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CLINICAL—LIVER, PANCREAS, AND BILIARY TRACT

Dissociation Between Intrahepatic Triglyceride Content and Insulin Resistance in Familial Hypobetalipoproteinemia

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BACKGROUND & AIMS: Hepatic steatosis is associated with insulin resistance, but it is not clear whether increased intrahepatic triglyceride (IHTG) content causes the resistance or is a marker. Subjects with familial hypobetalipoproteinemia (FHBL) have high levels of IHTG because of a genetic defect in hepatic export of triglycerides, and provide a unique cohort to study the relationship between steatosis and insulin sensitivity. **METHODS:** One group of lean subjects with normal IHTG content (2.2% ± 0.6% of liver volume) (n = 6), and 3 groups of overweight and obese subjects matched for body mass index, were studied: (1) normal IHTG content (3.3% ± 0.5%; n = 6), (2) high IHTG content (21.4% ± 2.6%) due to nonalcoholic fatty liver disease (NAFLD; n = 6), and (3) high IHTG content (18.1% ± 2.2%) due to FHBL (n = 3). A hyperinsulinemic-euglycemic clamp procedure, in conjunction with glucose tracer infusion, was used to determine multiorgan insulin sensitivity. **RESULTS:** Hepatic insulin sensitivity (reciprocal of glucose rate of appearance [μmol · kg fat-free mass^{-1} · min^{-1}] × insulin [mU/L]) was greatest in the Lean group (2.0 ± 0.4); it was the same among subjects with FHBL (0.8 ± 0.1) and the group with normal IHTG content, matched for body mass index (0.7 ± 0.1), but greater than the NAFLD group (0.3 ± 0.1) ($P < .01$). Muscle insulin sensitivity (percent increase in glucose uptake during insulin infusion) was greatest in the Lean group (576% ± 70%). Muscle insulin sensitivity was similar in subjects with FHBL and those with normal IHTG (319% ± 77%, 326% ± 27%, respectively), but greater than the NAFLD group (145% ± 18%) ($P < .01$). **CONCLUSIONS: Steatosis is dissociated from insulin resistance in FHBL, which suggests that increased IHTG content is a marker, not a cause, of metabolic dysfunction.**

Keywords: Steatosis; Insulin sensitivity; Obesity; Clamp.

Nonalcoholic fatty liver disease (NAFLD) is a common complication of obesity.[1] Excessive intrahepatic triglyceride (IHTG) content is associated with insulin-resistant glucose metabolism in both liver and skeletal muscle and impaired insulin-mediated suppression of lipolysis in adipose tissue.[2–6] In fact, we have found that IHTG is a better predictor of multiorgan insulin resistance than body mass index (BMI), percent body fat, and visceral fat mass.[7] However, it is not known whether excessive IHTG content causes insulin resistance or is simply a marker of systemic metabolic dysfunction.

Patients who have familial hypobetalipoproteinemia (FHBL) provide a unique opportunity for exploring the relationship between IHTG content and insulin action, because the genetic truncation of apolipoprotein B (apoB) impairs hepatic very-low density lipoprotein triglyceride (TG) export and causes an accumulation of IHTG.[8] The amount of IHTG in patients with FHBL is about a 3-fold higher than healthy volunteers matched on age, gender, and BMI.[9] The effect of steatosis induced by FHBL on insulin action is not clear because of limited and potentially conflicting data from previous studies.[10–12] In 1 study, insulin and glucose areas under the curve during an oral glucose tolerance test were ~50% greater in nonobese subjects with FHBL than healthy nonobese volunteers, but the differences between groups were not statistically significant.[10,11] Data from another study found that insulin resistance, assessed by using the homeostasis model of insulin resistance, in nonobese subjects with FHBL was similar to values obtained in

Abbreviations used in this paper: apoB, apolipoprotein B; BMI, body mass index; IHTG, intrahepatic triglycerides; FFM, fat-free mass; FHBL, familial hypobetalipoproteinemia; NAFLD, nonalcoholic fatty liver disease; Rd, rate of disappearance; TG, triglyceride; TTR, tracer-to-tracee ratio.

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healthy control subjects, and lower than more obese subjects with NAFLD.[12] We are not aware of any studies that evaluated specific organ insulin sensitivity in subjects with FHBL.

Therefore, the purpose of the present study was to determine whether increased IHTG content caused by a genetic defect in TG secretion is associated with multiorgan insulin resistance, as reported in subjects who have increased IHTG content as part of typical NAFLD. A hyperinsulinemic-euglycemic clamp procedure, in conjunction with stable isotopically labeled tracer infusion, was performed in overweight and obese subjects with FHBL and subjects matched on BMI who had either normal or increased IHTG content to assess hepatic and skeletal muscle insulin sensitivity. We hypothesized that insulin sensitivity would be better in subjects who have increased IHTG content because of FHBL than those who have typical NAFLD.

Materials and Methods

Subjects

Three groups of overweight and obese subjects participated in this study: (1) normal IHTG content (≤5.5% of liver volume) (n = 6, all women, age 43 ± 3.8 years), (2) excessive IHTG content (>10% of liver volume) due to NAFLD (n = 6, 2 men, 4 women, age 38.2 ± 5.9 years), and (3) excessive IHTG content (>10% of liver volume) with FHBL due to apoB gene heterozygosis (n = 3, 1 man, 2 women, age 59.7 ± 2.9 years). A 4th group consisted of lean healthy individuals with normal IHTG content (≤5.5% of liver volume) (n = 6, all women, age 56 ± 1.1 years). Fewer subjects were recruited to the FHBL group than the other groups because it is difficult to find eligible participants for this cohort. Subjects in the first 3 groups were matched on BMI and the NAFLD and FHBL groups were also matched on IHTG content. All subjects completed a comprehensive medical evaluation, which included a 2-hour oral glucose tolerance test. No subject had any history or evidence of liver disease other than NAFLD, consumed >20 g/day of alcohol, had impaired glucose tolerance, diabetes, or other serious illnesses. Subjects gave their written informed consent before participating in this study, which was approved by the Human Research Protection Office of Washington University School of Medicine.

Body Composition Analyses

Visceral adipose tissue mass and IHTG content were determined by using magnetic resonance imaging and magnetic resonance spectroscopy and (Siemens, Erlanger, Germany), as we described previously.[13] Fat mass and fat-free mass (FFM) were determined by using dual-energy x-ray absorptiometry (Hologic QDR 4500, Waltham, MA).

Hyperinsulinemic-Euglycemic Clamp Procedure

Subjects were admitted to the Clinical Research Unit at Washington University School of Medicine the night before the clamp procedure and consumed a standard meal at 1800 hours. After subjects fasted overnight, a catheter was inserted into an antecubital vein to infuse tracer, insulin, and dextrose. Another catheter was inserted into a contralateral radial artery to obtain blood samples. After a baseline blood sample was obtained to determine the background plasma glucose tracer-to-tracee ratio (TTR), a primed-continuous infusion of [6,6-$^2H_2$]glucose (priming dose: 22.5 μmol/kg; infusion rate: 0.25 $\mu mol \cdot kg^{-1} \cdot min^{-1}$) was initiated. At 210 minutes, an insulin infusion was started (initiated with a 2-step priming dose of 160 mU/m^2 per minute for 5 minutes, followed by 80 mU/m^2 per minute for 5 minutes) and maintained at a rate of 50 mU/m^2 per minute for 180 minutes. Dextrose (20%) was infused at a variable rate to maintain plasma glucose concentration at 100 mg/dL. The dextrose solution was enriched with [6,6-$^2H_2$]glucose (~2.5%) to minimize changes in plasma glucose TTR during the clamp procedure.[14] The infusion of [6,6-$^2H_2$]glucose was stopped during the clamp procedure (from 210 to 390 minutes) to account for the expected decline in hepatic glucose production. Blood samples were taken every 10 minutes during the last 30 minutes of the basal period and the clamp procedure to determine plasma glucose and insulin concentrations and glucose basal and clamp TTRs.

Analyses of Samples and Calculations

Plasma glucose, insulin, and apoB concentrations were measured by using an automated glucose analyzer (Yellow Spring Instruments Co, Yellow Springs, OH), a chemiluminescent immunometric assay (Immulite 1000), and immunonephelometry,[15] respectively. Plasma glucose TTRs were determined by using electron impact ionization gas chromatography-mass spectroscopy (MSD 5973 system with capillary column; Hewlett-Packard; Palo Alto, CA), as described previously.[16,17]

During steady-state conditions, total (endogenous and exogenous) glucose rate of appearance in plasma is equal to glucose rate of disappearance (Rd), and was calculated by dividing the glucose tracer infusion rate by the average plasma glucose TTR during the last 30 minutes of the basal period and the hyperinsulinemic-euglycemic clamp procedure. Endogenous glucose rate of appearance was calculated by subtracting the known exogenous unlabeled glucose infusion rate from the total rate of appearance. Skeletal muscle insulin sensitivity was assessed by calculating the relative increase from basal in glucose Rd during insulin infusion. Hepatic insulin sensitivity was assessed by the Hepatic Insulin Sensitivity Index, which is the inverse of the product of the basal hepatic glucose

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