Normal Postprandial Lipemia in Men With Low Plasma HDL Concentrations

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To examine the relation between postprandial lipemia and high density lipoprotein (HDL) concentrations, we measured the plasma triglyceride and retinyl palmitate responses to 50-g fat meals of 1) 25 men with low HDL cholesterol concentrations (<36 mg • dl⁻¹) and normal fasting triglyceride concentrations, 2) 25 men with normal HDL cholesterol (>40 mg • dl⁻¹) and normal fasting triglyceride concentrations, and 3) 20 men with mild to moderate fasting hypertriglyceridemia (250-347 mg • dl⁻¹). The average magnitude of postprandial lipemia induced by the fat meals was markedly higher in the hypertriglyceridemic men (593±311 mg • dl⁻¹ • 8 hr) than in either of the normolipidemic groups. In normotriglyceridemic men with low HDL cholesterol, mean postprandial lipemia (283±158 mg • dl⁻¹ • 8 hr) was similar to the corresponding value of men with normal HDL (283±150 mg • dl⁻¹ • 8 hr). Postprandial plasma retinyl palmitate concentrations, which reflect chylomicron remnant metabolism, also were similar in normal-HDL and low-HDL groups. These data suggest that defects in chylomicron-triglyceride clearance that give rise to excess postprandial lipemia are not a common occurrence in normolipidemic men with low HDL cholesterol concentrations. Accordingly, the low HDL cholesterol concentrations measured in the normotriglyceridemic men in this study must be attributable to factors other than an exaggerated postprandial lipemia. (Arteriosclerosis and Thrombosis 1992;12:972-975)

KEY WORDS • triglycerides • high density lipoproteins • postprandial lipemia

Several studies have indicated that the plasma concentration of high density lipoproteins (HDLs) is an index of coronary risk (see Reference 1 for review). Because coronary heart disease remains a primary cause of morbidity in Western populations, the factors that determine the plasma concentrations of HDL have become a subject of considerable medical interest. Observations in patients with genetic deficiency states of hepatic lipase, 2 lipoprotein lipase, 3 cholesterol ester transfer protein, 4-5 and lecithin cholesterol acyltransferase 6 have revealed an important role for each of these enzymes in HDL metabolism, but the extent to which HDL concentrations are modulated by physiological variations in the activities of these enzymes is not known.

The metabolism of HDL is closely linked to the intravascular processing of the triglyceride-rich lipoproteins. 7 This relation is illustrated by the lipoprotein profiles of people with hypertriglyceridemia, which are characterized by low HDL cholesterol concentrations, and by epidemiological studies, which have consistently indicated a negative correlation between HDL and fasting plasma triglyceride concentrations. In most studies the correlation coefficient between these parameters is too low to indicate triglyceride levels as the primary determinant of HDL concentrations. 8 However, because most people spend much of each day in a postprandial state, measurements of fasting plasma triglyceride concentrations may not be an accurate reflection of the average 24-hour triglyceride level. Indeed, considerably stronger correlation coefficients have been reported between HDL concentrations (particularly HDL₂) and measurements of triglyceride levels in the postprandial state. 10,11 Accordingly, it has been postulated that low HDL concentrations in normolipidemic men are caused by latent defects in triglyceride catabolism, which become apparent only on challenge with a dietary fat load. 11

Recently, we reported that some endurance athletes who exhibit minimal postprandial lipemia in response to fatty meals have relatively low HDL cholesterol concentrations. 12 These data indicate that efficient triglyceride clearance is not sufficient to ensure high HDL cholesterol levels, and factors unrelated to triglyceride clearance may be responsible for substantial variations in HDL cholesterol levels. Because endurance athletes are a highly select group, however, the clinical relevance of these findings is not clear. The present study therefore was undertaken to determine whether postprandial lipemia is impaired in normotriglyceridemic men with low HDL cholesterol concentrations. To this end, we compared the plasma triglyceride responses to meals containing 50 g fat in men with HDL cholesterol concentrations ≤35 mg • dl⁻¹ with those of men whose HDL cholesterol concentrations were >40 mg • dl⁻¹.

Methods

The procedures used in this study were approved by the appropriate institutional review boards.
Subjects

Seventy men aged between 32 and 71 years were recruited from outpatient clinics at the Veterans Affairs Medical Center at Dallas. The men were divided into three groups according to plasma lipid determinations made on 3 separate days. Twenty-five men who had HDL cholesterol levels ≤35 mg • dl⁻¹ and fasting plasma triglyceride levels <200 mg • dl⁻¹ comprised the low-HDL group. Twenty-five men who had HDL cholesterol levels >40 mg • dl⁻¹ and fasting plasma triglyceride levels <200 mg • dl⁻¹ were designated the normal-HDL group. The other 20 men had fasting triglyceride levels between 250 and 350 mg • dl⁻¹ and were designated hypertriglyceridemic. The mean values for age, height, weight, and weight were similar in the three groups (see Table 1). None of the men were diabetic, and none had taken lipid-lowering medication before the study. Five men in the low-HDL group and five in the normal-HDL group smoked cigarettes.

Procedures

All procedures were performed in the metabolic ward of the Veterans Affairs Medical Center in Dallas. The men abstained from alcohol (for 72 hours) and from vigorous exercise, food, and beverages except water (for 12 hours) before each test. After an overnight fast, each man consumed 120 ml heavy whipping cream (50 g fat), 5 g chocolate powder, and 120 ml water. Vitamin A (50,000 units; Aquasol, Armour Pharmaceutical, Kankakee, Ill.) was added to the meal to label the chylomicron remnants. Blood samples were drawn into vacuum tubes containing EDTA before and at hourly intervals for 8 hours after the meal. In general, the fat meals were well tolerated, and none of the men had diarrhea or other symptoms of fat malabsorption.

Analytical Methods

The cholesterol contents of the total HDL fraction (HDL₇₀) and the HDL₃ subfraction were measured by using the precipitation methods described by Gidez et al.¹³ HDL₂ cholesterol was calculated from the difference between HDL₇₀ cholesterol and HDL₃ cholesterol. Plasma total cholesterol, HDL₇₀ cholesterol, and plasma triglyceride concentrations were determined by enzyme assay using commercial kits (cholesterol reagent No. 236691, Boehringer Mannheim, Indianapolis, Ind., and triglyceride reagent No. 338-50, Sigma Chemical Co., St. Louis, Mo.). Vitamin A palmitate was measured in methanol-hexane extracts of whole plasma by reversed-phase high-performance liquid chromatography as described previously.¹² Intra-assay variation of the plasma lipid parameters were cholesterol, <2%; triglyceride, <2%; HDLr cholesterol, <5%; HDL₃ cholesterol, <8%; and vitamin A palmitate, <6%. Interassay variations in plasma lipid values calculated from a pooled plasma standard included in each assay were <5% for cholesterol, triglyceride, and HDL₇₀ cholesterol.

Statistical Methods

Postprandial lipemia was defined as the area under the curve described by serum triglyceride concentrations (normalized to the 0-hour value) plotted against time. This area was calculated by using the trapezoidal rule. Statistical tests were performed with the BMDP computer program (BMDP Statistical Software Inc., Los Angeles, Calif.). The fasting lipid values used for statistical analyses were those obtained on the morning of the oral fat tolerance test. For each parameter, equality of variance was tested by Levene's F test. Each mean value measured in the normal-HDL group was compared with the corresponding values in the low-HDL group by using both an unpaired t test and the Mann-Whitney rank test. In every case, the same result was obtained from both tests; therefore, only the results obtained with the t tests will be considered here. The mean values for age, height, weight, postprandial lipemia, and postprandial retinyl palmitate of the low-HDL group and the hypertriglyceridemic group were compared by unpaired t tests. In addition, each of these parameters was compared among all three groups by one-way analysis of variance. In each case, the outcome of the two tests was the same; therefore, only the results of the t test were considered further.

Results

Fasting Plasma Lipids

The mean fasting concentration of plasma total cholesterol was lower in the low-HDL group than in the
Postprandial Triglyceride and Retinyl Palmitate Concentrations

The area under the curve of postprandial plasma triglyceride concentrations (postprandial lipemia) ranged from 42 to 720 mg·dl⁻¹·8 hr in men with low HDL levels and from 66 to 501 mg·dl⁻¹·8 hr in men with normal HDL levels. The mean postprandial lipemia of men with low HDL cholesterol was similar to that of men with normal HDL cholesterol levels (see Figure 1). The mean postprandial lipemia of all 50 normolipidemic men in the study was 293±142 mg·dl⁻¹·8 hr (mean±SD). Two of the men in the low-HDL group and none of the men in the normal-HDL group had postprandial lipemia in excess of two standard deviations above the mean. The mean area under the curve of postprandial plasma retinyl palmitate concentrations was similar in the low-HDL group (6,074±2,880 ng·ml⁻¹·8 hr) and the normal-HDL group (5,460±2,589 ng·ml⁻¹·8 hr). The hypertriglyceridemic men exhibited considerable heterogeneity in their plasma triglyceride responses to the fat meal. On average, postprandial lipemia (see Figure 1) and postprandial retinyl palmitate (9,025±3,225 ng·ml⁻¹·8 hr) concentrations were significantly higher in the hypertriglyceridemic men than in the other two groups, but in some hypertriglyceridemic men the magnitude of postprandial lipemia was clearly within the normal range.

Discussion

Compelling evidence has been provided for a metabolic interaction between HDL and triglyceride-rich lipoproteins, and it seems likely that the plasma levels of HDL are determined, at least in part, by the concentration of triglycerides in the circulation. Certainly the enzymes involved in triglyceride metabolism also affect HDL concentrations. Patsch et al.⁷ have reported a strong inverse relation between postprandial lipemia and HDL cholesterol concentrations in normal individuals. Accordingly, they suggested that subtle defects in triglyceride clearance cause excess postprandial lipemia that may be responsible for low HDL concentrations in men whose triglyceride concentrations are normal under fasting conditions. The importance of these defects as a cause of low HDL cholesterol is not known because the postprandial plasma triglyceride excursions of normotriglyceridemic men with low HDL concentrations have not been systematically evaluated.

In the present study, we have approached this question by comparing the plasma triglyceride responses to a standard fat meal of normolipidemic men with HDL cholesterol levels ≤35 mg·dl⁻¹ with those of normolipidemic men with HDL levels >40 mg·dl⁻¹. The difference in HDL levels between the two groups was due largely to a relative deficiency of HDL₂ cholesterol in the low-HDL group. The mean value for postprandial lipemia was similar in the two groups, indicating that defective clearance of chylomicron-triglycerides is not a common cause of low HDL levels in the men in this study. It is possible that the failure to find a significant difference in postprandial lipemia between the two groups reflects a lack of statistical power, rather than the absence of a true difference in postprandial lipemia.

The difference in the mean values of postprandial lipemia between the two groups represents a small fraction (about 7%) of the mean value, however, and it seems most unlikely that a difference in postprandial lipemia of this magnitude could be responsible for the large difference in HDL cholesterol levels between the two groups. Furthermore, 23 men with low HDL levels had postprandial lipemia in the same range as the men with normal HDL levels (<501 mg·dl⁻¹·8 hr); therefore, the low HDL levels in these men must be attributed to factors other than excess postprandial lipemia. Postprandial plasma retinyl palmitate concentrations, an index of chylomicron remnant clearance, were not significantly different between the two groups. This finding suggests that the low HDL levels in the men in this study are not due to defective clearance of chylomicron remnants.

Two of the men in the low-HDL group had levels of postprandial lipemia >560 mg·dl⁻¹·8 hr, which was more than two standard deviations above the mean value of the 50 normal men in the study. In these two individuals, the magnitude of postprandial lipemia was, respectively, 21% and 44% greater than that of any of the men with normal HDL levels; defective clearance of chylomicron-triglycerides thus may have been a cause of low HDL levels in these two men.

It might be argued that the lack of evidence for defective chylomicron-triglyceride clearance in the men
with low HDL levels in this study is an artifact resulting from insufficient resolution of the testing procedure. This possibility seems unlikely for the following reasons. First, the interindividual variation in postprandial lipemia spanned a 10-fold range in the normolipidemic men in this study. Because the absorption of dietary fats is essentially complete in normal men and because none of the men showed any symptoms of fat malabsorption, the wide range of postprandial triglyceride values almost certainly reflects interindividual differences in triglyceride clearing ability. In support of this contention, we have shown previously that the plasma triglyceride responses to meals similar to those used in the present study are inversely related to the rate of clearance of an intravenously administered fat emulsion in normolipidemic men. Second, in a previous study we found that discrimination between men with enhanced chylomicron clearance (endurance athletes) and those with normal clearance (normolipidemic sedentary men) could be achieved as clearly with 40-g fat loads as with 140-g fat loads. To determine whether the present testing procedure provides sufficient resolution to detect mild defects in triglyceride metabolism, we examined the postprandial plasma triglyceride and retinyl palmitate responses of 20 men with mild to moderate hypertriglyceridemia (fasting plasma triglyceride between 250 and 350 mg·dl⁻¹). The mean magnitude of postprandial lipemia was significantly higher in the hypertriglyceridemic men than in either of the normolipidemic groups. Given these considerations, it seems likely that the testing procedure used in this study would detect defects in chylomicron clearance of sufficient magnitude to cause low HDL levels. Therefore, the observation that postprandial lipemia is not demonstrably abnormal in 23 of the 25 hypoalphalipoproteinemic men in this study suggests that subtle defects in chylomicron clearance are not a common cause of low HDL levels. The hypertriglyceridemic group also indicates the concentrations of plasma triglycerides that are required to produce low HDL concentrations. In this study, HDL cholesterol levels were similar in the low-HDL and in the hypertriglyceridemic groups. Because both fasting and postprandial triglyceride levels were approximately two-fold higher in hypertriglyceridemic men than in normolipidemic men with low HDL levels, the low HDL cholesterol concentrations in the latter group must be attributable factors other than plasma triglyceride levels.

A positive correlation between fasting plasma triglyceride concentrations and postprandial lipemia has been found in several previous studies, and Weintraub et al. reported greatly elevated postprandial lipemia in men with fasting triglyceride concentrations between 315 and 2,758 mg·dl⁻¹ (mean, 808±679 mg·dl⁻¹). In the present study, the hypertriglyceridemic group was limited to individuals with apparently mild defects in triglyceride metabolism. In this group postprandial plasma triglyceride excursions were highly heterogeneous, and in some individuals the magnitude of postprandial lipemia was clearly well within the normal range. A similar heterogeneity in the postprandial responses of hypertriglyceridemic patients was reported previously by Grundy and Mok. This finding suggests that some individuals with moderate fasting hypertriglyceridemia maintain the ability to clear chylomicron-triglycerides from the circulation at a normal rate.

Hypertriglyceridemia in these men may therefore be due to increased production of endogenous triglyceride-rich lipoproteins or to the production of endogenous triglyceride-rich lipoproteins that are resistant to lipolysis in the circulation, rather than to a defect in intra-vascular lipolytic capacity.

Acknowledgments

We gratefully acknowledge the excellent technical assistance of Richard Cornett and Kathleen Gray of the Metabolic Ward, Veterans Affairs Medical Center at Dallas, and Anh Nguyen and Kathy Schutt of the Center for Human Nutrition, Southwestern Medical Center at Dallas.

References

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doi: 10.1161/01.ATV.12.8.972

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