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Fatty acid oxidation in normotriglyceridemic men

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BACKGROUND: Moderate hypertriglyceridemia is frequently associated with central obesity, insulin resistance, and atherogenic dyslipidemia. We showed previously that moderately obese men with hypertriglyceridemia have reduced fatty acid oxidation postabsorptively and postprandially. In the present study, we examined the oxidation of fatty acids in normotriglyceridemic men.

OBJECTIVE: The study objective was to determine the relation between plasma triglyceride levels and fatty acid oxidation in normotriglyceridemic men.

STUDY DESIGN: Twenty-four healthy, nonobese White and African American men participated in a cross-sectional metabolic study for evaluation of fatty acid oxidation. Men were healthy, and none took hypolipidemic or hypoglycemic agents. They ingested 200 mg of fat/hour/kg of body weight over a 10-hour period. Plasma levels of triglyceride, nonesterified fatty acids, 3-β-hydroxybutyrate, insulin, and glucagon were measured postabsorptively and postprandially. Chylomicron-triglyceride halflife was also calculated.

RESULTS: Nonobese White and African-American men had similar anthropometry, levels of plasma triglyceride, lipoprotein cholesterol, nonesterified fatty acids, 3-β-hydroxybutyrate, insulin, and glucagon postabsorptively and postprandially. For the group as a whole, there was a positive and significant correlation between plasma fatty acids and 3-β-hydroxybutyrate and an inverse association between plasma triglyceride levels and 3-β-hydroxybutyrate at baseline. All subjects had increased levels of metabolites of interest postprandially. However, there were no significant changes in plasma insulin, glucagon, or the ratio of insulin to glucagon. The postprandial levels of 3-β-hydroxybutyrate correlated positively with nonesterified fatty acids and inversely with the half-life of chylomicron triglyceride.

CONCLUSION: Normotriglyceridemia is strongly associated with oxidation of fatty acids by the liver suggesting the possibility that the fatty acid oxidation pathway is a potential target of intervention to prevent hypertriglyceridemia and concomitant fatty liver.

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Introduction

Hypertriglyceridemia is a component of atherogenic dyslipidemia and the metabolic syndrome.[1] The latter imparts increased risk for atherosclerotic cardiovascular

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disease. Fasting triglycerides are carried by apolipoprotein B-containing triglyceride-rich lipoproteins. These lipoproteins almost certainly contribute significantly to atherosclerotic cardiovascular disease risk accompanying atherogenic dyslipidemia. The mechanisms underlying hypertriglyceridemia continue to be the subject of great interest. The association of hypertriglyceridemia with the metabolic syndrome suggests important roles for obesity (particularly abdominal obesity), elevated nonesterified fatty acids (NEFA), and accumulation of ectopic fat in the liver. This is exemplified by the so-called "hypertriglyceridemia-waist" syndrome.[2]

One defense against ectopic fat accumulation and hypertriglyceridemia may be increased oxidation of fatty acids in the liver. We have previously shown that moderately obese patients with hypertriglyceridemia have a reduced level of 3-β-hydroxybutyrate.[3] The latter is a measure of fatty acid oxidation.[4,5] This association suggests that failure to enhance fatty acid oxidation with an increased fat load on the liver leads to a shunting of excess TGs into triglyceride-rich lipoproteins. In the present study, we examined whether fatty acid oxidation correlates with fasting triglycerides (TG) levels over the normal range. We also examined whether fatty acid oxidation increases in response to oral fat loading; if so, this could also protect against ectopic fat accumulation in the liver.

Study design and methods of procedure

This study was designed to examine fatty acid oxidation in healthy, nonobese (waist girth $<$ 90 cm) men with normal plasma TG ($<$150 mg/dL). Subjects were self-identified as White (Europid) or African American. The study volunteers were seen at the Clinical Translational Research Center (CTRC) of the University of Texas Southwestern Medical Center at Dallas where the study was conducted. The study was approved by the Institutional Review Boards for Investigation in Humans of the University of Texas Southwestern Medical Center and the VA North Texas Health Care System. All enrollees were from the Dallas-Fort Worth area and were seen at the CTRC.

Men were evaluated for inclusion into the study, and the screening procedures involved a brief clinical history and physical examination, anthropometry, measurement of blood pressure and vital signs and a comprehensive metabolic panel measured after a 12 hour fast. Subjects were excluded from the study if they had history of hypertriglyceridemia, liver disease, or persistent elevation of transaminases ($>$1.5 $\times$ ULN) or renal disease, infectious disease, diabetes mellitus, uncontrolled hypertension, hypothyroidism, or endocrine disorders that precluded participation into the study. Subjects with history of heart disease also were excluded from the study. None of the study volunteers were taking hypolipidemic agents or supplements affecting levels of plasma triglycerides at the time of the study. None reported history of excess alcohol intake.

Forty-three healthy males were recruited into the study. They were identified through advertisements from the Dallas-Fort Worth community. Sixteen men did not qualify to participate in the study, and 3 were withdrawn at their request or at the investigators' initiative for lack of compliance. Twenty-four men (10 white and 14 African Americans) completed the study.

Subjects who qualified for the study were invited for a second visit to do an extended fat-tolerance test. The test was designed to evaluate beta-oxidation of fatty acids by simultaneously measuring 3-β-hydroxybutyrate, NEFA, and plasma TG at baseline (postabsorptive state) and during intake of an oral fat challenge (postprandially). Briefly, this test involved an oral administration of heavy cream (dairy heavy cream, 40% [w/v] fat emulsion, with a ratio of polyunsaturated to saturated fat [P/S ratio] of 0.06 and containing 0.001% [w/v] cholesterol and 2.8% [w/v] carbohydrates). The drink was divided in hourly doses according to body weight estimating a rate of fat administration of 200 mg/kg of body weight per hour given over a 10-hour period. Arterialized blood samples were collected from a hand vein that had been pre-warmed in an isothermal box as detailed previously.[3] The blood samples were drawn at -30, -15, 0, 30, 60 minutes and hourly for 9 additional hours. Levels of fasting and postprandial insulin and glucagon were measured by radioimmunoassay (Millipore Co, Boston, MA). Chylomicron TG was defined as the TG increment over baseline TG during dietary fat loading.

The key parameters measured in the study included baseline and postprandial levels of plasma TG, NEFA, 3-β-hydroxybutyrate, insulin, and glucagon. Previous studies have shown that during continuous feeding of dietary fat a steady state in plasma TG is achieved from 5 to 10 hours, and this observation was reproduced in this study (Fig. 1); for this reason, hourly values during this period were averaged and represented postprandial values. Data for independent variables (anthropometric and metabolic) are summarized as means $\pm$ SD. Comparisons of means for fasting baseline to postprandial levels of 3-β-hydroxybutyrate, nonesterified fatty acids and TGs were done by 2-sample *t* test. Data not normally distributed were compared

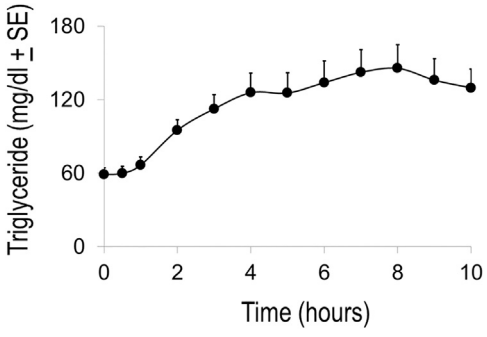

Figure 1 Plot of plasma triglyceride levels during an extended fat tolerance test for the group as a whole. This curve shows the rise in plasma triglyceride levels and the eventual attainment of a steady state.

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