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Effects of acute dietary weight loss on postprandial plasma bile acid responses in obese insulin resistant subjects

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SUMMARY

Background & aims: Bile acids (BA) are pleiotropic hormones affecting glucose and lipid metabolism. The physiochemical properties of different BA species affect their enterohepatic dynamics and their affinity for bile acid receptors. The BA pool composition is altered in patients with type 2 diabetes and obesity. In this study we used a 2-week very-low-calorie diet (VLCD) to investigate the effects of weight loss on BA pool composition and postprandial dynamics.
Methods: We performed mixed meal tests in obese, insulin resistant subjects before and after the VLCD. We measured postprandial plasma levels of glucose, insulin, BA and the BA-induced enterokine fibroblast growth factor 19 (FGF19).
Results: The VLCD decreased weight by 4.5 ± 2.3 kg ($p < 0.0001$) within 14 days. Weight loss increased peak postprandial deoxycholate (DCA) levels (median [IQR]: 0.90 [0.90] vs. 1.25 [1.35] μmol/L; $p = 0.045$*). Other BA species, glucose, insulin and FGF19 levels and prandial excursions were not significantly affected. The VLCD decreased resting and postprandial energy expenditure by 7 and 11% respectively.
Conclusions: VLCD induced weight loss increased postprandial DCA peak levels and decreased resting energy expenditure in obese insulin resistant subjects.

1. Introduction

BA are increasingly recognized as pleiotropic hormones with effects on glucose and lipid metabolism, in addition to their role as intestinal emulgators [1]. This has led to multiple observations that BA metabolism is altered in metabolic disease such as obesity and type 2 diabetes mellitus [2,3]. Patients with type 2 diabetes mellitus show increased fasting levels of deoxycholic acid (DCA), a secondary BA formed by microbial conversion of cholic acid (CA) [4]. Recently, it was also shown that insulin resistance in healthy human subjects is positively correlated to levels of a certain subset of BA that are hydroxylated at the 12α position (12α-OH BA, i.e. CA and DCA) [5]. It is presently unclear whether these changes are causally involved in insulin resistance. Roux-en-Y gastric bypass surgery also increase plasma BA levels. Therefore, BA are putative mediators for the beneficial effects on metabolism and body weight present after bariatric surgery [6].

Primary BA are synthesized from cholesterol in the hepatocyte and subsequently conjugated with glycine (G) or taurine (T), yielding glyco- and tauroconjugates of CA and chenodeoxycholate (CDCA). Exposure to microbiota in the distal ileum and colon leads to deconjugation and dehydroxylation of CA and CDCA yielding the secondary BA DCA and lithocholic acid (LCA), respectively. Intestinal reabsorption from the intestinal lumen and hepatic extraction

Abbreviations: BA, bile acid; CA, cholic acid; DCA, deoxycholic acid; CDCA, chenodexocholic acid.

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from the portal circulation occur through passive and active transport. Subsequently, hepatic return completes the enterohepatic cycle. BA enter the systemic circulation in a pattern of postprandial peaks followed by lows, periodically exposing peripheral tissues to concentrations that may be high enough to activate the Farnesoid X Receptor (FXR) and G-protein-coupled transmembrane BA receptor (GPBAR1/TGR5) [7–10].

These BA receptors are present on tissues inside and outside the trajectory of the enterohepatic circulation. FXR is a nuclear receptor that regulates BA homeostasis in the liver, amongst others by exerting negative feedback control of bile salt synthesis. In contrast, TGR5 is a transmembrane receptor that is abundantly expressed in the gut, brown adipose tissue (BAT) and skeletal muscle [7,8]. Activation of FXR and TGR5 induces secretion of fibroblast growth factor 19 (FGF19) from enterocytes and glucagon-like peptide-1 (GLP-1) from enteroendocrine L-cells, respectively [11–13]. In turn, FGF19 suppresses hepatic BA synthesis and gluconeogenesis via the FGF receptor 4 (FGFR4). GLP-1 increases the amount of insulin that is released by the pancreatic beta cell in response to glucose [14] making it useful in diabetes therapy. Possibly, BA can also directly stimulate beta cell insulin release via both FXR and TGR5 [15,16].

Is had been shown that postprandial circulating glycine-conjugated BAs are lower in obese subjects, but it is unknown whether this is reversible [3]. We assessed the effects of a two-week very low calorie diet (VLCD) weight loss intervention on fasting and postprandial plasma BA profiles.

2. Materials and methods

2.1. Subjects

We recruited a total of 12 male and female insulin resistant obese subjects (HOMA-IR >2.7, BMI >30 kg/m^2, age 18–55 years). Exclusion criteria were any previous surgery or current diseases of the liver, biliary or gastrointestinal tract; ethanol abuse; weight loss or weight gain in excess of 10% of body weight in the 6 months prior to start of the study; use of any medication or herbal supplement; fasting plasma glucose >7.0 mmol/L, HbA1c > 53 mmol/mol, creatinine >120 μM, or abnormal renal, liver or thyroid function defined as >2 times the upper limit of the reference interval. Written informed consent was obtained from all subjects before start of the study. The study was approved by the AMC Medical Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki (sixth revision, 2008).

2.2. Hypocaloric VLCD diet

Subjects were instructed to follow a 450 kcal/day diet for 14 days. The diet consisted of 3 sachets of a liquid meal replacement formula (Modifast Intensive®, Nutrition et Santé, France). Modifast Intensive® is a commercially available diet product, supplying 51% of energy as carbohydrates, 20% as protein and 29% as fat. Subjects were encouraged to complement the diet with low-caloric raw vegetables. Daily phone calls were conducted by the investigators to ensure diet compliance.

In order to counteract the insulin-desensitizing effects of prolonged fasting on glucose and lipid metabolism, the diet period was followed by three days on a eucaloric free diet [17]. Subjects were instructed to eat their estimated daily caloric need (estimated using the Harris Benedict equation).

2.3. Study design

The study was performed between May 2012 and February 2014 at the Department of Endocrinology and Metabolism of theAcademic Medical Center Amsterdam. On study days, subjects were admitted at 07:30 h to the Metabolic Unit after an overnight fast. A cannula was inserted into an antecubital vein for blood sampling. This hand was kept in a heated hand box throughout the test to arterialize venous blood. At 09:30 h, 3 blood samples were taken at 10-minute intervals for the determination of basal plasma glucose and insulin concentrations. At 10:00 h, subjects consumed a standard meal consisting of 50 g of parmesan cheese, 60 g of boiled egg and 75 g of glucose dissolved in 200 ml water (559 kcal; 30% from fat, 16% from protein, 54% from carbohydrates), after which blood samples were obtained at 0, 15, 30, 45, 60, 75, 90, 120, 150, 180 and 240 min after the meal. Blood was collected into chilled tubes containing either EDTA or Heparin as anticoagulant on ice and immediately centrifuged, and plasma was subsequently stored at −20 °C until analysis. For GLP-1 assays, a dipeptidyl peptidase inhibitor (Ile-Pro-Ile, Sigma–Aldrich, St. Louis, MO, USA) was added at 0.01 mg/ml and plasma was stored at −80 °C. Resting energy expenditure was measured for a 10 min-interval at baseline, 90 and 240 min after the meal by indirect calorimetry using a ventilated hood system (Vmax Encore 29; SensorMedics, Anaheim, CA). Energy expenditure was calculated as described by Frayn [18]. The abbreviated Weir equation was used to calculate 24-hour energy expenditure.

2.4. Laboratory analysis

Plasma glucose concentrations were analyzed bedside using the glucose oxidation method (EKF Diagnostics, Barleben/Magdeburg, Germany). Insulin was determined on an IMMULITE 2000 system (Siemens Healthcare Diagnostics, Breda, the Netherlands). GLP-1 concentrations were measured by ELISA using a commercially available assay (EMD Millipore, Billerica, MA, USA). BA were determined using a UPLC-tandem MS method to detect CA, CDCA, DCA and UDCA in their conjugated and unconjugated forms [19]. FGF19 was measured using an in-house developed ELISA as published previously [20].

2.5. Calculations and statistical analysis

HOMA-IR was calculated from fasting plasma glucose (FPG) and fasting plasma insulin (FPI) as described by Wallace and Matthews [21]. Fractions of a particular BA species were calculated as the sum of individual measurements of nonconjugated and glycine- and taurine-conjugated forms. Total BA were calculated by adding up all individual BA measurements. Area-under-the-curve (AUC) and incremental AUC (iAUC) were calculated using the trapezoidal method. Statistical analysis was performed using IBM SPSS Statistics 22 (IBM, Armonk, NY, USA). Data was visually and statistically assessed for normality and logarithmically transformed were appropriate. Comparisons between 2 test conditions were made using either paired t-testing for normally distributed data or Wilcoxon matched-pairs signed rank testing for nonparametric data. Correlations were assessed using Pearson's correlation for normally distributed populations or Spearman's Rho for nonparametric data. Data presented are mean and standard deviation ($\mu \pm \sigma$) for normally distributed variables or median and interquartile range (m [IQR]) for other variables. Graphs were made using GraphPad Prism 6.0 (GraphPad Software Inc., La Jolla, CA, USA).

3. Results

3.1. Baseline

We included 12 obese, insulin resistant subjects. Subject characteristics and clinical chemistry pre- and post-VLCD are summarized

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