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Original article

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Emma C.E. Meessen [a], Guido J. Bakker [b], Max Nieuwdorp [b], Geesje M. Dallinga-Thie [b], E. Marleen Kemper [c], Steven W. Olde Damink [d, e], Johannes A. Romijn [f], Bolette Hartmann [g, h], Jens J. Holst [g, h], Filip K. Knop [h, i, j, k], Albert K. Groen [b], Frank G. Schaap [d, e], Maarten R. Soeters [a, *]

[a] Department of Endocrinology and Metabolism, Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam University Medical Centers – Location AMC, University of Amsterdam, Amsterdam, the Netherlands
[b] Department of Vascular Medicine, Amsterdam University Medical Centers – Location AMC, University of Amsterdam, Amsterdam, the Netherlands
[c] Department of Hospital Pharmacy, Amsterdam University Medical Centers – Location AMC, University of Amsterdam, Amsterdam, the Netherlands
[d] Department of Surgery, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University, the Netherlands
[e] Department of General, Visceral and Transplantation Surgery, RWTH University Hospital Aachen, Germany
[f] Department of Internal Medicine, Amsterdam University Medical Centers – Location AMC, University of Amsterdam, Amsterdam, the Netherlands
[g] Department of Biomedical Sciences and NNF Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[h] Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[i] Center for Clinical Metabolic Research, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark
[j] Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[k] Steno Diabetes Center Copenhagen, Gentofte, Denmark

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SUMMARY

Background & aims: To investigate the acute effects of intravenous vs enteral meal administration on circulating bile acid and gut hormone responses.
Methods: In a randomized crossover design, we compared the effects of duodenal (via a nasoduodenal tube) vs parenteral (intravenous) administration over 180 min of identical mixed meals on circulating bile acid and gut hormone concentrations in eight healthy lean men. We analysed the bile acid and gut hormone responses in two periods: the intraprandial period from time point (T) 0 until T180 during meal administration and the postprandial period from T180 until T360, after discontinuation of meal administration.
Results: Intravenous meal administration decreased the intraprandial (AUC (μmol/L*min) duodenal 1469 ± 284 vs intravenous 240 ± 39, $p < 0.01$) and postprandial bile acid response (985 ± 240 vs 223 ± 5, $p < 0.05$) and was accompanied by decreased gut hormone responses including glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1, glucagon-like peptide 2 and fibroblast growth factor 19. Furthermore, intravenous meal administration elicited greater glucose concentrations, but similar insulin concentrations compared to enteral administration.
Conclusions: Compared to enteral administration, parenteral nutrition results in lower postprandial bile acid and gut hormone responses in healthy lean men. This was accompanied by higher glucose concentrations in the face of similar insulin concentrations exposing a clear incretin effect of enteral mixed meal administration. The alterations in bile acid homeostasis were apparent after only one intravenous meal.

* Corresponding author. Department of Endocrinology and Metabolism, room K2-283, Amsterdam University Medical Centers, Location AMC, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands..
E-mail address: m.r.soeters@amsterdamumc.nl (M.R. Soeters).
URL: http://metabolism.maartensoeters.nl, http://zorgophetbord.nl, http://amsterdamumc.nl

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Abbreviations

AUC	Area under the curve
Apo	Apolipoprotein
BMI	Body mass index
C4	7α-hydroxy-4-cholesten-3-one
CA	Cholic acid
CCK	Cholecystokinin
CDCA	Chenodeoxycholic acid
DCA	Deoxycholic acid
FXR	Farnesoid X receptor
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide 1
GLP-2	Glucagon-like peptide 2
HDL-C	High-density lipoprotein cholesterol
IFALD	Intestinal failure associated liver disease
IL-6	Interleukin-6
LCA	Lithocholic acid
LDL-C	Low-density lipoprotein cholesterol
MMT	Mixed meal test
MCP-1	Monocyte chemoattractant protein-1
REE	Resting energy expenditure
TGR5	Takeda G protein coupled 5 receptor
T	Time point
UDCA	Ursodeoxycholic acid
xBRS	Baroreceptor sensitivity

1. Introduction

Parenteral nutrition (i.e. intravenous administration of nutrition) is a lifesaving therapy that is employed when enteral nutrition is not possible. Parenteral nutrition is used for a variety of conditions that affect the gut by providing nutrition, in a way that bypasses the gastrointestinal tract [1–3]. As a result, the enterohepatic cycle, which allows periodic bile acid signalling in tissues in the enterohepatic trajectory, is impaired [4]. This may contribute to the frequently observed intestinal failure associated liver disease (IFALD) and the impaired anabolic response observed with parenteral nutrition [5,6].

Nutrient ingestion elicits a metabolic, endocrine and inflammatory response (increase in leukocytes and cytokines), which maintains the balance between anabolism and catabolism in humans [7]. Important players in postprandial anabolism are bile acids, which act as signalling molecules in addition to their role in fat digestion and absorption [8,9].

The primary bile acids (cholic acid (CA) and chenodeoxycholic acid (CDCA)) are formed from cholesterol in the liver, conjugated to either glycine or taurine and stored to some extent in the gallbladder. After meal ingestion, bile acids are released into the small intestine, where they activate the ileal intranuclear farnesoid X receptor (FXR) and the transmembrane Takeda G protein-coupled receptor 5 (TGR5) in enterocytes and in entero-endocrine cells K and L cells respectively [9–13]. The gut microbiota deconjugate and dehydroxylate bile acids, thus converting the primary bile acids into secondary bile acids (deoxycholic acid (DCA) from CA, lithocholic acid (LCA) and ursodeoxycholic acid (UDCA) from CDCA) [14]. Intestinal FXR activation prompts negative feedback regulation of hepatic bile acid synthesis via the secretion of intestinally produced fibroblast growth factor 19 (FGF19) [15]. FGF19 also induces hepatic glycogen and protein synthesis while inhibiting gluconeogenesis and lipogenesis in the liver [16,17]. Direct hepatic FXR activation also decreases bile acid synthesis in the liver via repression of the gene encoding the key enzyme CYP7A1 [18]. Bile acid-activated receptor TGR5 stimulates the release of glucose-dependent insulinotropic polypeptide (GIP) from the enteroendocrine K cells and glucagon-like peptide 1 (GLP-1) and glucagon-like peptide 2 (GLP-2) secretion from the enteroendocrine L cells [9,11]. GIP and GLP-1 promote insulin release in humans [19–21]. GLP-1 decreases food intake and may increase energy expenditure, whereas the effects of GIP currently on food intake or energy expenditure are unresolved [22–25]. GLP-2 promotes intestinal epithelial cell proliferation, nutrient absorption and maintenance of the intestinal barrier [26,27]. As evident from above actions, direct and indirect signalling actions of bile acids are an integral part of postprandial nutrient handling. Moreover, both FXR and TGR5 activation exert several anti-inflammatory effects on postprandial metabolism via different pathways [7].

Enteral nutrient ingestion is accompanied by bile acid entry into the small intestine which contributes to the postprandial anabolic state [7,8]. Importantly, several animal models and human studies showed impaired responses of FGF19, GLP-1 and GLP-2 during parenteral nutrition [4,28,29]. Nevertheless, the exact and acute effects of the intravenous administration route on bile acid homeostasis, to our knowledge, are unknown. Therefore, we compared the acute effects of duodenal vs. intravenous administration of identical meals on circulating bile acid and gut hormone concentrations in healthy lean men.

2. Materials and methods

2.1. Subjects

We included eight healthy lean (body mass index (BMI) between 18.5 and 25.0 kg/m^2) Caucasian men with and HOMA-IR index $\leq$ 2.0 (calculated as (fasting insulin (pmol/L)*fasting glucose (mmol/L))/135)). We applied the following exclusion criteria: major illness in the past 3 months, use of any medication, gastro-intestinal disease that may influence bile acid homeostasis, history of cholecystectomy, use of tobacco, drugs, and/or >3 alcohol units per day, nephropathy (defined as creatinine > 120 μmol/L), fasting glucose $\geq$ 5.6 mmol/L, > 2 times upper reference limit of plasma tests (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma glutamyl transferase, bilirubin and lipids (total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides). Oral and written informed consent was obtained from all subjects before the start of the study, which was conducted in agreement with the principles of the Declaration of Helsinki (2013). The study was approved by the Medical Ethics Committee of the Academic Medical Center (AMC), Amsterdam, The Netherlands (registration number METC2017_272).

2.2. Mixed meal test protocol

The study was performed from February 2018 until May 2018 at the Amsterdam University Medical Centers (Amsterdam UMC), location AMC. On two separate study days (performed in randomized order), subjects underwent an enteral (duodenal meal infusion via a nasoduodenal tube) and parenteral

(intravenous meal infusion) mixed meal test (MMT), respectively. On both days, PeriOlimel N4E (Baxter B.V., Utrecht, The Netherlands), which is a registered emulsion for peripheral parenteral nutrition, was administered. PeriOlimel N4E (0.7 kcal/mL) consists of 6.3% amino acid solution, 18.75% glucose solution and 15% lipid solution. An equal dosage (20% of resting energy expenditure (REE) as measured by indirect calorimetry) and was administered over a period of 180 min, using an identical infusion rate on both days. Thus besides the different administration routes, the study days were identical. In the three days prior to the study days, subjects were asked to refrain from heavy exercise (>one hour) and alcohol consumption. After an overnight fast, subjects attended the Amsterdam UMC between 07:30 and 08:00 AM. Baseline (fasted) REE and baroreceptor sensitivity (described below) were measured. In case of the parenteral MMT, two cannulas were inserted into the antecubital veins, one in each arm. One cannula was used for venous blood withdrawal and the second for intravenous administration of the PeriOlimel N4E. In case of the enteral MMT, only one cannula was placed into an antecubital vein. The nasoduodenal tube for enteral meal administration was placed using the Cortrak method [30]. Blood samples were drawn just before the start of the meal infusion (fasted state) and at time points (T) 30, 60, 90, 120, 150, 180, 240, 300 and 360 min after the start of meal infusion. Blood samples were collected in EDTA, heparin and serum tubes and immediately (except for serum, after 30 min) centrifuged (4 °C, 15 min, 3000 RPM). For the analysis of intact GLP-2, a dipeptidyl peptidase inhibitor (Diprotin A, Bachem, Switzerland) was added at 0.01 mg/ml to a chilled EDTA vacutainer. Plasma was stored at −80 °C until analyses.

2.3. Laboratory analyses

Total bile acid concentrations were measured by an enzymatic cycling method according to the manufacturer's protocol (Diazyme Laboratories, Poway, California, United States). We determined bile acid composition (CDCA, CA, DCA, LCA and UDCA and their conjugates) on three different time points by LC/MS/MS: T0, T180 and T360 min after the initiation of meal infusion [31]. FGF19 and 7α-hydroxy-4-cholesten-3-one (C4) were analysed with an in-house developed ELISA or LC-MS assay, respectively [32]. Total GIP, total GLP-1 and glucagon were measured with commercially available kits (Mercodia, Uppsala, Sweden). Intact GLP-2 was measured using an in-house developed radio-immuno assay [33]. Bedside plasma glucose concentrations were analysed with a YSI glucose analyser (YSI − xylem brand, Yellow Springs, USA). Insulin was analysed with Immulite 2000 (Siemens Healthcare Diagnostics, Breda, the Netherlands). Lipid data from the MMTs: plasma total cholesterol, HDL-C, and triglycerides were analysed with commercial assays (Diasys and WAKO) on the Selectra (Sopachem, Ochten, The Netherlands). LDL-C levels were calculated using the Friedewald formula [34]. Apolipoprotein (apo) B and apo A1 were analyzed using a commercial nephelometric assay on the Selectra auto-analyzer. Interleukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1) were determined using commercially available ELISA kits (IL-6 Human ELISA Kit, High Sensitivity Invitrogen, MCP-CCL2 Human Uncoated, Thermo Fisher Scientific, Waltham, Massachusetts, U.S.A.,). Leukocyte cell counts were determined automatically using an XN-9000 analyzer (Kobe, Hyōgo Prefecture, Japan) within 45 min after collection in EDTA tubes that were stored at room temperature. CRP, liver enzymes and lipids (measured during screening) were determined with Roche Cobas c702 (Roche Diagnostics, Almere, The Netherlands).

2.4. Energy expenditure

We measured energy expenditure by indirect calorimetry at baseline, 180 and 340 min after the start of the meal infusion. A ventilated canopy was used (Vmax Encore 29; SensorMedics, Anaheim, United States), REE was calculated with the Weir equation and substrate oxidation was determined as previously published by Frayn [35].

2.5. Baroreceptor sensitivity

During the study days, continuous blood pressure was measured using finger arterial photoplethysmography (Portapres, Finapres Medical Systems, Amsterdam, The Netherlands) to obtain the baroreceptor sensitivity (xBRS). The xBRS is a measure to quantify how much control the baroreflex has on the heart rate. The xBRS was calculated using beat-to-beat SBP and R–R interval in a sliding window of 10 s [36].

2.6. Subjective and objective appetite

At the end of the study day, subjective and objective appetite was estimated from the food intake at an *ad libitum* solid mixed homogeneous lunch. Before and after the *ad libitum* meal, visual analogue scale (VAS) scores regarding hunger (100 = never been so hungry) and appetite (100 = can eat a lot) were recorded.

2.7. Calculations and statistical analyses

We analysed the bile acid and gut hormone responses during the infusion of the duodenal/intravenous meal: the intraprandial period (T0 - T180); and after discontinuation of the infusion, the postprandial period (T180 - T360). The intraprandial period was displayed with a grey shaded area in the graphs. We assessed intra- and postprandial responses by the area under the curve (AUC) and the AUCs were calculated using the trapezoid rule. We compared the AUCs with a paired T-test when data were normally distributed or otherwise the Wilcoxon-signed rank test was used. We could not calculate the AUC for GLP-2 because we missed several time points due to insufficient volume of remnant plasma for the laboratory analysis of GLP-2. Therefore we assessed the effects on GLP-2 with a mixed effect model. The administration route was set as fixed effect whereas the time points and subject numbers were set as random effects. Some of the parameters were only measured at three or four time points. For these parameters, we analysed the effect of meal administration with two-way repeated measures ANOVA. Because of the repeated measures design of the study, we did not assume sphericity and applied the Greenhouse-Geisser correction for the comparisons between time points and the interaction “administration route*time point”. Furthermore, the Bonferroni test was used to correct for multiple testing.

Data were presented as mean ± standard error of mean (SEM) unless otherwise stated. The Shapiro–Wilk test was applied to test whether the data were normally distributed. Statistical analyses were executed with IBM SPSS Statistics 25 (IBM, Armonk, New York, United States) and Graphpad Prism 8.02 (GraphPad Software Inc., La Jolla, California, United States). Graphs were created with GraphPad Prism 8.02. p values ≤ 0.05 were considered statistically significant.

3. Results

3.1. Subjects characteristics

We included eight healthy lean men (age 29 ± 3 years, BMI 22.9 ± 0.7 kg/m^2, fasting glucose 5.1 ± 0.1 mmol/L, fasting insulin 31.3 ± 4.8 pmol/L and HOMA-IR 1.2 ± 0.2). All subjects completed the study procedures without serious adverse events. One subject experienced headache (self-limiting) during the enteral MMT. The total amount of energy the subjects received was 365 ± 16 kcal with the following macronutrient composition: glucose 98 ± 4 g, amino acid 33 ± 1 g and lipid 78 ± 3 g.

3.2. The effect of intravenous meal infusion on plasma parameters

An intra- and postprandial bile acid response was not seen with intravenous meal infusion (Fig. 1A). Interestingly, both the glycine and taurine conjugated bile acids (except for taurine conjugated LCA and glycine conjugated UDCA) were significantly lower with the intravenous meal administration at T180 as compared to the enteral administration (Fig. 2, Supplemental Fig. 1). The unconjugated bile acids were not significantly affected by the administration route (Supplemental fig. 1).

In accordance with the lower bile acid responses with intravenous administration, we observed decreased intra- and postprandial responses of the gut hormones FGF19, GIP, GLP-1 and GLP-2 (Fig. 1B-E). C4 concentrations, a marker for hepatic bile acid synthesis, were not suppressed 'postprandially' with intravenous meal administration and even increased at T360 ($p = 0.01$) whereas enteral nutrition supressed C4 concentrations (Fig. 1F). Furthermore, 6 h after the initiation of intravenous meal infusion, C4 levels were higher than the overnight fasted C4 levels ($p = 0.04$).

Intravenous meal administration increased intra- and postprandial glucose concentrations (Fig. 3A). We did not find an effect of the administration routes on intra- and postprandial insulin responses (Fig. 3B), which encompasses the incretin effect. Furthermore, intravenous meal infusion did not affect the intraprandial glucagon responses, but tended to decrease postprandial glucagon responses ($p = 0.051$, Fig. 3C).

In addition to the bile acid and gut hormone responses, we investigated the acute inflammatory response during the course of nutrient infusion and after discontinuation. Intravenous feeding increased IL-6 concentrations, but did not affect MCP-1 (Fig. 4A-B). Furthermore, leukocyte counts and differential counts were not affected by the administration route (Fig. 4C, Supplemental Figs. 2 and 3). However, we did observe differences in the factor time for the absolute and relative counts of different leukocytes (Supplemental Figs. 2 and 3). Interestingly, absolute lymphocyte counts decreased with duodenal and intravenous meal administration after 120 min of meal infusion, whereas the other leukocytes were unaffected or increased. Regarding the relative counts,

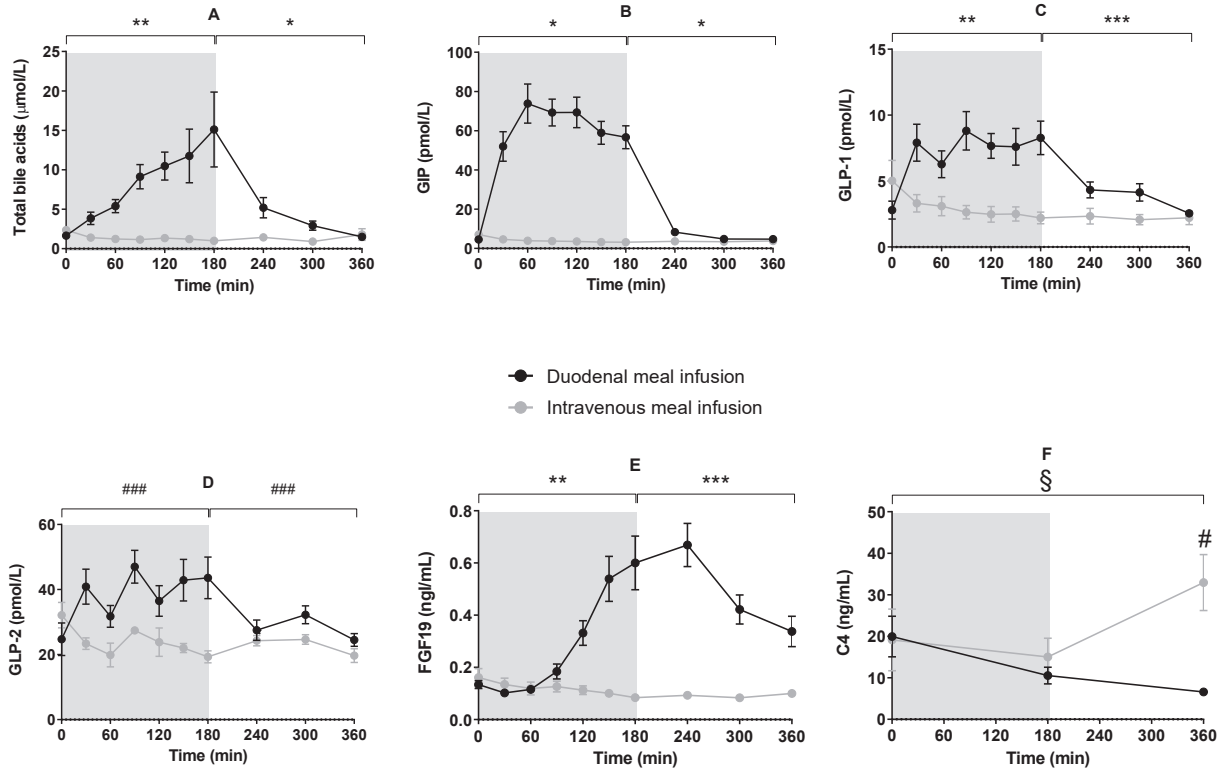

Fig. 1. The intra- and postprandial responses of gut hormones to enteral and parenteral mixed meal tests in healthy lean men. In a randomized crossover design, eight healthy lean mean underwent two identical mixed meal tests. Subjects underwent an enteral (duodenal meal infusion) and parenteral (intravenous meal infusion) mixed meal test after an overnight fast. The intraprandial (grey shaded area, time 0–180 min) and postprandial (non-shaded area, time 180–360 min) excursion of (A) total bile acids, (B) GIP, (C) GLP-1, (D) GLP-2, (E) FGF19 and (F) C4. The black line represents the enteral mixed meal test and the grey line parenteral mixed meal test. Data are presented as mean ± SEM. *p ≤ 0.05, **p < 0.01, ***p < 0.001 assessed by area under the curve and tested with a paired T-test or Wilcoxon rank test, ###p < 0.001 assessed by mixed effect models, §p < 0.05 assessed by two-way repeated measures ANOVA and #p < 0.05 time point 360 assessed by Wilcoxon rank test. Abbreviations: GIP = gastric inhibitory polypeptide, GLP-1 = glucagon-like peptide-1, GLP-2 = glucagon-like peptide-2, FGF19 = fibroblast growth factor 19 and C4 = 7α-hydroxy-4-cholesten-3-one.

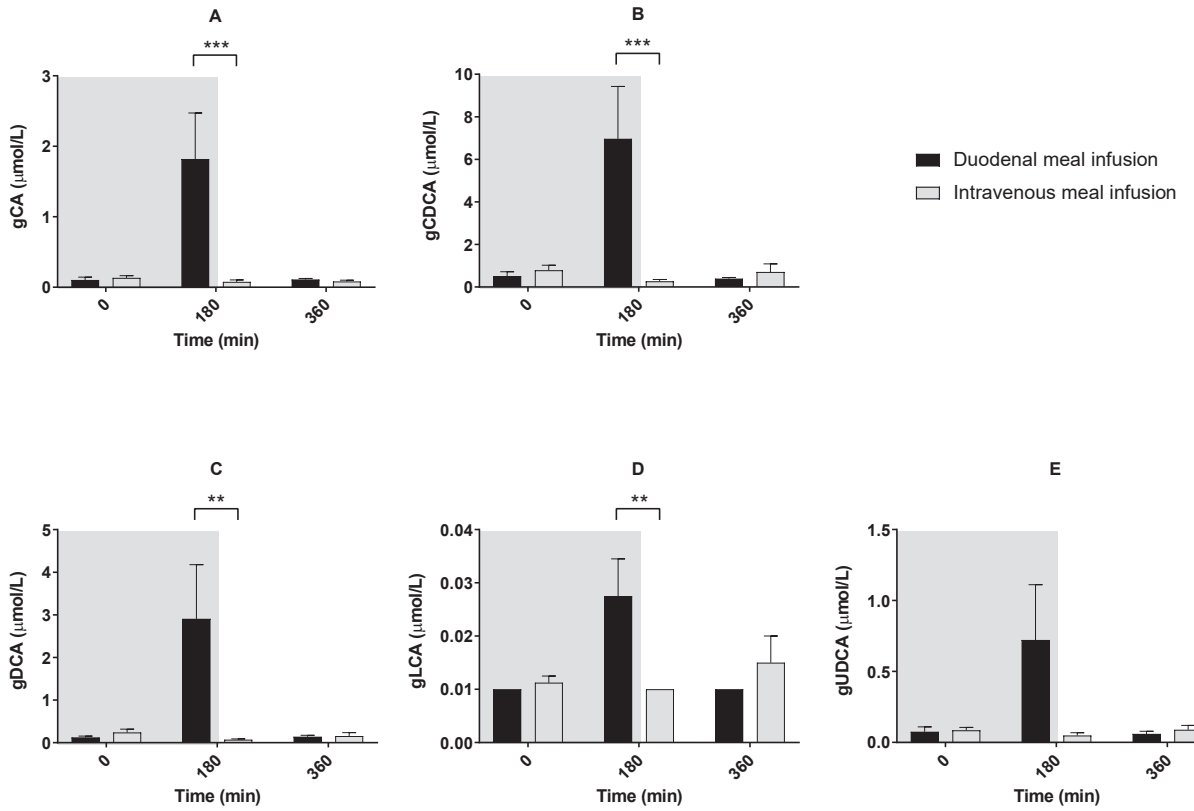

Fig. 2. Overview of individual glycine conjugated bile acids. Fasted subjects (N = 8) underwent an enteral and parenteral mixed meal test in a randomized crossover design. The concentrations of the individual glycine-conjugated bile acids at time point 0, 180 and 360. The black bars = duodenal meal infusion and the grey bars = intravenous meal infusion. Data are presented as mean with SEM. *p ≤ 0.05, **p < 0.01, ***p < 0.001 after posthoc analysis by two-way repeated measures ANOVA. Abbreviations: g = glycine, CA = cholic acid, CDCA = chenodeoxycholic acid, DCA = deoxycholic acid, LCA = lithocholic acid and UDCA = ursodeoxycholic acid.

not only the lymphocytes, but also the monocytes, eosinophils and basophils decreased with meal infusion, irrespective of the administration route.

CRP and liver enzymes did not differ between the MMTs (Supplemental table 1). Furthermore, we did not find any differences in the postprandial lipid response (Supplemental table 2).

3.3. The effect of intravenous meal infusion on energy expenditure and baroreceptor sensitivity

We did not find an effect of administration route on resting energy expenditure and substrate oxidation (Fig. 5A-B). Furthermore, we found no differences in baroreceptor sensitivity (Fig. 5C).

3.4. The effect of intravenous meal infusion on subjective and objective appetite

At the start of the *ad libitum* meal, subjects were hungrier, as assessed by VAS scores, after duodenal meal infusion compared to intravenous infusion ($p < 0.05$, Table 1). We did not find differences in appetite before the start of the *ad libitum* meal, and in both hunger and appetite scores after the *ad libitum* meal. Additionally, we did not find differences in energy intake or total eating time (Table 1).

4. Discussion

Our study demonstrates that intravenous feeding impairs the postprandial plasma bile acid response in healthy lean men and this is accompanied by decreased plasma FGF19, GIP, GLP-1 and GLP-2 excursions. This study also highlights the incretin effect during mixed meal testing: intravenous meal administration increased glucose concentrations without differences in insulin concentrations. Our observations emphasize the pivotal role of the intestine in physiological response to nutrient administration.

The observed lack of intra- and postprandial plasma bile acid elevations, is likely explained by the absence of triggers for gallbladder emptying (cholecystokinin (CCK)) and/or bile ductular secretion (secretin). Secretion of these peptides is induced by nutrients in the stomach and upper small intestine [37,38]. On the other hand, in the fasted state, the gallbladder tone is not static and some bile flows into the duodenum [39]. This occurs periodically (~120 min) in a cyclic manner [39]. The magnitude of gallbladder emptying likely does not result in portal bile acid return that lead to spill over of bile acids into the circulation. The absence of gallbladder contraction is not the only factor explaining the lack of a postprandial elevation of bile acids after intravenous feeding, since cholecystectomized patients do have a postprandial peak in plasma bile acids which may be less pronounced, but remains substantial [40]. Furthermore, bypassing the gut leaves out intestinal transit as an important denominator of circulating bile acid concentrations [41].

Only conjugated bile acid levels were affected by the nutritional administration route, in contrast to unconjugated bile acids. These findings are in agreement with previous studies, since unconjugated bile acids follow a diurnal rhythm (being formed by bacterial degradation in the lower gut), whereas the conjugated bile acids release is dependent on meal ingestion [42,43].

Lack of plasma total bile acid elevations with intravenous feeding, was accompanied by impaired gut hormone release

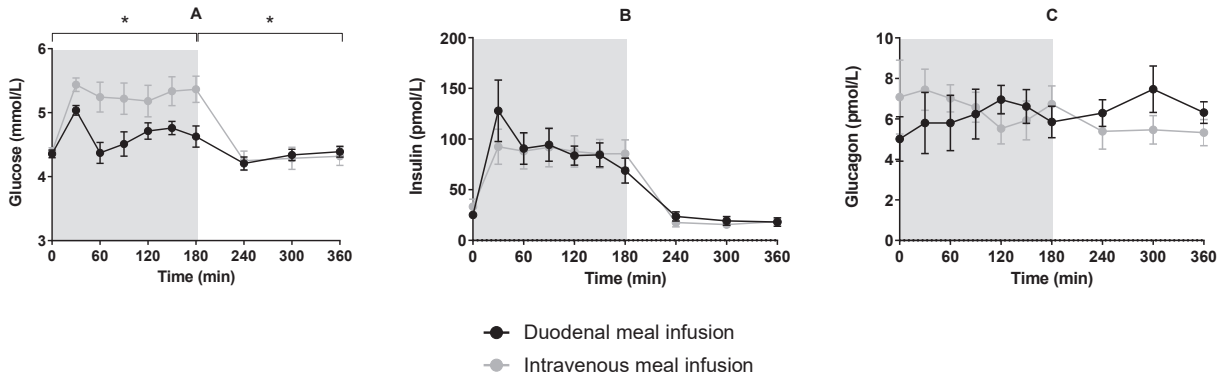

Fig. 3. The intra- and postprandial responses of glucose, insulin and glucagon to duodenal and intravenous meal infusion. Fasted subjects (N = 8) underwent an enteral and parenteral mixed meal test in a randomized crossover design. The intraprandial (grey shaded area, time 0–180 min) and postprandial (non-shaded area, time 180–360 min) excursion of (A) glucose, (B) insulin and (C) glucagon. The black line represents the enteral mixed meal test and the grey line parenteral mixed meal test. Data are presented as mean ± SEM. *p ≤ 0.05 assessed by area under the curve (paired T-test/Wilcoxon rank test).

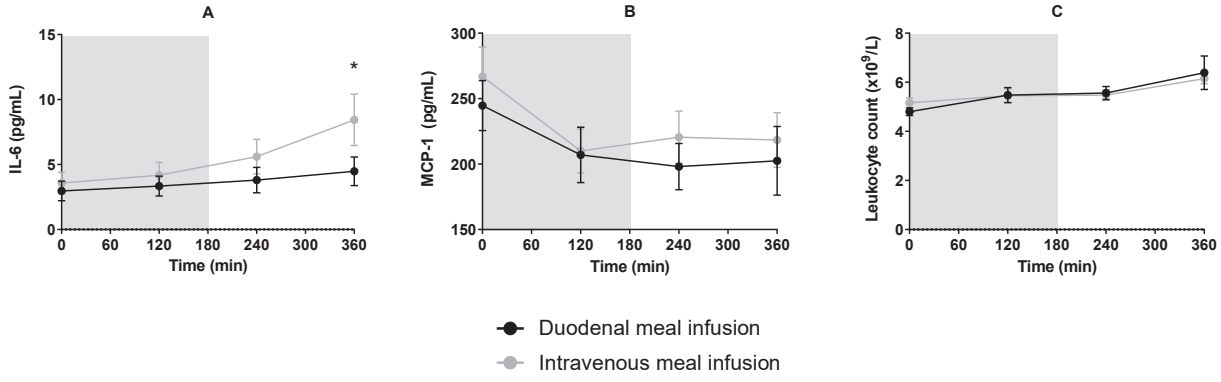

Fig. 4. The intra- and postprandial inflammatory responses to parenteral and enteral mixed meal tests in eight healthy lean men. In a randomized crossover design, eight healthy lean mean underwent two identical mixed meal tests. Subjects underwent an enteral (duodenal meal infusion) and parenteral (intravenous meal infusion) mixed meal test after an overnight fast. Figure 4 shows the intraprandial (grey shaded area, time 0–180 min) and postprandial (non-shaded area, time 180–360 min) excursion of (A) IL-6, (B) MCP-1 and (C) leukocyte count. The black line represents the enteral mixed meal test and the grey line parenteral mixed meal test. Data are presented as mean ± SEM. *p ≤ 0.05 after posthoc analysis by two-way repeated measures ANOVA. Abbreviations: IL-6 = interleukin-6 and MCP-1 = monocyte chemoattractant protein-1.

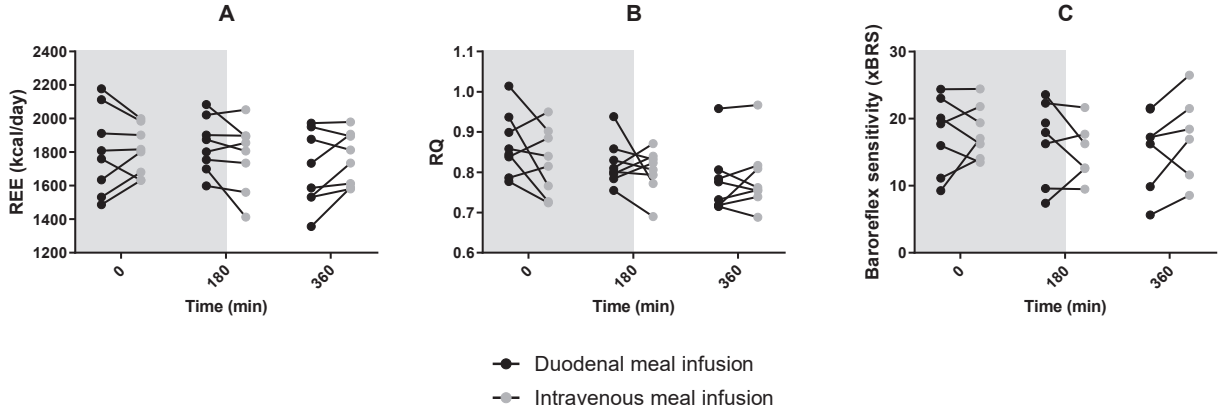

Fig. 5. The effects of enteral and parenteral nutrition on resting energy expenditure, substrate oxidation and baroreflex sensitivity in eight healthy lean men. In a randomized crossover design, eight healthy lean mean underwent two identical mixed meal tests. Subjects underwent an enteral (duodenal meal infusion) and parenteral (intravenous meal infusion) mixed meal test after an overnight fast. Figure 5 shows intraprandial (grey shaded area, time 0–180 min) and postprandial (white area, time 180–360 min) effects of the administration route on (A) REE, (B) RQ and (C) Baroreflex sensitivity. The black line represents the enteral mixed meal test and the grey line parenteral mixed meal test. Data are presented as mean ± SEM. Abbreviations: REE = resting energy expenditure, RQ = respiratory quotient.

Table 1
Overview of the VAS scores and ad libitum food intake after enteral and parenteral mixed meal tests in eight healthy lean men. In a randomized crossover design, eight healthy lean mean underwent two identical mixed meal tests. Subjects underwent an enteral (duodenal meal infusion) and parenteral (intravenous meal infusion) mixed meal test after an overnight fast. At the end of the study day, subjective and objective appetite was measured with VAS scores (recording hunger and appetite) and a homogenous solid *ad libitum* lunch. Data are presented as mean ± SD.*$p \leq 0.05$, tested with paired t-test.

	Duodenal meal infusion	Intravenous meal infusion	*P* value
VAS hunger (mm)			
Before *ad libitum* lunch	75 ± 10	66 ± 9	0.02*
After ad *libitum* lunch	16 ± 15	15 ± 11	0.85
Delta	60 ± 21	52 ± 13	0.35
VAS appetite (mm)			
Before *ad libitum* lunch	76 ± 12	73 ± 15	0.56
After *ad libitum* lunch	13 ± 11	14 ± 13	0.66
Delta	64 ± 18	59 ± 18	0.38
Ad libitum lunch			
Energy intake (kcal)	1244 ± 435	1169 ± 292	0.49
Total eating time (min)	12 ± 6	10 ± 4	0.28

including FGF19, GIP, GLP-1 and GLP-2. A similar phenomenon was found in neonatal piglets where bile acids, FGF19, GLP-1 and GLP-2 concentrations were decreased after 6 weeks of parenteral nutrition. These decreased concentrations were partly restored by oral administration of CDCA [4], showing that bile acid supplementation partly reestablishes the enterohepatic bile acids signalling pathways.

As expected, the lack of plasma FGF19 excursion following intravenous feeding, did not suppress C4 levels. C4 is used as a marker for hepatic bile acid synthesis, since it reflects CYP7A1 activity [44]. CYP7A1, the key enzyme of hepatic bile acid synthesis via the classical pathway, is inhibited via hepatic FXR activation or in response to intestinally produced FGF19 [18]. Six hours after the start of the intravenous meal infusion, plasma C4 levels were still elevated compared to the overnight fasted baseline levels. This suggests that intravenous meal infusion stimulated hepatic bile acid synthesis [45]. *Fxr*-null mice showed increased hepatic *Cyp7a1* gene expression, which reflects dis-inhibited bile acid synthesis [46]. Kim et al. used hepatic liver- and intestinal-specific *Fxr*-null mice models and showed that *Cyp7A1* expression is more affected by intestinal Fxr activation [47].

The postprandial GLP-1 responses to mixed meal stimulation depend partially on intestinal glucose absorption [48]. Our findings support this notion since there is no intestinal (luminal) glucose absorption with intravenous meal infusion. However, our findings support that GLP-1 release is also bile acid-dependent [48].

Intravenous meal administration increased glucose concentrations compared to enteral meal administration, whereas the insulin concentrations did not differ between the study days. This reflects the incretin effect and our study is the first study which demonstrated that this effect is present during mixed meal testing whereas previous studies focused on individual nutrients [49,50]. This is consistent with the concept that the incretin hormones act by increasing the beta cell sensitivity to glucose, whereby the same amount of insulin may be secreted at a lower glucose level. In contrast, it has been shown that cholecystectomized patients have increased glucose concentrations without any differences in insulin or incretin concentrations [40]. The elevated postprandial glucose concentrations observed may be due to luminal bile acids. Thus, the lack of difference in incretin responses is probably due to the presence of nutrients in the intestinal lumen which also induces TGR5 activation and stimulate secretion by other mechanisms [7,40].

We previously described that enteral meal ingestion elicits pro- and anti-inflammatory effects [7]. Macronutrients, especially dietary fat and carbohydrates, induce an acute postprandial inflammatory response characterized by cytokine production and activation of the nuclear factor kappa B pathway in mononuclear cells [51,52]. In addition to their effects on energy metabolism, activation of the bile acid receptors FXR and TGR5 exerts several anti-inflammatory effects [7]. In line with this, we only observed an increase in plasma IL-6 concentrations in subjects who received intravenous feeding. Possibly, the increase in IL-6 originates from endothelial cells as a result from intravenous meal infusion itself and not due to the impaired bile acid response, as we did not find an effect on other cytokines or leukocytes [53].

Our study has a few limitations. First, we included healthy men, but the postprandial bile acid responses in women may be different [54]. Furthermore, most of the bile acids circulate within the enterohepatic cycle and only a smaller amount appears in the peripheral circulation [31]. We collected venous blood samples and we were not able to collect portal vein samples. Moreover, we only investigated the effects of continuous duodenal feeding. Future studies will encompass bolus duodenal feeding (administration in 30–60 min).

In summary, intravenous meal administration eliminated the physiological plasma bile acid response. The low plasma bile acids were accompanied by impaired gut hormone responses (FGF19, incretins and GLP-2). These alterations were detected after only a single intravenous meal infusion and may contribute to parenteral nutrition-associated side effects including IFALD and impaired anabolic response. Furthermore, this study highlights the importance of enteral nutritional strategies (e.g. oral bile acid or nutrient supplementation with parenteral nutrition) to improve health by maintaining physiological circulating postprandial bile acid and gut hormone responses in patients who use short- and long-term parenteral nutrition.

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Authors contributions

ECEM designed the study, performed clinical experiments, did statistical analysis, wrote and edited the manuscript. GJB designed the study, performed clinical experiments, did statistical analyses and edited the manuscript. MN, GDT, EMK, JAR and AK reviewed the manuscript. BH, JJH and FKK executed laboratory analyses and reviewed the manuscript. SWOD and FGS designed the study, executed laboratory analyses and reviewed the manuscript. MRS

reviewed the design of the study, reviewed and edited the manuscript.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2020.06.032.

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