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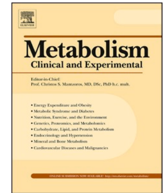

Leptin acutely increases hepatic triglyceride secretion in patients with lipodystrophy

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ABSTRACT

Background and aims: Metreleptin ameliorates hepatic steatosis partially independent of its anorexic action. We previously showed that metreleptin increases hepatic very low-density lipoprotein triglycerides (VLDL1-TG) export in rodents and healthy humans requiring intact hepatic autonomic innervation. The primary aim of this study was to investigate whether metreleptin has anti-steatotic properties in patients with lipodystrophy by increasing VLDL1-TG export. In addition, we present a case of generalized lipodystrophy undergoing metreleptin treatment after liver transplantation, a model for hepatic autonomic denervation.

Methods: In this randomized, placebo-controlled, crossover trial (EudraCT 2017-003014-22) we assessed the acute effects of a single metreleptin injection in 10 patients (8 females, 2 males; mean age ± SD: 49 ± 14 yrs; 9

Abbreviations: MASLD, metabolic dysfunction-associated steatotic liver disease; HCL, hepatocellular lipid content; MRS, magnetic resonance spectroscopy; VLDL1-TG, very low-density lipoprotein 1 triglycerides; ANGPTL3, plasma angiopoietin-like protein 3; IGFBP2, insulin-like-growth-factor-binding protein 2; NEFA, non-esterified fatty acids; LPL, lipoprotein lipase; γATP, γ adenosine triphosphate; Pi, inorganic phosphate; NADH, nicotinamide adenine dinucleotide; $^{1}H/^{31}P$–MRS, ^{1}Hydrogen/^{31}Phosphate magnetic resonance spectroscopy; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; NMR, nuclear magnetic resonance; ITC, isothermal titration calorimetry; bLPL, bovine LPL; AGES, Austrian Agency for Health and Food Safety; BMI-SDS, Body Mass Index Standard Deviation Score; MASH, metabolic dysfunction-associated steatohepatitis; MTTP, microsomal triglyceride transfer protein.

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familial partial and 1 generalized lipodystrophy) on hepatic VLDL1-TG secretion and hepatocellular lipid content (HCL) measured via an intravenous fat emulsion test and ^{1}H-magnetic resonance spectroscopy, respectively.
Results: We found that a single injection of metreleptin increased hepatic VLDL1-TG secretion by 75 % (mean difference ± SD: +219 ± 149 mg/h metreleptin vs. placebo; $p = 0.001$), without significant changes in HCL within 3 h (mean difference ± SD: −8 ± 14 % metreleptin vs. placebo, $p = 0.14$). Metreleptin therapy in a patient with generalized lipodystrophy following liver transplantation failed to ameliorate hepatic steatosis despite improving glucose and lipid metabolism.
Conclusions: Leptin acutely increases hepatic VLDL1-TG secretion in patients with lipodystrophy, likely contributing to metreleptin's body weight-independent anti-steatotic effects. The case report suggests that intact autonomic liver innervation may be required for this action, warranting further research.

1. Introduction

Lipodystrophy syndromes are rare, heterogeneous, genetic or acquired disorders characterized by a complete or partial deficiency of white adipose tissue, occurring in the absence of nutritional deprivation or a catabolic state [1]. Among the numerous forms of lipodystrophy, two main phenotypes are distinguished based on the extent of adipose tissue deficiency: generalized lipodystrophy, where there is virtually no adipose tissue, and partial lipodystrophy, where minor adipose tissue depots are preserved [2,3]. Due to the impaired capacity to form subcutaneous adipocytes, excessive diet-derived calories are stored as ectopic fat in non-adipose tissue organs such as the liver, pancreas and muscle [4]. In approximately 80 % of patients with lipodystrophy, the excessive accumulation of fat in the liver leads to metabolic dysfunction-associated steatotic liver disease (MASLD) [5]. MASLD is closely linked to hypertriglyceridemia, lipotoxicity, insulin resistance, and type 2 diabetes with the potential to progress to steatohepatitis, cirrhosis and end-stage liver disease [6]. Ectopic fat accumulation in muscle and pancreas is also associated with insulin resistance and beta-cell failure [7]. Consequently, the metabolic complications of lipodystrophy closely resemble those seen in obesity-related metabolic syndrome [4]. In contrast to obesity, patients with lipodystrophy often express low levels of leptin due to adipose tissue deficiency, resulting in hyperphagia, which in turn aggravates their metabolic phenotype [1,8].

Metreleptin, a recombinant form of human leptin, is approved as an adjunct to diet for treating the metabolic complications of lipodystrophy. Even though adipose tissue mass does not recover, metreleptin ameliorates hyperphagia, insulin sensitivity, hypertriglyceridemia, and MASLD [5,9–15]. The improvement in hepatocellular lipid content (HCL) as assessed by magnetic resonance spectroscopy (MRS) is in part a consequence of the reduced calorie intake; however, metreleptin decreases HCL also independently of its anorexic action [12]. Up until now, the direct hepatic effects of leptin in patients with lipodystrophy remain incompletely understood.

A previous study on leptin-deficient *ob/ob* mice demonstrated that leptin enhances the secretion of hepatic very low-density lipoprotein 1 triglycerides (VLDL1-TG) [16], a crucial anti-steatotic mechanism [17,18]. We confirmed these results first in a rat model [19] and more recently in healthy humans [20]. In this study, we observed that a single subcutaneous injection of metreleptin in healthy male volunteers increased hepatic VLDL1-TG secretion by 28 % requiring an intact autonomic innervation of the liver [20].

To investigate whether leptin acutely stimulates hepatic VLDL1-TG secretion in patients with lipodystrophy, we performed a crossover, randomized placebo-controlled trial (RCT, Study I) where we assessed VLDL1-TG export after a single subcutaneous injection of metreleptin. We further analyzed the acute impact of metreleptin on HCL, parameters of hepatic de novo lipogenesis, beta oxidation and lipid influx, and liver energy metabolism.

To explore whether metreleptin's anti-steatotic effect in patients with lipodystrophy requires an intact autonomic innervation of the liver, we describe an exceptionally rare case of a patient with congenital generalized lipodystrophy (CGL) type 2 treated with metreleptin following a liver transplantation due to end-stage steatotic liver disease (case report, Study II).

Finally, to contextualize the metabolic phenotype of the patients with lipodystrophy in Study I, we conducted an exploratory cohort comparison analyzing VLDL1-TG metabolism and lipoprotein lipase (LPL) activity in these patients versus healthy male subjects from our previous study who had undergone the same protocol [20] (exploratory cohort study, Study III).

2. Material and methods

Study I was part of a clinical trial registered under the EudraCT Number 2017-003014-22.

2.1. Study I (RCT)

2.1.1. Study population

For the RCT we recruited both male and female patients with generalized or partial lipodystrophy, aged 18 to 70 yrs. For safety reasons, main exclusion criteria included a recent history of pancreatitis and serum triglycerides exceeding 700 mg/dl on study days. A detailed list of inclusion and exclusion criteria is provided in supplemental **Table S1**.

We recruited patients from four European countries (Austria, Germany, Italy and Switzerland) between February 2020 and February 2023. Patients outside Austria were clinically assessed by the treating physicians. The diagnosis of lipodystrophy in the study participants was established by expert physicians and was based on medical history, physical examination and metabolic phenotype in accordance with current guidelines [1,21]. By the time of the trial, the genetic cause had been identified for 8 participants (**Table S2**).

Eligible patients who were willing to participate in the study were contacted by our team and underwent screening for inclusion and exclusion criteria. All patients signed an informed consent. Patients received an honorarium as compensation of their time.

2.1.2. Study outcomes

The outcomes of this study were pre-specified as secondary objectives of the main trial. The main outcome parameter was VLDL1-TG secretion rate. Further outcomes included HCL, unsaturation index, and parameters of liver energy metabolism; parameters of glucose and lipid metabolism; plasma angiopoietin-like protein 3 (ANGPTL3); insulin-like-growth-factor-binding protein 2 (IGFBP2); and plasma non-esterified fatty acids (NEFA). Additionally, we explored correlations between HCL and parameters of glucose and lipid metabolism.

2.1.3. Study design

Study I was a placebo-controlled, randomized, within-subject crossover trial conducted at the Division of Endocrinology and Metabolism at the Medical University of Vienna, Austria. An overview of the study design is shown in Fig. 1A. Each participant received a single subcutaneous injection of metreleptin (0.1 mg/kg body weight) and a single injection of placebo (saline solution 0.9 %) on two separate study days with at least 24 h in between. Baseline leptin levels were comparable between treatments (Table 1) confirming that the washout period

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was sufficient. The sequence of subcutaneous placebo/metreleptin was randomized by the study team using randomizer.org.

Due to logistic constraints, a fully double-blinded design was not feasible for the investigator responsible for administering the study drug. However, personnel conducting MR imaging and study participants were blinded to the treatment sequence.

2.1.4. Study protocol

Patients receiving chronic metreleptin treatment prior to the study were instructed to taper off metreleptin under close clinical observation and to discontinue the treatment for at least two weeks before the study. Moreover, all patients were advised to follow a balanced diet (55 % carbohydrate, 30 % fat, 15 % protein), avoid alcoholic beverages, and abstain from excessive sports for three days before the study. The participant's adherence to these recommendations was confirmed by a dietary recall at the beginning of the study.

In the morning of the study days, blood samples were drawn from patients who had fasted overnight (>12 h) to measure baseline metabolic parameters. We then assessed HCL, unsaturation index and parameters of liver energy metabolism with liver MR. Immediately after the initial MR session, either placebo or metreleptin was administered. A second liver MR was conducted 3 h later. Afterwards, we collected plasma samples and conducted an intravenous fat emulsion test followed by density gradient ultracentrifugation to determine hepatic VLDL1-TG secretion [22,23]. Patients fasted until the end of the protocol. By the time VLDL1-TG concentrations were assessed, patients had fasted for at least 16 h, which eliminates potential interference from chylomicrons. Blood glucose was measured regularly to detect

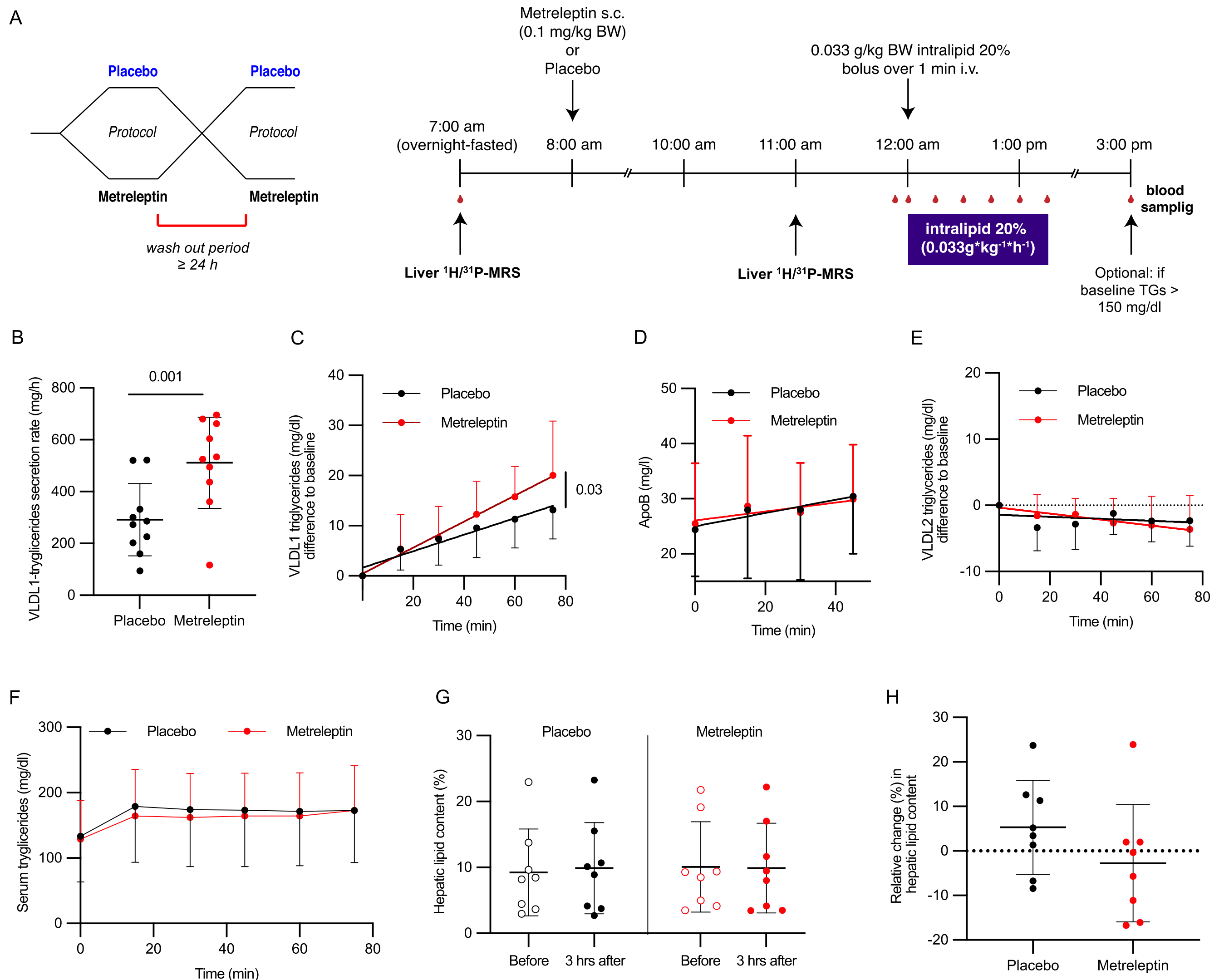

Fig. 1. Clinical trial design and effects of a single subcutaneous metreleptin injection on lipid metabolism in patients with lipodystrophy.
A: Study protocol. B: Very low-density lipoprotein 1 triglyceride (VLDL1-TG) secretion rate after placebo vs. metreleptin (mean ± SD, $n = 10$). C: Linear regression of the difference to baseline of plasma VLDL1-TG during intralipid infusion after placebo vs. metreleptin (mean ± SD, n = 10). D: Linear regression of apolipoprotein B concentration in isolated VLDL1-TG subfraction during the first 45 min of the intralipid protocol (mean ± SD, $n = 9$). E: Linear regression of the difference to baseline of plasma VLDL2-TG during intralipid infusion after placebo vs. metreleptin (mean ± SD, n = 10). F: Serum TG during intralipid infusion after placebo vs. metreleptin (mean ± SD, n = 10). G: Hepatic lipid content (HCL) before and 3 h after placebo vs. metreleptin (mean ± SD, $n = 8$). H: Relative change in HCL (%) after placebo vs. metreleptin administration (mean ± SD, n = 8). Abbreviations: BW, body weight; ^{1}H/^{31}P-MRS, ^{1}Hydrogen/^{31}Phosphate magnetic resonance spectroscopy. All data used to generate these figures are included in online supplementary files. Only significant p-values (<0.05) are shown.

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Table 1
Laboratory parameters of study patients.

Parameter	Placebo		Metreleptin	
	Baseline	4.5 h after injection	Baseline	4.5 h after injection
Blood glucose (mg/dl)	**103 ± 19**	**83.0 ± 8.7****	**107 ± 21**	**83.7 ± 6.9****
Serum insulin (mU/l)	**18.6 ± 9.7**	**12.0 ± 7.1****	**21.5 ± 9.5**	**11.2 ± 5.2****
Serum C-peptide (ng/ml)	**3.5 ± 1.3**	**2.7 ± 0.8****	**3.8 ± 1.2**	**2.7 ± 0.6****
Serum TGs (mg/dl)	**155 ± 77**	**138 ± 80***	165 ± 110	130 ± 160
Serum LDL cholesterol (mg/dl)	71.7 ± 40	74.9 ± 42	74.5 ± 40	76.2 ± 41
Serum HDL cholesterol (mg/dl)	41.7 ± 7.7	40.3 ± 8.2	42.6 ± 8.5	41.5 ± 9.0
Serum apolipoprotein B (mg/dl)	81.3 ± 24	80.6 ± 23	85.2 ± 24	83.3 ± 23
Serum cortisol (μg/dl)	**15.6 ± 2.9**	**8.7 ± 3.3****	**16.2 ± 3.3**	**9.9 ± 3.6****
Plasma leptin (ng/ml)	**2.0 ± 1.3**	**1.5 ± 1.0****	**1.8 ± 1.1**	**38.3 ± 11.6**, #**
Plasma IGFBP2 (ng/ml)	185 ± 47	194 ± 54	184 ± 52	190 ± 57
Plasma Adiponectin (μg/ml)	2.4 ± 1.2	2.3 ± 1.0	2.6 ± 1.3	2.4 ± 1.2

Data are presented as mean ± SD, $n = 10$. Parameters with significant changes before and after placebo/metreleptin are highlighted in bold.* $p < 0.05$ vs. baseline. ** $p < 0.01$ vs. baseline. # $p < 0.001$ placebo vs. metreleptin 4.5 h after injection. Abbreviations: TG, triglycerides; IGFBP2, insulin-like-growth-factor-binding protein 2.

hypoglycemia, a possible side effect of metreleptin. Two participants who were on long-acting and short-acting insulin did not inject short-acting insulin during the study since they were fasting.

2.1.5. Methods

2.1.5.1. Assessment of VLDL1-TG secretion with an intravenous fat emulsion test. The detailed methods for the determination of VLDL1-TG secretion rate and VLDL2-TG measurements have been published [24]. Here, a reduced dose of intralipid was used to avoid hypertriglyceridemia due to a presumed lower LPL activity in patients with lipodystrophy [25]. Briefly, a bolus of 20 % intralipid (0.033 g/kg body weight) was injected over 1 min followed by a continuous infusion for 75 min at a rate of 0.033 g/kg body weight/h. By infusing intralipid, we competitively blocked the breakdown of endogenous VLDL1-TG particles by LPL, allowing VLDL1-TG particles secreted from the liver to accumulate in the circulation over time. During the intralipid infusion, blood samples were drawn every 15 min and stored on ice immediately after collection. From these plasma samples we isolated the VLDL1-TG fraction through a density gradient ultracentrifugation protocol [24] and quantified the TG content in this VLDL1-TG fraction with a colorimetric TG assay. The VLDL1-TG secretion rate was determined from the slope of the linear increase of VLDL1-TG concentration (mg/dl) over time multiplied by plasma volume (4 % of body weight [26]) in deciliters. In case of missing data due to analytical error during the ultracentrifugation procedure, the slope was calculated from available VLDL1-TG concentration (at least 4 time points where available for each patient). Apolipoprotein B concentration was assessed in VLDL1-TG subfraction at timepoints 0, 15, 30 and 45 min during the intralipid protocol with an ELISA kit (R&D Systems).

2.1.5.2. Liver measurements with MRS. HCL, unsaturation index, and parameters of liver energy metabolism (γ adenosine triphosphate, γATP; inorganic phosphate, P_i; γATP synthesis rate, and nicotinamide adenine dinucleotide, NADH) were assessed by ^{1}Hydrogen/^{31}Phosphate MRS (^{1}H/^{31}P–MRS) with a 7-Tesla Magnetom System (Siemens Healthineers, Erlangen, Germany) using a double tuned ^{1}H/^{31}P surface RF coil (Rapid Biomedical, Rimpar, Germany) [20]. Flux through ATP-synthase in the liver tissue was measured by a dynamic ^{31}P saturation transfer MRS experiment as described in [27] and the ATP synthesis rate was calculated by multiplying the forward equilibrium exchange rate constant, k, of the reaction ADP + Pi → ATP by the concentration of Pi as described earlier [28]. Concentrations of ^{31}P containing metabolites were assessed by 3D ^{31}P-MRS data acquisition and phantom replacement method [29]. HCL and unsaturation index of hepatic lipids were measured by an ultra-short echo time single voxel localized ^{1}H-MRS method optimized and described in [30].

In participants who could not undergo 7-Tesla MRS examination due to patient compliance and/or presence of metal implants, the HCL and unsaturation index of hepatic lipids were assessed in a clinical 3-Tesla MR system (PrismaFit, Siemens Healthineers, Erlangen, Germany). Here, patients were lying in supine position and a combination of a whole body transmit coil and a flexible 18-channel body matrix receiver coil was used. The measurement was again performed by an ultra-short echo time single voxel localized ^{1}H-MRS method optimized and described in [30] and confirmed manufacturer product sequences: quantitative Dixon MRI and multi echo single voxel MRS measurement (qDixon, HISTO included in LiverLab, Siemens Healthineers, Erlangen, Germany). The cross validation of 3-Tesla and 7-Tesla measurements was performed previously [30].

In our laboratory, the reproducibility of HCL MRS-based measurement at 3-Tesla in the breath hold was assessed in a test-retest manner by Anderwald et al. [31] and yielded a coefficient of variation smaller than 5 % of the measured value. Bredella et al. [32] performed test-retest measurements in a similar setting with a multi-echo MRS breath hold technique. Correlation analysis between the data before and after repositioning for breath-hold ^{1}H-MRS was $r = 0.99$, $p = 0.0003$. Using Bland Altman analysis, the mean difference between same-day scans for the breath-hold technique was 0.29 % of total signal with a 95 % confidence interval between −1.46 and 2.05 % of total signal. For 7-Tesla MRS, the test-retest measurements on 10 volunteers with a HCL range of 0.8 to 14 % of total signal yielded a coefficient of variation of 4 % [33].

Based on our previous findings [34], an MRS signal of <3.1 % HCL corresponds to the absence of significant hepatic steatosis; a signal between 3.1 % and 5.0 % indicates mild steatosis; 5.0 % to 6.9 % indicates moderate steatosis; and a signal >6.9 % indicates severe steatosis.

2.1.5.3. Hormones and metabolites. Immediately after collection, blood samples at baseline and 4.5 h after placebo or metreleptin injection were sent to the ISO-certified Department of Laboratory Medicine of the Medical University of Vienna (https://www.kimcl.at) to measure blood glucose, serum insulin, C-peptide, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, apolipoprotein B and cortisol by routine laboratory methods. For patients not receiving insulin therapy, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was calculated as fasting insulin (μU/ml) × fasting glucose (mg/dl) divided by 405.

Additional blood samples for later measurements were immediately cooled on ice and centrifuged. EDTA plasma was stored at −80 °C in small aliquots to avoid multiple freeze-thaw cycles. ANGPTL3, IGFBP2, and leptin were measured with commercially available ELISA kits (ANGPTL3: R&D Systems, USA; IGFBP2 and leptin: Mediagnost, Reutlingen, Germany). NEFA (FUJIFILM Wako Chemicals, Neuss, Germany) and ketone bodies (FUJIFILM Wako Chemicals) were measured with colorimetric assays according to the manufacturer's instructions.

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VLDL1- and VLDL2-TG concentrations were assessed with colorimetric assays from Merck, Darmstadt, Germany and DiaSys Diagnostic Systems GmbH, Holzheim, Germany.

2.1.5.4. Lipidomics. Using gas chromatography as previously described [19,20], we analyzed the fatty acid composition of plasma (before and after metreleptin and placebo) and of VLDL1-TG fractions following treatments. For the analysis of VLDL1-TG composition, we utilized samples of isolated VLDL1-TG at a timepoint 45 min into the intralipid protocol. Briefly, after the addition of 16-methylheptadecanoic acid as internal standard to 100–300 μl of the sample, we extracted the lipids using chloroform-methanol (3:1) Folch extraction followed by centrifugation and evaporation of the lower phase under nitrogen. To prepare fatty acid methyl esters a mixture of methanol-toluene (5:1) and acetyl chloride was added and samples were heated to 100 °C for 1 h. After the samples were cooled to room temperature, 6 % sodium carbonate was added and samples were centrifuged. The upper layer was analyzed by gas chromatography using a 6890 N/5973 N GC–MS system (Agilent, Santa Clara, CA) equipped with a PTV injector and a DB-23 column (60 m, 0.25 mm ID, film thickness 0.15 mm, Agilent J&W), using helium as carrier gas. Peak identification and quantification were performed by comparison of integrated peak areas to standard chromatograms.

2.1.5.5. Nuclear MR measurements. VLDL-TG concentration before and after both treatment conditions was quantified from unprocessed plasma samples using high-throughput proton nuclear MR (NMR) by Nightingale Health Ltd. (Helsinki, Finland). The experimental procedures and applications of the NMR platform have been previously detailed by Soininen et al. [35].

2.1.5.6. Exogenous LPL activity analysis. Since post-heparin plasma was not available to measure total lipase activity, we used isothermal titration calorimetry (ITC) to examine the net effect of activating and inactivating regulators of LPL in plasma (i.e., exogenous LPL activity) as previously described [36]. Experiments were performed on a MicroCal PEAQ-ITC (Malvern) [37]. Briefly, the calorimetric cell was filled with human plasma, which was diluted 2-fold with a final concentration of 50 mg/ml bovine serum albumin (BSA), 20 mM HEPES, pH 7.4 buffer. The ITC syringe contained 200 nM purified bovine LPL (bLPL) in 150 mM NaCl, 20 mM HEPES, pH 7.4 buffer with 50 mg/ml BSA and 10 IU/ml heparin for stabilization of bLPL. Three sequential injections with a final concentration of 1 nM bLPL were made into the ITC cell to determine the initial reaction rate and the change in heat rate was followed for 90 s after each injection. Measurements were performed as duplicates where possible. The calorimetric cell was washed with 10 % Decon 90 after each measurement. The heat rate detected by ITC corresponds to the release of fatty acids and is related to the catalytic activity of LPL [36]. Specific activity of bLPL was calculated as the slope of the relationship between heat rate and LPL concentration.

2.1.6. Sample size

Since there are no previous studies that investigated the acute effects of metreleptin on VLDL1-TG export in humans with lipodystrophy, the sample size calculation was based on our rodent studies with an unpaired design, where an intracerebroventricular leptin stimulus led to a 30–40 % increase in hepatic VLDL1-TG secretion compared to vehicle [19]. Previous research showed a mean VLDL1-TG secretion rate of approximately 333 mg/kg/day in healthy volunteers, with a standard deviation of about 147 mg/kg/day [23]. Assuming an alpha value of 0.05, a sample size of ≥13 participants yields a statistical power of ≥0.8 in an unpaired setting. However, given the crossover design in our trial, which allows for paired statistical analysis with a higher statistical power, and an expected increased response to leptin treatment in hypoleptinemic clinical states such as lipodystrophy [38], we estimated that a sample size of 10 patients would be sufficient to achieve an adequate power.

2.2. Study II (case report)

To explore the effects of metreleptin when the liver is decoupled from the autonomic nervous system, we present an exceptionally rare case of a female patient living with CGL type 2 who has undergone a liver transplantation and only afterwards started with metreleptin treatment. Clinical metabolic parameters and MR imaging data of the liver before and after metreleptin treatment were collected in the treating center (Division of Pediatric Endocrinology, Department of Pediatrics, Cukurova University, Adana, Turkey).

2.3. Study III (exploratory cohort study)

To contextualize the metabolic phenotype of the patients with lipodystrophy we performed an exploratory comparison of the 10 patients in Study I and 13 healthy volunteers from our previous trial, who underwent a similar intravenous fat emulsion test and MR protocol [20]. Specifically, we assessed differences in VLDL1-TG metabolism and in LPL activity.

2.4. Statistics

The Shapiro-Wilk test was used to assess the normality of data. Mean ± SD and median (first quartile, Q1 - third quartile, Q3) were applied for normally and non-normally distributed data, respectively. In cases where a variable exhibited discordant distributions across different conditions, the data were consistently presented using the median (Q1-Q3) to ensure uniformity in reporting.

For Study I, paired two-tailed Student's *t*-tests or Wilcoxon signed-rank test were used to compare univariate outcomes for normally and non-normally distributed data, respectively. Associations between continuous variables were described by Pearson's correlation coefficient and Spearman's correlation if appropriate.

For Study III, exploratory analyses comparing two groups were conducted using unpaired two-tailed Student's t-test for normally distributed data or Mann-Whitney test for non-normally distributed data. For comparisons involving four groups (before/after metreleptin in lipodystrophy vs. healthy volunteers, or after placebo/metreleptin in lipodystrophy vs. healthy volunteers), mixed models were fitted with treatment and patient group (including an interaction term) as fixed effects and patient as random effect. If appropriate we considered different error variances for the two patient groups in our mixed model. QQ plots and residual plots were used to evaluate model assumptions and ensure the validity of the statistical analyses.

Statistical significance was set at a p value <0.05. Since Study I had a single, predefined primary outcome, no correction for multiple testing was applied. All remaining p-values should be interpreted descriptively.

Data were analyzed using GraphPad Prism 9 for macOS Version 9.1.2 (GraphPad Software, San Diego, California USA, www.graphpad.com) and R 4.3.3 for fitting mixed models.

2.5. Study approval

Studies I and III were approved by the ethics committee of the Medical University of Vienna (Nr.:1884/2017) and by the Austrian Agency for Health and Food Safety (AGES). Written informed consent was obtained from all patients participating in the trial. The study was pre-registered on the European Clinical Trial database (EudraCT Nr. 2017-003014-22) and followed the recommendations of the Declaration of Helsinki for human experimentation.

Publication of the case report included in this manuscript was approved by the ethics committee of the Dokuz Eylul University (Nr.: 2017/03-25).

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3. Results

3.1. Study I (RCT)

3.1.1. Study cohort

The recruitment process is illustrated in the CONSORT flowchart shown in **Fig. S1**. We recruited 10 patients (8 females, 2 males; mean age ± SD: 49 ± 14 yrs) with either familial partial lipodystrophy ($n = 9$) or congenital generalized lipodystrophy ($n = 1$). Baseline characteristics and detailed genetic background of the participants are provided in **Table S2**.

MR data are available for 9 patients; of these, 5 were eligible for 7-Tesla MR, while 4 underwent 3-Tesla MR imaging. A measurement error occurred in the assessment of HCL in one patient eligible for the 7-Tesla MR at baseline before metreleptin injection, therefore this participant was excluded from the analysis of HCL changes.

3.1.2. Metreleptin increases hepatic VLDL1-TG secretion in patients with lipodystrophy

Hepatic VLDL1-TG secretion rate after a single subcutaneous injection of metreleptin was significantly higher compared to the placebo condition (mean change ± SD: +219 ± 149 mg/h metreleptin vs. placebo; $p = 0.001$; Fig. 1B and C). The increase in VLDL1-TG secretion was observed in all participants, with a mean effect size of 75 %. Apolipoprotein B concentration in the VLDL1 subfraction during the intralipid protocol showed no difference between treatments (Fig. 1D). VLDL2-TG levels and the rise in serum TGs following the intralipid infusion were comparable between the two conditions (Fig. 1E and F).

We found a trend towards an increase in HCL after placebo administration, which was absent following the metreleptin injection in the same patients (mean change ± SD after placebo: +0.6 ± 0.9 %, $p = 0.08$; after metreleptin −0.2 ± 1.3 %, $p = 0.73$) (Fig. 1G). The comparison between HCL relative change after placebo vs. after metreleptin missed statistical significance (mean difference ± SD: −8 ± 14 % metreleptin vs. placebo, $p = 0.14$) (Fig. 1H).

3.1.3. No acute effects of metreleptin on lipid and glucose metabolism

Four and a half h after the injection of placebo or metreleptin, we observed several changes in parameters of glucose and lipid metabolism including significant reductions in blood glucose, serum insulin, and C-peptide as well as a trend towards lower serum TGs, without significant differences between treatment conditions (Table 1). Plasma leptin decreased in the placebo condition, whereas after metreleptin injection the levels increased into the pharmacological range. Metreleptin had no acute effects on apolipoprotein B, LDL and HDL cholesterol, adiponectin or on IGFBP2.

3.1.4. No acute effects of metreleptin on lipolysis, beta oxidation, hepatic de novo lipogenesis and LPL activity

Circulating NEFA, an indicator of white adipose tissue lipolysis, showed a comparable increase after both placebo and metreleptin administration (mean relative change ± SD after placebo: +28 ± 36 %, $p = 0.04$; after metreleptin: +35 ± 38 %, $p = 0.02$) (Fig. 2A). We found no changes in plasma ketone bodies, which serve as indirect markers of hepatic beta oxidation, before and after placebo or metreleptin (median relative change (Q1–Q3) after placebo: +21.6 % (−3.7 % to 68.2 %), $p = 0.20$; after metreleptin: +34.4 % (−25.9 % to 112.5 %), $p = 0.20$) (Fig. 2B).

Metreleptin had no acute effect on various indicators of hepatic de novo lipogenesis, including the lipogenic index (C16/C18:2n6 ratio as proposed by Paglialunga et al. [39], median difference (Q1–Q3): 0.06 (−0.49 to 0.15) metreleptin vs. placebo, $p = 0.58$) (Fig. 2C), fatty acid composition of VLDL1 particles and plasma (Fig. 2D and E), or the proportion of saturated and monounsaturated fatty acids in VLDL1 particles (saturated fatty acids, mean difference ± SD: −0.21 ± 2.45 % metreleptin vs. placebo, $p = 0.79$; monounsaturated fatty acids, median difference (Q1–Q3): −0.96 % (−2.15 % to 0.06 %) metreleptin vs. placebo, $p = 0.09$) (Fig. 2F) [39,40]. Similarly, no significant changes were observed in the unsaturation index of the liver assessed through ^{1}H-MRS (mean relative change ± SD after placebo: −10 ± 36 %, $p = 0.25$; after metreleptin: +19 ± 46 %, $p = 0.18$) (Fig. 2G).

Notably, the mean ± SD percentage of linoleic acid in VLDL1 particles was 15.6 ± 3.1 %, which is comparable to previous reports [41] and markedly lower than the linoleic acid content of the intralipid solution (44–62 %), confirming that intralipid was efficiently removed during the ultracentrifugation process before isolating VLDL1 particles.

Since no post-heparin plasma to determine total lipase activity was available, we used ITC to assess the net effect of circulating LPL regulators on LPL activity. This exogenous LPL activity showed a mild decrease after placebo injection but was not affected by metreleptin administration (mean relative change ± SD after placebo: −5.7 ± 6.5 %, $p = 0.02$; after metreleptin: −1.9 ± 8.8 %, $p = 0.41$) (Fig. 2H). Plasma concentration of the LPL inhibitor ANGPLT3 did not change with either treatment (mean relative change ± SD after placebo: +0.5 ± 14.3 %, $p = 0.74$; after metreleptin: −5.3 ± 16.5 %, $p = 0.30$) (Fig. 2I).

3.1.5. No acute effects of metreleptin on hepatic energy metabolism

Metreleptin injection was associated with a mild but statistically significant reduction in Pi (mean relative change ± SD after placebo: +9 ± 23 %, $p = 0.54$; after metreleptin: −16 ± 13 %, $p = 0.05$) (Fig. 3A). However, γATP, Pi/γATP ratio, ATP synthesis rate as well as NADH concentration in the liver were not acutely affected by leptin administration (γATP, mean relative change ± SD after placebo: +2.6 ± 8.1 %, $p = 0.47$, after metreleptin: −7.1 ± 9.5 %, $p = 0.16$, Fig. 3B; Pi/γATP ratio mean relative change ± SD after placebo: +5.4 ± 18.5 %, $p = 0.62$, after metreleptin: −9.0 ± 14.2 %, $p = 0.23$, Fig. 3C; ATP synthesis rate mean relative change ± SD after placebo: +25 ± 97 %, $p = 0.87$, after metreleptin: −32 ± 30 %, $p = 0.10$, Fig. 3D; NADH mean relative change ± SD after placebo: +11 ± 31 %, $p = 0.53$, after metreleptin: −7.3 ± 26 %, $p = 0.75$).

3.1.6. No association between MASLD and common markers of insulin resistance in the lipodystrophy cohort

To assess whether MASLD is associated with insulin resistance and dyslipidemia in lipodystrophy, we investigated the correlations between baseline HCL and parameters of glucose and lipid metabolism in our cohort (**Fig. S2A–C**). Notably, we observed no significant associations between HCL and HbA1c, fasting TG levels, or fasting insulin levels.

3.2. Study II (case report)

A detailed description of this case report of a patient with CGL type 2 is provided in **supplementary file 1**. Briefly, the patient underwent liver transplantation due to progression of MASLD to liver cirrhosis at the age of 12 yrs. Her post-transplant immunosuppressive treatment included tacrolimus and, for the first 9 months after the transplant, also dexamethasone and mycophenolate mofetil. **Fig. S3A** and **B** shows chronological graphs for liver transaminases, triglycerides and HbA1c. Follow-up MRI revealed hepatic steatosis in the transplanted liver at 9 and at 30 months after transplantation (**Fig. S3C**, MR images available in **Fig. S4**). 35 months after the transplantation, the patient started metreleptin treatment due to worsening of glycemic control and hypertriglyceridemia despite intensified insulin therapy. Notably, metreleptin did not normalize liver enzymes, but improved hypertriglyceridemia and glycemic control without relevant impact on the Body Mass Index Standard Deviation Score (BMI-SDS = −2.5 before metreleptin and −2.6 eleven months after metreleptin) [42]. Despite amelioration in glucose and lipid metabolism, hepatic steatosis was still detectable with MR imaging up to 2 yrs after metreleptin therapy started (**Fig. S3C**, MR images available in **Fig. S4**).

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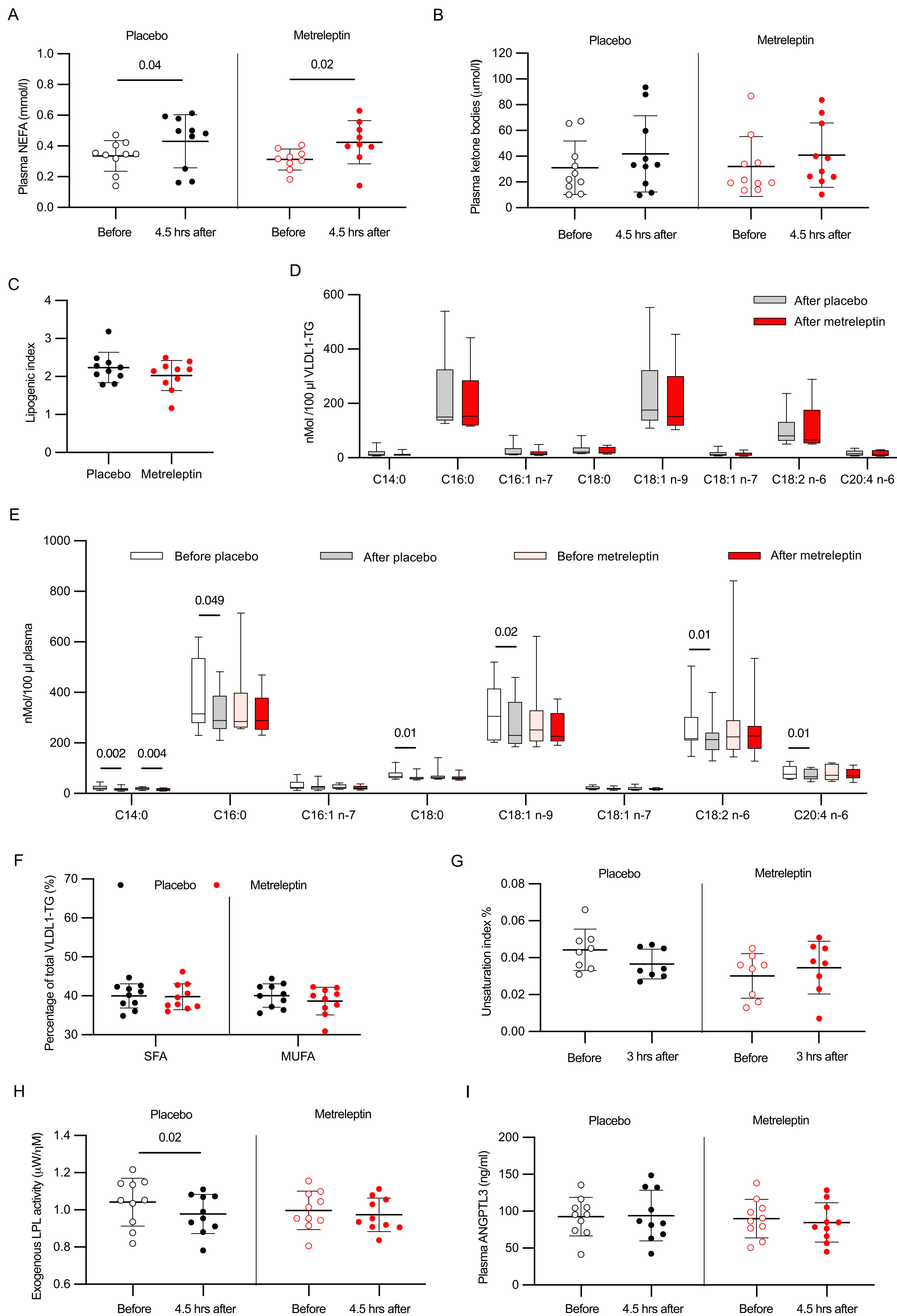

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Fig. 2. Effects of a single injection of metreleptin on lipolysis, beta oxidation, hepatic de novo lipogenesis and lipoprotein lipase activity.
A: Plasma non-esterified fatty acids (NEFA) before and after placebo vs. metreleptin (mean ± SD, n = 10). B: Plasma ketone bodies before and after placebo vs. metreleptin (mean ± SD, n = 10). C: Concentration of long-chain fatty acids in very low-density lipoprotein 1 triglycerides (VLDL1-TG) particles at timepoint 45 min into the intralipid protocol after placebo vs. metreleptin (whiskers of box blots represent the minimum and the maximum values, n = 10). D: Lipogenic index (C16/C18:2n6 ratio) of VLDL1-TG subfraction at timepoint 45 min into the intralipid protocol after placebo vs. metreleptin (mean ± SD, n = 10). E: Concentration of long-chain fatty acids in plasma before and after placebo vs. metreleptin (whiskers of box blots represent the minimum and the maximum values, n = 10). F: Percentage of saturated fatty acids (SFA) and of mono-unsaturated fatty acids (MUFA) in the VLDL1-TG subfraction at timepoint 45 min into the intralipid protocol after placebo vs. metreleptin (mean ± SD, n = 10). G: Unsaturation index of the liver assessed through ^{1}H-MRS before and 3 h after placebo vs. metreleptin (mean ± SD, n = 10). H: Exogenous lipoprotein lipase activity (LPL) in plasma before and 4.5 h after placebo vs. metreleptin (mean ± SD, n = 10). I: Plasma angiopoietin-like protein before and 4.5 h after placebo vs. metreleptin (mean ± SD, n = 10). All data used to generate these figures are included in online supplementary files. Only significant p-values (<0.05) are shown.

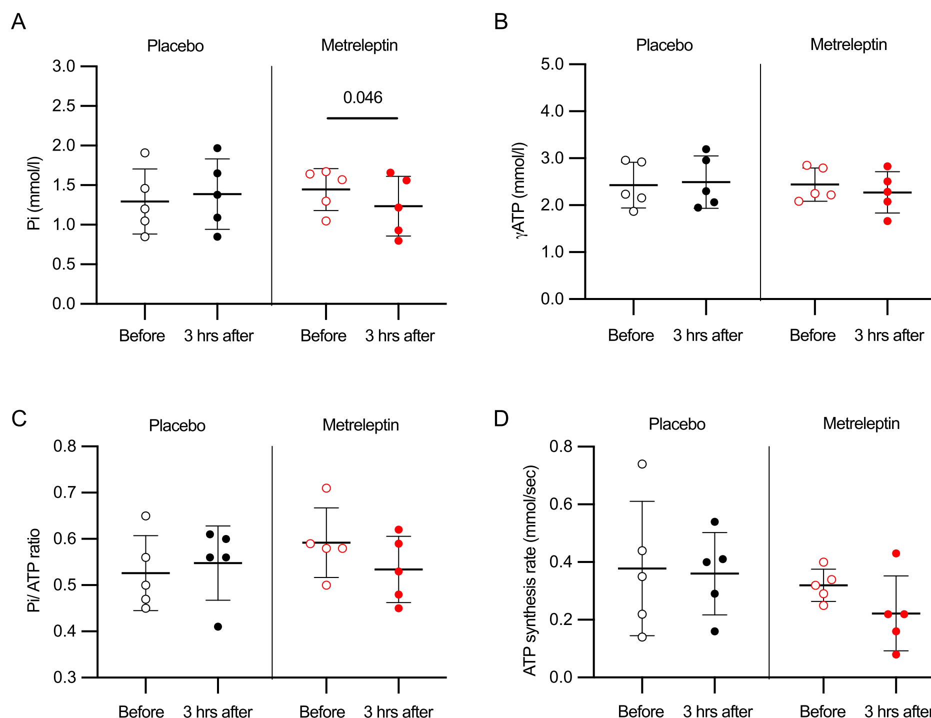

Fig. 3. Effects of a single injection of metreleptin on hepatic energy metabolism in patients with lipodystrophy.
A: Hepatic inorganic phosphate (Pi) before and 3 h after placebo vs. metreleptin (mean ± SD). B: γ adenosine triphosphate (γATP) before and 3 h after placebo vs. metreleptin (mean ± SD). C: Pi/γATP ratio before and 3 h after placebo vs. metreleptin (mean ± SD). D: ATP synthesis rate before and 3 h after placebo vs. metreleptin (mean ± SD). All data used to generate these figures are included in online supplementary files. Only significant p-values (<0.05) are shown.

3.3. Study III (exploratory cohort study)

3.3.1. Study cohorts

We performed an exploratory comparison of the 10 patients with lipodystrophy of study I and 13 healthy volunteers from our previous trial who underwent a similar intravenous fat emulsion test and MR protocol [20]. The two groups differed in terms of age (mean ± SD: 25.1 ± 5.1 yrs in the healthy cohort vs. 49 ± 14 yrs in the cohort with lipodystrophy, $p < 0.001$) and sex (13 male healthy subjects vs. 7 females and 3 males in the cohort with lipodystrophy). As expected, patients with lipodystrophy exhibited greater insulin resistance, hypertriglyceridemia (**Table S2**) and had higher HCL compared to healthy subjects (HCL mean ± SD: 1.5 ± 0.8 % in healthy individuals vs. 11.1 ± 7.6 % in the cohort with lipodystrophy, p < 0.001).

3.3.2. Reduced baseline VLDL1-TG secretion and LPL activity in patients with lipodystrophy compared to healthy individuals

The relative increase in VLDL1-TG secretion following an acute metreleptin injection in patients with lipodystrophy was more than doubled compared to that observed in healthy subjects (28 % in healthy controls vs. 75 % in the cohort with lipodystrophy), despite significantly lower post-injection plasma leptin levels (median (Q1–Q3): 97.9 (92.7 to 119.7) ng/ml in healthy controls vs. 37.4 (32.3 to 45.4) ng/ml in the cohort with lipodystrophy, p < 0.001).

Absolute VLDL-TG concentrations in unprocessed plasma assessed by NMR were significantly higher in the cohort with lipodystrophy in both conditions (Fig. 4A) [20], whereas hepatic VLDL1-TG secretion rates were similar to those of healthy controls regardless of the treatment (Fig. 4B). However, after adjusting for HCL, both plasma VLDL-TG concentrations and hepatic VLDL1-TG secretion rates were significantly lower in patients with lipodystrophy compared to healthy subjects (Fig. 4C and D).

Patients with lipodystrophy showed increased baseline levels of the LPL inhibitor ANGPLT3 (Fig. 4E) and lower exogenous LPL activity in all conditions (Fig. 4F).

4. Discussion

In our placebo-controlled, randomized, within-subject crossover study (Study I), we found that a single injection of metreleptin acutely increases hepatic VLDL1-TG secretion in patients with lipodystrophy and low endogenous leptin levels.

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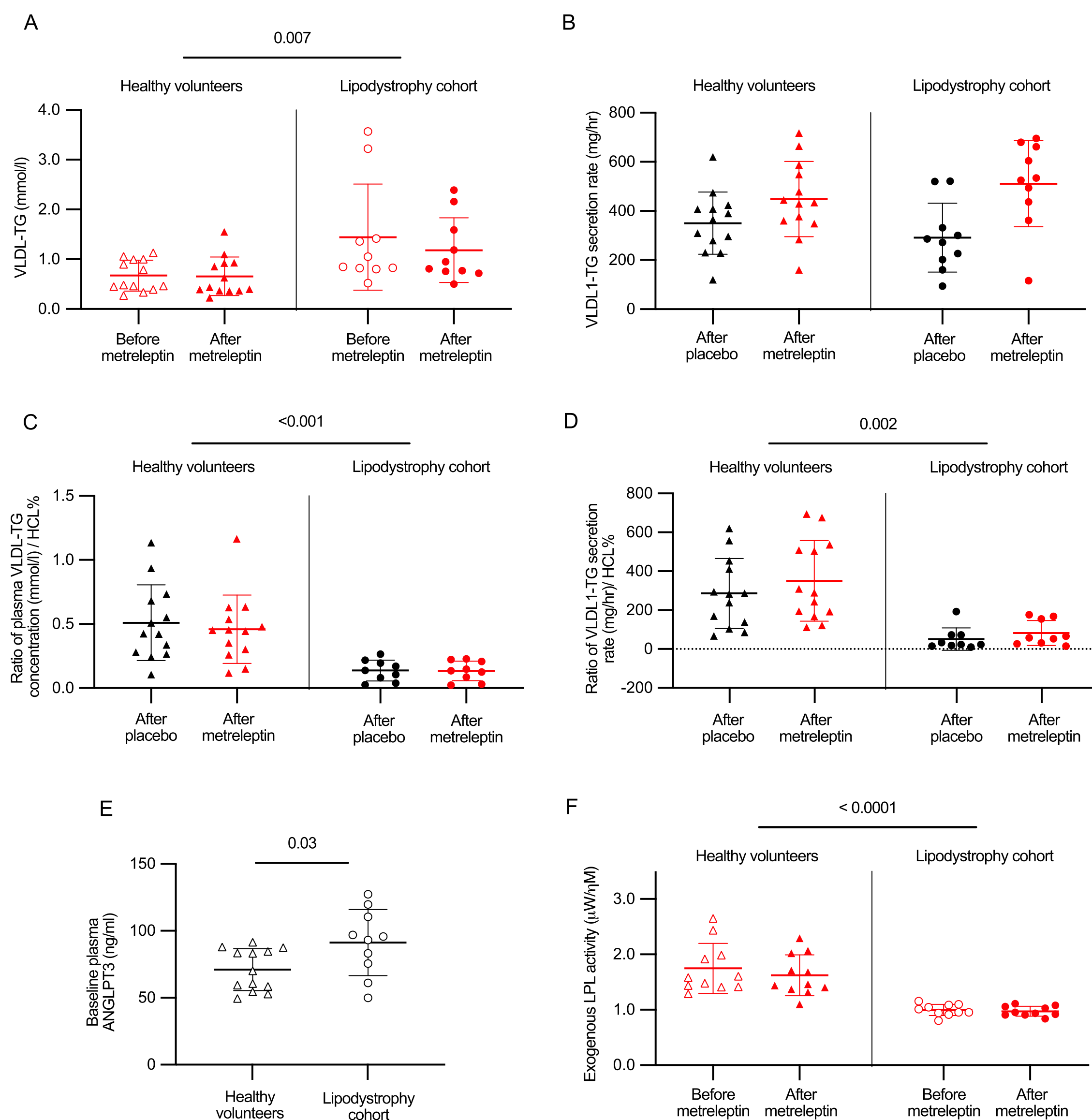

Fig. 4. Exploratory comparison of VLDL-TG metabolism and lipoprotein lipase activity between patients with lipodystrophy and healthy male volunteers (Study III). A: Concentration of VLDL-TG (mmol/l) in unprocessed plasma in patients with lipodystrophy and in healthy male volunteers before and 4.5 h after metreleptin injection (mean ± SD). B: Hepatic VLDL1-TG secretion rate (mg/h) 4.5 h after placebo and 4.5 h after metreleptin in patients with lipodystrophy and in healthy male volunteers (mean ± SD). C: Ratio of plasma concentration of VLDL-TG (mmol/l) and hepatic lipid content (HCL%) after placebo and after metreleptin in patients with lipodystrophy and in healthy male volunteers (mean ± SD). D: Ratio of hepatic VLDL1-TG secretion rate (mg/h) and HCL% after placebo and after metreleptin in patients with lipodystrophy and in healthy male volunteers (mean ± SD). E: Mean baseline plasma angiopoietin-like protein 3 (ANGLPT3) in patients with lipodystrophy and in healthy male volunteers (mean ± SD). F: Exogenous lipoprotein lipase activity (LPL) in plasma before and 4.5 h after metreleptin in patients with lipodystrophy and in healthy male volunteers (mean ± SD). The p-values displayed in the figures correspond to the main effect of the patient group factor in the mixed model. None of the interaction effects between treatment and patient group reached significance. As expected, given the increase in VLDL1-TG secretion after metreleptin in both cohorts, the main effect for the treatment factor was significant in B ($p = 0.03$) and D ($p = 0.02$). Only significant p-values (<0.05) are shown. All data used to generate these figures are included in online supplementary files.

While these results confirm our previous findings in healthy subjects [20], the effect in the cohort with lipodystrophy was more than twice stronger, despite significantly lower post-injection leptin levels. This suggests that the impact of metreleptin on VLDL1-TG export in patients with lipodystrophy is greater compared to subjects without lipodystrophy, consistent with the permissive role of endogenous leptin, which exerts stronger effects when leptin is deficient [38].

Several studies have demonstrated that long-term metreleptin therapy effectively improves MASLD in both adult and pediatric patients with lipodystrophy [5,11,12,14]. Metreleptin's anorexic effect contributes to its anti-steatotic action, yet it has been shown to reduce MASLD in lipodystrophy even when caloric intake was controlled for [12]. Furthermore, metreleptin led to improvements in MASLD as early as three days after therapy initiation, prior to any significant effect on body weight, in a patient with congenital leptin deficiency [43]. These findings in patients with hypoleptinemia suggest that leptin may exert an anti-steatotic effect independent of food intake and body weight, though the underlying mechanisms remained unclear so far. Given that hepatic TG export through VLDL1 particles represents a key anti-steatotic mechanism [17,18,20], our data suggest that the acute ability of metreleptin to increase hepatic VLDL1-TG export plays a role in its direct anti-steatotic action. Whether metreleptin also chronically stimulates hepatic VLDL1-TG secretion remains to be determined.

Our previous study in healthy male volunteers showed a mild, but

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consistent increase in HCL after placebo, likely due to prolonged fasting and increased lipid flux from white adipose tissue to the liver, as reflected by elevated NEFA levels [20,44]. In contrast, HCL remained stable after metreleptin, suggesting that metreleptin-induced VLDL1-TG export counteracted the increased lipid influx to the liver [20]. The cohort with lipodystrophy also exhibited elevated NEFAs under both conditions and no significant changes in HCL following metreleptin; however, after placebo HCL only showed a trend towards an increase, missing statistical significance ($p = 0.08$). Therefore, we cannot conclude that metreleptin acutely affected HCL within a 3-h time window as observed in healthy male volunteers. This may be due to the smaller sample size and the much higher HCL levels and variability in the cohort with lipodystrophy in combination with the short time course. Nevertheless, metreleptin's antisteatotic effects in states of leptin deficiency are well established and changes in HCL have been detected as early as three days after starting metreleptin in congenital leptin deficiency [43].

Previous studies in patients with lipodystrophy described that a 6-month therapy with metreleptin was associated with a decrease in lipolysis [12] and de novo lipogenesis [45], as well as with an increase in hepatic beta oxidation [45]. While these changes have a positive impact on HCL, in the setting of a chronic study it is impossible to differentiate whether they are direct effects of metreleptin or a mere consequence of reduced calorie consumption. A study that corrected for calorie intake showed that metreleptin over 14 days had no effect on lipolysis [12]. Similarly, in our current study and previous trial in healthy male volunteers [20], we did not observe any acute effect of metreleptin on lipolysis, de novo lipogenesis, or beta oxidation. However, since these parameters were assessed indirectly, their potential contribution to metreleptin's direct anti-steatotic effects cannot be ruled out. Further studies are needed to elucidate the weight-independent effects of metreleptin on these HCL determinants and their role in MASLD in lipodystrophy.

Metreleptin injection was associated with a significant decrease in liver P_i with no changes in γATP, P_i/γATP ratio, ATP synthesis rate and NADH concentration. These results are in line with those in healthy male subjects [20] and suggest that leptin does not acutely regulate energy metabolism in the liver.

Consistent with our previous findings in healthy male volunteers [20], despite the increase in VLDL1-TG secretion, total serum TG did not differ after metreleptin injection compared to placebo. This suggests that metreleptin stimulates the uptake of TG into other metabolically active tissues such as the muscle or the heart.

In our case report of a girl with CGL2 and liver transplantation (Study II), we observed that while metreleptin improved glycemic control and reduced serum triglycerides, it did not improve hepatic steatosis in liver MR imaging under stable BMI-SDS. This raises the possibility that the weight-loss-independent anti-steatotic effects of metreleptin in lipodystrophy may require autonomic innervation of the liver. Based on our previous findings in rodents and healthy humans indicating that metreleptin stimulates hepatic lipid secretion via the vagus nerve [19,20], we speculate that the failure to increase VLDL1-TG export may have contributed to the lack of improvement in MASLD. However, since we did not assess hepatic VLDL1-TG export or other determinants of HCL in this patient directly, we cannot definitively determine which anti-steatotic mechanism(s) of metreleptin may have been impaired. Additionally, interpreting this case is complex due to the potential influence of immunosuppressants on insulin sensitivity and liver function. While the patient had previously received dexamethasone and mycophenolate mofetil, metreleptin was initiated two years after their discontinuation, during a stable regimen of tacrolimus. Therefore, an interference of dexamethasone and mycophenolate mofetil with metreleptin's action is unlikely, whereas a potential influence of tacrolimus cannot be ruled out. Of note, even if metreleptin requires intact autonomic innervation of the liver to directly improve MASLD, patients with lipodystrophy who have undergone liver transplantation may still benefit indirectly from metreleptin due to improvements in their metabolic profile and reductions in hyperphagia. In fact, another case report of a 41-year-old female patient with acquired generalized lipodystrophy after liver transplantation demonstrated an improvement in hepatic steatosis under metreleptin therapy, which was associated with a 4 kg weight loss (~8 % of body weight) [46]. Nonetheless, our case report serves to raise awareness within the lipodystrophy community that the response to metreleptin in liver-transplanted patients with lipodystrophy and MASLD may be compromised.

Finally, while it is reasonable to hypothesize that the mechanisms by which metreleptin acutely stimulates VLDL1-TG export in lipodystrophy are similar to those in healthy individuals [20], further studies are needed to clarify this aspect and whether this has an impact on MASLD response to metreleptin in patients with lipodystrophy after liver transplantation.

Regarding possible hepatocellular effectors mediating the increase in VLDL1-TG export, our previous rodent studies found that a low dose intracerebroventricular leptin infusion targeting the brain led to increased liver expression of microsomal triglyceride transfer protein (MTTP), the rate-limiting enzyme responsible for lipidation during VLDL assembly [19]. In accordance, in both the cohort with lipodystrophy of Study I and the healthy volunteers [20] we found no differences in apolipoprotein B concentration in the VLDL1-TG subfraction between treatments, suggesting that the increase in VLDL1-TG export is due to elevated lipidation rather than increased numbers of particles. However, the exact molecular mechanism connecting brain leptin action with liver parasympathetic innervation and ultimately MTTP expression in rodents and humans is unknown.

A recent study found that patients with lipodystrophy not receiving metreleptin treatment had higher circulating total TG-rich lipoprotein particle concentrations compared to controls with metabolic dysfunction-associated steatohepatitis (MASH) without lipodystrophy [47]. Since TG-rich lipoprotein particles in the fasting state are primarily composed of VLDL, the authors proposed that there may be an upregulation of hepatic VLDL-TG export in lipodystrophy. However, this study did not directly assess VLDL1-TG secretion rate; additionally, a reduction in LPL activity reported in patients with lipodystrophy [25,48] could have contributed to this finding. In the exploratory cohort comparison (Study III), we also observed significantly higher baseline plasma VLDL-TG concentrations in the cohort with lipodystrophy compared to healthy individuals from our previous study [20], whereas the hepatic VLDL1-TG secretion rates were similar in the two cohorts. Of note, after adjusting for HCL, patients with lipodystrophy showed considerably lower plasma VLDL-TG concentrations and hepatic VLDL1-TG secretion rates in relation to their HCL content compared to healthy subjects. This adjustment is necessary since patients with lipodystrophy had markedly higher HCL and it has been shown that VLDL export increases with rising HCL as a protective mechanism to counteract steatosis [49,50]. The here observed reduced VLDL1-TG secretion rates after adjusting for HCL suggest that lipodystrophy is associated with decreased hepatic VLDL1-TG export capacity, which favors the development of MASLD and corroborates our hypothesis that metreleptin treatment in the state of hypoleptinemia improves MASLD by restoring a key anti-steatotic mechanism.

Reduced LPL activity has been reported in lipodystrophy [48,51], and it has been linked to elevated levels of circulating LPL inhibitors including ANGLPT3, ANGLPT8, and apolipoprotein C-III [25,52]. Consistent with these findings, we observed reduced exogenous plasma LPL activity and increased ANGPLT3 levels in patients with lipodystrophy compared to healthy subjects (Study III). With regard to the effects of metreleptin on LPL activity in lipodystrophy, a long-term treatment study has shown a reduction in the LPL inhibitor ANGPTL8 and in the LPL activator apolipoprotein C-II, yet without a net change in overall LPL activity [52]. Findings on other LPL inhibitors, such as ANGPTL3 [25,52] and apolipoprotein C-III [52,53], are conflicting. In the acute setting of our trial, we observed no significant changes in

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circulating ANGPTL3 and exogenous LPL activity following metreleptin administration in the cohort with lipodystrophy.

Of the nine patients with partial lipodystrophy who had available MR data, three had HCL measures between 3.1 and 5 %, indicating mild hepatic steatosis, and six had HCL levels >6.9 %, corresponding to severe hepatic steatosis [34]. Interestingly, we found no association between HCL and other metabolic parameters such as HbA1c, fasting insulin, or fasting triglycerides. In partial lipodystrophy, metreleptin is currently only approved by the EU, UK, Japan and Brazil when patients are not well controlled with standard metabolic treatments, which is often interpreted to refer to glucose control and hypertriglyceridemia. However, our data suggest that MASLD represents an entity that can sometimes be dissociated from HbA1c und TG levels in lipodystrophy. Our findings are supported by the results of an open label study [13], in which metreleptin for 12 months in patients with partial lipodystrophy and MASH led to an improvement in liver histology without changes in TGs, HbA1c and body weight. Further studies are needed to evaluate whether patients with partial lipodystrophy and isolated MASLD profit from leptin treatment.

Lastly, the effectiveness of metreleptin in the treatment of MASLD has implications that go beyond patients with lipodystrophy. There seems to be a continuum between partial lipodystrophies and individuals with no clinical lipodystrophy but reminiscent features, such as a tendency to store fat preferentially in the abdominal compartments rather than in the subcutaneous tissue of the lower extremities [54]. This "lipodystrophy-like" phenotype is associated with metabolic complications including MASLD and cardiovascular disease [55–58]. Epidemiologically speaking, about 22–25 % of patients with MASLD have normal body weight [59]. For these patients, there are currently no specific therapeutic options. Also based on the study of Akinci et al. [13], which showed anti-steatotic potential of leptin treatment in patients with MASH and relative hypoleptinemia (leptin levels below the 25th percentile for their BMI) but without lipodystrophy, we speculate that selected patients with lean MASLD could benefit from metreleptin treatment. Further studies are needed to investigate the effect and safety profile of metreleptin in such a lipodystrophy-like patient collective with MASLD.

4.1. Strengths and limitations

The main strength of Study I is the crossover, randomized, placebo-controlled within subject design. Despite the rarity of the disease, we were able to include 10 patients of both sexes thanks to the international recruitment across Europe. Although seven patients display the same genetic mutation and four siblings/parent-child pairs were recruited, the cohort was epidemiologically and clinically heterogeneous, increasing the external validity of the trial. However, the limited sample size and the inclusion of only four different forms of lipodystrophy (CGL2 and three FPLD subtypes) may restrict the generalizability of the findings to all lipodystrophy syndromes.

A further limitation that should be mentioned is that two patients exhibited particularly high TG levels (>300 mg/dl) before the intralipid protocol. Since this protocol is based on the competition between intralipid and endogenous VLDL1-TG, it is possible that the LPL activity in these cases was not completely inhibited so that the VLDL1-TG secretion may be underestimated. However, this was the case in both placebo and metreleptin condition of these patients and is therefore not expected to represent a significant bias.

To avoid confounding effects of leptin's anorexic action, in this study we investigated the acute effects of a single injection of metreleptin. Whether this effect persists under prolonged metreleptin administration remains to be determined.

Further determinants of HCL such as de novo lipogenesis, adipose tissue lipolysis and beta oxidation were only investigated through indirect measures, therefore their exact role in the food independent anti-steatotic effects of leptin remains to be clarified.

No adverse effects of metreleptin occurred during the study.

Due to the rarity of the clinical combination of lipodystrophy, liver transplantation and metreleptin therapy, it was not possible to recruit such patients in higher numbers for an RCT. However, we were able to find a case (Study II) with these exact features and back-to-back MR imaging before and after metreleptin treatment allowing us to observe whether leptin is still able to improve MASLD when the liver is decoupled from autonomic innervation.

Finally, our exploratory comparison between the cohort with lipodystrophy and the healthy individuals in Study III has limitations since the subjects were not matched for sex, age or metabolic health. Sex differences could be relevant since previous research observed that women exhibit lower plasma VLDL-TG concentrations and lower VLDL-TG secretion rates compared to men, regardless of adiposity; differences in VLDL-TG clearance were also described [50]. Sex differences within the cohort with lipodystrophy were not explored due to the limited sample size in this rare disease.

5. Conclusions

A single metreleptin injection in patients with lipodystrophy led to an acute 75 % increase in hepatic VLDL1-TG secretion, a key process that protects the liver from steatosis.

This newly described mechanism in lipodystrophy likely contributes to the direct, body weight-independent anti-steatotic effects of metreleptin, which may have therapeutic relevance for a broader spectrum of patients with lipodystrophy-like phenotypes and relative leptin deficiency. The lack of improvement in hepatic steatosis under metreleptin treatment in a liver-transplanted patient with CGL2 despite ameliorated glucose and lipid metabolism suggests that metreleptin may require intact autonomic innervation of the liver to exert its direct anti-steatotic effects, as we previously observed in rodents and healthy volunteers [19,20]. However, further investigation is needed to confirm this hypothesis in lipodystrophy.

CRediT authorship contribution statement

Marianna Beghini: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Matthäus Metz:** Writing – review & editing, Methodology, Investigation, Data curation. **Clemens Baumgartner:** Writing – review & editing, Investigation. **Peter Wolf:** Writing – review & editing, Supervision. **Magdalena Bastian:** Writing – review & editing. **Martina Hackl:** Writing – review & editing, Methodology. **Sabina Baumgartner-Parzer:** Writing – review & editing, Resources. **Rodrig Marculescu:** Writing – review & editing, Investigation. **Michael Krebs:** Writing – review & editing. **Jürgen Harreiter:** Writing – review & editing, Supervision. **Stephanie Brandt:** Writing – review & editing. **Konstanze Miehle:** Writing – review & editing. **Giovanni Ceccarini:** Writing – review & editing. **Silvia Magno:** Writing – review & editing. **Caterina Pelosini:** Writing – review & editing. **Christel Tran:** Writing – review & editing. **Alessandra Gambineri:** Writing – review & editing. **Carolina Cecchetti:** Writing – review & editing. **Liliana-Imi Gard:** Writing – review & editing, Methodology. **Robert Risti:** Writing – review & editing, Methodology. **Aivar Lõokene:** Writing – review & editing, Methodology. **Lorenz Pfleger:** Writing – review & editing, Investigation. **Michael Trauner:** Writing – review & editing, Resources. **Alexandra Kautzky-Willer:** Writing – review & editing, Resources. **Michael Stumvoll:** Writing – review & editing. **Martin Wabitsch:** Writing – review & editing. **Ferruccio Santini:** Writing – review & editing. **Ihsan Turan:** Writing – review & editing, Investigation. **Baris Akinci:** Writing – review & editing, Investigation. **Florian Frommlet:** Writing – review & editing, Formal analysis. **Herbert Stangl:** Writing – review & editing, Methodology. **Clemens Fürnsinn:** Writing – review & editing, Methodology. **Thomas Scherer:** Writing – review & editing, Visualization, Supervision, Resources, Project administration,

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Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

The following individuals have received fees for consulting and/or received travel funds and/or grant support and/or participated in studies sponsored by Amryt Pharmaceuticals now a wholly owned subsidiary of Chiesi Farmaceutici SpA: M. Beghini, K.M., G.C., S.M., C.P., A.G., M.S., M.W., F.S., B.A. and T.S.

M. Krebs has received research support from AstraZeneca and Fit for Me, speaker and consulting fees from Merck, Wörwag, Lilly, Takeda, Ipsen and Sanofi and travel support from Pfizer, Novo Nordisk, Merck, Ipsen, HRA Pharma and Boehringer-Ingelheim.

K.M. received speaker's honoraria and acted as a scientific advisor for Amryt Pharmaceuticals now a wholly owned subsidiary of Chiesi Farmaceutici SpA.

G.C. has received fees for consulting and/or received travel funds or participated in studies sponsored by Rhythm Pharmaceuticals.

M.T. has received research grants from Albireo, Alnylam, Cymabay, Falk, Gilead, Intercept, MSD, Takeda and Ultragenyx and travel grants from Abbvie, Falk, Gilead Intercept and Jannsen. He further has advised for Abbvie, Albireo, BiomX, Boehringer Ingelheim, Falk Pharma GmbH, Genfit, Gilead, Hightide, Intercept, Janssen, MSD, Novartis, Phenex, Pliant, Regulus, Siemens and Shire and has served as speaker for BMS, Falk, Gilead, Intercept, Madrigal and MSD. He is a co-inventor of patents for the medical use of norUDCA (nor-ursodeoxycholic acid/norucholic acid) filed by the Medical Universities of Graz and Vienna.

B.A. ran projects for and/or served as a consultant, board member, steering committee member, and/or speaker to Amryt Pharmaceuticals now a wholly owned subsidiary of Chiesi Farmaceutici SpA, Alnylam, Regeneron, ThirdRock Ventures, Astra Zeneca, Novonordisk, Boehringer Ingelheim, Sanofi, Bilim Ilac, ARIS, and Servier.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2025.156261.

Data availability

The data used to generate the graphs and the tables of the paper can be found in the file Data S1 – Source Data. Any additional information required to reanalyze the data is available from the corresponding author upon reasonable request.

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