replacement therapy, lipid-lowering drugs, or other drugs affecting lipid or glucidic metabolism. Polygenic hypercholesterolemia was defined as LDL cholesterol $>$ 160 mg/dL in the study subject and in one or more family members in the absence of xanthomas in the family. Mixed hyperlipemia was defined as LDL cholesterol level $\geq$ 160 mg/dL and triglycerides $\geq$ 200 mg/dL; 6 of the 16 subjects fulfilled all the criteria for diagnosis of familial combined hyperlipemia.[13] Normolipemic subjects had LDL cholesterol levels $<$ 160 mg/dL and triglyceride levels $<$ 180 mg/dL. The diet regimen before the test was homogeneous in the three groups. Hyperlipemic subjects followed a lipid-lowering American Heart Association step II diet (total calories as fats $<$ 30%, saturated fats $<$ 7%, cholesterol 200 mg/d). Limitations for monosaccharides and alcohol were prescribed in subjects with mixed hyperlipemia. Normolipemic subjects had a normocaloric hypolipidic diet with the same characteristics for at least 2 weeks before the oral fat-tolerance test. All subjects were asked to abstain from alcohol for at least 24 hours before the test.

Procedures

Participants started the test at 8 AM at the Lipid Clinic of our institution. The standardized high-fat meal consisted of whipping cream, liquid chocolate, and nonfat dry milk and contained 65 g of fat, 25 g of carbohydrates, 6 g of proteins per m^2 body surface area.[5,14,15]

The corresponding caloric intake was 700 kcal/m^2, 83% derived from fat, 14% from carbohydrates, and 3% from proteins. The cholesterol content was 240 mg, and the ratio of polyunsaturated to saturated fats was 0.06. In each subject, a baseline venous blood sample was collected at 8 AM after a 14-hour fast. Study subjects consumed the test meal at 8:30 AM. Thereafter, participants were offered water throughout the postprandial period, but no food or caloric drink was allowed. At baseline and 4, 6, and 8 hours after the meal, the following variables were determined: total cholesterol level, triglyceride levels, levels of HDL cholesterol and its HDL_2 and HDL_3 subfractions, LDL cholesterol level, LDL particle size, and Lp(a) level. Serum insulin and lipoprotein lipase *Hin*dIII genotype were tested only at baseline.

Total cholesterol, triglyceride, and HDL cholesterol levels were determined by a colorimetric method (Dimension Autoanalyzer; DADE Inc., Newark, NJ), and LDL cholesterol level was calculated from the Friedewald equation.[16] Plasma Lp(a) concentration was measured by enzyme-linked immunosorbent assay. HDL_2 and HDL_3 cholesterol concentrations were determined after precipitation with two different reagents containing polyethylene glycol (Immuno AG, Vienna, Austria). An aliquot of plasma (blood anticoagulated with EDTA) was used to determine LDL size by gradient gel electrophoresis according to the method of Rainwater et al.[17] A 2% to 16% polyacrilamide gel was prepared; samples for seeding were preincubated and stained with Sudan Black, then seeded with thyreoglobulin, ferritin, catalase, lacticodehydrogenase, albumin, and latex of a known size to be used as standard migration distances. The LDL and standard migration distances were read on a densitometry (590 nm). A quadratic equation (polynomial regression of Stokes) was used to convert migration distance into particle diameter; the estimated diameter of the greatest peak in each scan was identified as the LDL particle diameter. Insulin level was determined in duplicate by radioimmunoassay. Lipoprotein lipase *Hin*dIII polymorphism genotyping was performed by DNA extraction, polymerase chain reaction, and *Hin*dIII restriction enzyme digestion of the amplified products.[18] Informed consent was obtained by all participants, and the study was approved by the local ethics committee.

Statistical Analysis

The Kolmogorov-Smirnov algorithm was used to determine whether each variable had a normal distribution, and only the distribution of Lp(a) was significantly different from the normal distribution. Parameters are expressed as means ± SD except for Lp(a), which is expressed as median (25th to 75th percentile). ANOVA, corrected with Tukey's post hoc test, tested the between-group differences in demographic, lipid, and metabolic variables. ANOVA for repeated measurements was used to assess differences among various times of observation.

The magnitude of postprandial triglyceride changes was estimated as 8-hour incremental area under the curve (AUC).[5] Triglycerides were plotted against time, and the AUC from the beginning of the test to the 8th hour was calculated by the trapezoidal method after subtraction of the baseline values. The differences among the three groups in triglyceride incremental AUC were assessed by analysis of covariance (ANCOVA) after adjustment for body mass index and fasting insulin level. For Lp(a), statistical differences between groups and intragroup variations from baseline values were calculated by use of Kruskal-Wallis and Friedman tests and Tukey's post hoc test for multiple comparisons. Univariate correlations were obtained with Pearson's correlation test, and stepwise multiple linear regression tested the relationship of several variables to triglyceride incremental AUC.

RESULTS

The three groups did not differ by age and smoking habits (Table 1). Insulin level, waist-hip ratio, body mass index, and plasma triglyceride level were higher, and HDL cholesterol and HDL_2 cholesterol levels were significantly lower, in women with mixed hyperlipemia than in the other two groups. By selection, total and LDL cholesterol were greater in both hyperlipemic groups than in normal women; LDL particle size and HDL_3 cholesterol level were lower in subjects with mixed hyperlipemia than in normal subjects.

Postprandial lipid parameters after the oral fat load are reported in Table 2. Subjects with mixed hyperlipemia showed a significant increase in serum triglycerides after 4 hours, and the maximal value was reached 6 hours after the meal. A significant reduction was observed in HDL and HDL_2 cholesterol levels. Plasma Lp(a) levels decreased after 4 and 6 hours, in concomitance with the increase in triglyceride levels. A significant decrease in LDL size was observed at the 4th and

Table 1. Demographic Characteristics and Fasting Laboratory Parameters of the Study Population

	Normal (n = 17)	Hypercholesterolemia (n = 17)	Mixed Hyperlipemia (n = 16)
Age (yr)	57 ± 8	54 ± 6	55 ± 5
Body mass index (kg/m^2)	26.7 ± 1.3	25.9 ± 2.3	27.9 ± 1.6*†
Waist-hip ratio	0.84 ± 0.08	0.89 ± 0.05	0.97 ± 0.05*†
Insulin (mU/L)	7.6 ± 4.9	9.2 ± 6.6	22.5 ± 9.5*†
Triglycerides (mg/dL)	80 ± 35	113 ± 48	211 ± 43*†
Total cholesterol (mg/dL)	205 ± 22	269 ± 34*	260 ± 35*
LDL cholesterol (mg/dL)	129 ± 16	187 ± 34*	173 ± 31*
HDL cholesterol (mg/dL)	59 ± 18	58 ± 15	43 ± 11*†
HDL_2 cholesterol (mg/dL)	22 ± 11	20 ± 9	11 ± 3*†
HDL_3 cholesterol (mg/dL)	39 ± 8	38 ± 7	32 ± 9*
LDL size (nm)	27.0 ± 1.1	26.6 ± 1.6	25.4 ± 1.1*
Lp(a) (mg/dL)	7.3 (4.4-18.7)	20.7 (17.1-37.9)	11.4 (8.3-24.4)
Lipoprotein lipase *Hin*dIII genotype			
$H^{+/+}$	8/17	5/17	10/16
$H^{+/-}$	5/17	9/17	6/16
$H^{-/-}$	4/17	3/17	0/16

NOTE. Values are expressed as mean ± SD; Lp(a) is expressed as median (25% to 75%).

* $P < .05$ *v* normal subjects.

† $P < .05$ *v* hypercholesterolemia.

Table 2. Postprandial Lipid Parameters After the Oral Fat Load

	Triglycerides (mg/dL)	LDL Size (nm)	HDL-C (mg/dL)	HDL_2-C (mg/dL)	HDL_3-C (mg/dL)	Lp(a) (mg/dL)
Controls						
0 h	80 ± 35	27.0 ± 1.1	59.2 ± 18	22.5 ± 11	38.7 ± 8	7.3 (3-36)
4 h	162 ± 112*	27.5 ± 0.6	58.0 ± 20	23.5 ± 10	37.7 ± 11	6.5* (2-32)
6 h	177 ± 95*	27.2 ± 1.3	56.9 ± 20*	23.6 ± 10	36.9 ± 12	6.5* (2-29)
8 h	116 ± 52*	27.2 ± 1.1	59.3 ± 19	24.6 ± 10	37.2 ± 11	6.9 (2-28)
Hypercholesterolemia						
0 h	113 ± 48	26.6 ± 1.6	57.8 ± 15	20.2 ± 9	38.8 ± 7	20.7 (11-52)
4 h	209 ± 94*	26.7 ± 1.9	57.1 ± 10*	19.1 ± 8*	38.9 ± 8	20.0* (10-5
6 h	205 ± 11*	26.6 ± 1.9	55.5 ± 14*	19.4 ± 9	37.7 ± 8	21.9 (10-48)
8 h	148 ± 80*	26.8 ± 1.9	57.8 ± 14	20.6 ± 8	38.8 ± 8	21.9 (10-49)
Mixed hyperlipemia						
0 h	211 ± 43	25.4 ± 1.1	43.6 ± 11	11.5 ± 3	32.2 ± 9	11.4 (8-25)
4 h	402 ± 99*	24.7 ± 1.3*	41.3 ± 11*	9.2 ± 2	32.2 ± 8	10.7* (6-21)
6 h	460 ± 107*	24.7 ± 1.4*	39.7 ± 10*	8.5 ± 2*	31.1 ± 8	10.0* (6-21)
8 h	371 ± 123*	24.8 ± 3.5	41.3 ± 11*	10.0 ± 3	31.3 ± 10	10.5 (6-22)

Abbreviations: HDL-C, HDL cholesterol; HDL_2-C, HDL_2 cholesterol; HDL_3-C, HDL_3 cholesterol.
* $P < .05$ *v* baseline values.

6th hours (Fig 1). In women with hypercholesterolemia, triglyceride levels peaked at the 4th and 6th hours, with a concomitant decrease in HDL and HDL_2 cholesterol levels. Lp(a) had a significant decrease after 4 hours, and no variation in LDL size was observed. In normolipemic subjects, triglyceride levels increased at the 4th and 6th hours. A concomitant decrease in HDL cholesterol level was observed at the 6th hour. Lp(a) levels showed a concomitant decrease at the 4th and 6th hours. No other significant variations in HDL_2 and HDL_3 cholesterol levels or LDL size after the fat load were observed.

The incremental triglyceride AUC was greater in women with mixed hyperlipemia (1,326 ± 372 mg · dL^{-1} · h^{-1}) than in normal women (484 ± 384 mg · dL^{-1} · h^{-1}; $P < .0001$) and in women with hypercholesterolemia (473 ± 223 mg · dL^{-1} · h^{-1}; $P < .0001$). The differences remained significant after adjustment for baseline differences among groups in body mass index and insulin levels ($P < .003$ *v* controls; $P < .001$ *v* hypercholesterolemia). No differences in triglyceride incremental AUC were observed between hypercholesterolemic and normolipemic subjects. The allelic distribution of lipoprotein lipase *Hin*dIII polymorphism did not differ in the three groups ($P = .20$; Table 1). When the study population was divided on the basis of the presence or absence of at least one H^+ allele, triglyceride incremental AUC was significantly higher in H^+ allele carriers (n = 43, 801 ± 79 mg · dL^{-1} · h^{-1}) than in subjects with H^-/H^- genotype (n = 7, 393 ± 74 mg · dL^{-1} · h^{-1}; $P < .01$).

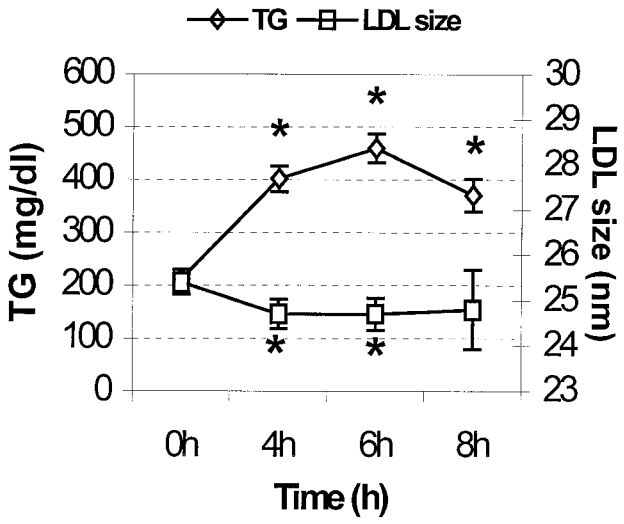

Fig 1. Postprandial serum triglyceride (TG) level and LDL particle size in 16 postmenopausal women affected by mixed hyperlipemia. Error bars represent SEM. * $P < .05$ compared with fasting values.

Using multiple linear regression analysis, we tested the independent relationship of several variables to triglyceride incremental AUC in the whole study population. Fasting insulin ($P < .0001$) and triglyceride ($P < .03$) levels and an elevated waist-hip ratio ($P < .04$) were all independent predictors of a greater incremental AUC. The resulting equation was triglyceride incremental AUC (mg · dL^{-1} · h^{-1}) = −708 + (23.5 × insulin [mU/L]) + (1.91 × triglycerides [mg/dL]) + (1,518 × waist-hip ratio). Overall, 74% of the observed variation in triglyceride incremental AUC was explained by the model (multiple $r = 0.86$). Age, body mass index, HDL and HDL_2 cholesterol levels, LDL size, and Lp(a) level failed to enter the multivariate equation.

DISCUSSION

The main finding of the present study is that postprandial lipid changes after a standardized oral fat-loading test showed marked differences in hyperlipemic and normolipemic postmenopausal women. Indeed, subjects with mixed hyperlipemia had a greater postprandial triglyceride response than hypercholesterolemic women and normolipemic control subjects. This result confirms and extends to the female sex previous studies reporting exaggerated postprandial triglyceridemia in men with endogenous hypertriglyceridemia,[19] which is largely attributable to increased retention of large VLDL particles as a

consequence of a removal defect.[20] However, a decreased chylomicron clearance capacity has also been observed in postmenopausal women because of the lack of endogenous estrogen.[21]

The postprandial triglyceride increase in women with mixed hyperlipemia was mirrored by a concomitant decrease in HDL and HDL_2 cholesterol and plasma Lp(a) concentrations. Normal and hypercholesterolemic women showed a significant decrease in HDL cholesterol level and a transient reduction in plasma Lp(a) levels. In this regard, Westerveld et al reported reduced plasma HDL cholesterol levels 3 to 8 hours after ingestion of an oral fat load in normolipemic postmenopausal women.[12] Moreover, an inverse relationship has been reported between fasting Lp(a) and triglyceride levels, suggesting that Lp(a) could form a metastable complex with triglyceride-rich lipoproteins, which could be removed at a higher rate,[22,23] thus providing a possible explanation for the postprandial decrease in plasma Lp(a) levels.

We also found a transient postprandial decrease in LDL particle size in women with mixed hyperlipemia (Fig 1), but not in hypercholesterolemic and normolipemic subjects. Fasting small LDL particles have been considered predictive of postprandial hyperlipemia,[24] but to our knowledge this is the first study to document a transient reduction of LDL particle size during a fat-loading test. Our findings suggest that a moderate postprandial increase in plasma triglyceride levels, as observed in normal and hypercholesterolemic women, may not be sufficient to induce a significant decrease of LDL particle size. In contrast, a more substantial degree of postprandial hypertriglyceridemia, as observed in subjects with mixed hyperlipemia, is able to shift the distribution of circulating LDL toward smaller and denser species. In addition, a significant univariate correlation was found between serum triglyceride and fasting insulin levels and LDL size, both in the fasting and the postprandial states (results not shown). Thus, our data provide support for the notion that serum triglycerides[25] and insulin[26] are important determinants of the distribution of LDL subfractions.

In the present study, postmenopausal women with mixed hyperlipemia showed higher fasting insulinemia and several markers of the insulin-resistance syndrome, including greater body mass index and waist-hip ratio, lower HDL cholesterol level, and smaller LDL size than in normal and hypercholesterolemic subjects. The combination of multiple markers of insulin resistance in patients with mixed hyperlipemia is well documented[27-29] and might have influenced the postprandial triglyceride response in our study. However, triglyceride incremental AUC remained significantly greater in women with mixed hyperlipemia than in the other two groups after adjustment for body mass index and fasting insulin, thus supporting the view of an independent association between fasting hyperlipemia and postprandial hypertriglyceridemia.

In our study, fasting insulinemia and waist-hip ratio were both independent determinants of triglyceride incremental AUC, along with fasting triglyceride levels. This finding confirms previous studies, carried out in men or in combined groups of men and women with an age distribution including both premenopausal and postmenopausal women, in which insulinemia[29,30] and abdominal fat accumulation[31] were both determinants of postprandial triglyceride response. Taken together, these data support the view that fasting hyperinsulinemia and visceral obesity, which may both be considered as markers of insulin resistance,[32] may contribute to postprandial hyperlipemia, probably through an increase in postprandial delivery of fatty acids to the circulation.[33,34]

We also assessed the role of *Hin*dIII polymorphism of lipoprotein lipase. Lipoprotein lipase is a key enzyme involved in the first catabolic step of triglyceryde-rich lipoproteins in plasma, and different mutations and polymorphisms have been described that impair the function of the enzyme.[35] *Hin*dIII polymorphism of lipoprotein lipase plays an important role in the determination of basal triglyceridemia, with a dose-dependent effect. Data on the relation between *Hin*dIII polymorphism and postprandial lipemia are scarce. In the only report on this topic,[36] no significant correlation was found between the presence of the H^+ allele and postprandial triglyceride levels. In our study, the distribution of *Hin*dIII genotypes did not differ in the three groups; however, the subjects with at least one H^+ allele had a greater triglyceride incremental AUC than H^- subjects, thus indicating a possible influence of H^+ allele on postprandial lipemia. Additional data are needed to support the hypothesis that *Hin*dIII lipoprotein lipase polymorphism can influence postprandial lipemia.

In summary, the present results indicate that after a fat-loading test, both normolipemic and hyperlipemic postmenopausal women are characterized by multiple disturbances of the lipoprotein metabolism, including abnormal elevation of triglyceride levels and reduction in HDL cholesterol and HDL_2 cholesterol concentrations. Postmenopausal women with mixed hyperlipemia exhibited an amplification of these abnormalities and a transient reduction in LDL particle size, which might be additional markers of cardiovascular risk. Fasting plasma triglyceride levels, insulin levels, and abdominal fat accumulation were independent determinants of these metabolic disturbances. The presence of other features of the insulin resistance syndrome, including reduced HDL cholesterol level, smaller LDL particle size, and lipoprotein lipase *Hin*dIII polymorphism, could contribute to the deterioration of the postprandial lipemic response in these subjects.

REFERENCES

1. Cohn JS: Postprandial lipid metabolism. Curr Opin Lipidol 5:185-190, 1994

2. Zilversmit DB: Atherogenesis: A postprandial phenomenon. Circulation 60:473-485, 1979

3. Simons LA, Dwyer T, Simons J, et al: Chylomicrons and chylomicron remnants in coronary artery disease: A case-control study. Atherosclerosis 65:181-189, 1987

4. Groot PH, van Stiphout WA, Krauss XH, et al: Postprandial lipoprotein metabolism in normolipidemic men with and without coronary artery disease. Arterioscler Thromb 11:653-662, 1991

5. Patsch JR, Miesenbock G, Hopferwieser T, et al: Relation of triglyceride metabolism and coronary artery disease. Studies in the postprandial state. Arterioscler Thromb 12:1336-1345, 1992

6. Meyer E, Westerveld HT, de Ruyter-Meijstek FC, et al: Abnor-

mal postprandial apolipoprotein B-48 and triglyceride responses in normolipidemic women with greater than 70% stenotic coronary artery disease: A case-control study. Atherosclerosis 124:221-235, 1996

7. Ginsberg HN, Blaner W, Jones J, et al: Postprandial lipemia is a predictor of the presence of coronary artery disease in males but not females. Circulation 88:I-363, 1993 (abstr)

8. van Beek AP, de Ruijter-Heijstek FC, Erkelens DW, et al: Menopause is associated with reduced protection from postprandial lipemia. Arterioscler Thromb Vasc Biol 19:2737-2741, 1999

9. Barrett-Connor E, Bush TL: Estrogen and coronary heart disease in women. JAMA 265:1861-1867, 1991

10. van der Schouw YT, van der Graaf Y, Steyerberg EW, et al: Age at menopause as a risk factor for cardiovascular mortality. Lancet 347:714-718, 1996

11. Colditz GA, Willett WC, Stampfer MJ, et al: Menopause and the risk of coronary heart disease in women. N Engl J Med 316:1105-1110, 1987

12. Westerveld HT, Meijer E, Erkelens DW, et al: Postprandial reduction in high-density lipoprotein cholesterol concentrations in postmenopausal women: Improvement by 17beta-estradiol. Metabolism 45:827-832, 1996

13. Schaefer EJ, Genest JJ, Jr., Ordovas JM, et al: Familial lipoprotein disorders and premature coronary artery disease. Atherosclerosis 108:S41-S54, 1994 (suppl)

14. Patsch JR, Karlin JB, Scott LW, et al: Inverse relationship between blood levels of high density lipoprotein subfraction 2 and magnitude of postprandial lipemia. Proc Natl Acad Sci USA 80:1449-1453, 1983

15. Bernhard F, Patsch JR: Strategies and methods for the assessment of disturbed postprandial lipid metabolism. Curr Opin Lipidol 4:428-433, 1993

16. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 18:499-502, 1972

17. Rainwater DL, Andres DW, Ford AL, et al: Production of polyacrylamide gradient gels for the electrophoretic resolution of lipoproteins. J Lipid Res 33:1876-1881, 1992

18. Ahn YI, Kamboh MI, Hamman RF, et al: Two DNA polymorphisms in the lipoprotein lipase gene and their associations with factors related to cardiovascular disease. J Lipid Res 34:421-428, 1993

19. Karpe F, Steiner G, Olivecrona T, et al: Metabolism of triglyceride-rich lipoproteins during alimentary lipemia. J Clin Invest 91:748-758, 1993

20. Karpe F, Hellenius ML, Hamsten A: Differences in postprandial concentrations of very-low-density lipoprotein and chylomicron remnants between normotriglyceridemic and hypertriglyceridemic men with and without coronary heart disease. Metabolism 48:301-307, 1999

21. Westerveld HT, Kock LA, van Rijn HJ, et al: 17 beta-Estradiol improves postprandial lipid metabolism in postmenopausal women. J Clin Endocrinol Metab 80:249-253, 1995

22. Bartens W, Rader DJ, Talley G, et al: Decreased plasma levels of lipoprotein(a) in patients with hypertriglyceridemia. Atherosclerosis 108:149-147, 1994

23. Walek T, von Eckardstein A, Schulte H, et al: Effect of hypertriglyceridaemia on lipoprotein(a) serum concentrations. Eur J Clin Invest 25:311-316, 1995

24. Karpe F, Tornvall P, Olivecrona T, et al: Composition of human low density lipoprotein: Effects of postprandial triglyceride-rich lipoproteins, lipoprotein lipase, hepatic lipase and cholesteryl ester transfer protein. Atherosclerosis 98:33-49, 1993

25. Tan CE, Foster L, Caslake MJ, et al: Relations between plasma lipids and postheparin plasma lipases and VLDL and LDL subfraction patterns in normolipemic men and women. Arterioscler Thromb Vasc Biol 15:1839-1848, 1995

26. Festa A, D'Agostino R Jr, Mykkanen L, et al: LDL particle size in relation to insulin, proinsulin, and insulin sensitivity. The Insulin Resistance Atherosclerosis Study. Diabetes Care 22:1688-1693, 1999

27. Reaven GM, Lerner RL, Stern MP, et al: Role of insulin in endogenous hypertriglyceridemia. J Clin Invest 46:1756-1767, 1967

28. McKane WR, Stevens AB, Woods R, et al: The assessment of hepatic and peripheral insulin sensitivity in hypertriglyceridemia. Metabolism 39:1240-1245, 1990

29. Axelsen M, Smith U, Eriksson JW, et al: Postprandial hypertriglyceridemia and insulin resistance in normoglycemic first-degree relatives of patients with type 2 diabetes. Ann Intern Med 131:27-31, 1999

30. Jeppesen J, Hollenbeck CB, Zhou MY, et al: Relation between insulin resistance, hyperinsulinemia, postheparin plasma lipoprotein lipase activity, and postprandial lipemia. Arterioscler Thromb Vasc Biol 15:320-324, 1995

31. Taira K, Hikita M, Kobayashi J, et al: Delayed post-prandial lipid metabolism in subjects with intra-abdominal visceral fat accumulation. Eur J Clin Invest 29:301-308, 1999

32. Laakso M: How good a marker is insulin level for insulin resistance? Am J Epidemiol 137:959-965, 1993

33. Frayn KN: Insulin resistance and lipid metabolism. Curr Opin Lipidol 4:197-204, 1993

34. Couillard C, Bergeron N, Prud'homme D, et al: Postprandial triglyceride response in visceral obesity in men. Diabetes 47:953-960, 1998

35. Lalouel JM, Wilson DE, Iverius PH: Lipoprotein lipase and hepatic triglyceride lipase: molecular and genetic aspects. Curr Opin Lipidol 3:86-95, 1992

36. Syvanne M, Talmud PJ, Humphries SE, et al: Determinants of postprandial lipemia in men with coronary artery disease and low levels of HDL cholesterol. J Lipid Res 38:1463-1472, 1997