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The effect of curcumin on hepatic fat content in individuals with obesity

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Abstract

Aim: To evaluate the effect of curcumin treatment on hepatic fat content in obese individuals.

Materials and Methods: In a double-blind, parallel-group trial, 37 obese, non-diabetic individuals were randomized to placebo or curcumin treatment for 6 weeks. Curcumin was dosed as lecithin-formulated tablet; 200 mg twice daily. The primary endpoint was hepatic fat content as assessed by magnetic resonance spectroscopy (MRS). Other endpoints included anthropometric measurements, hepatic biomarkers including FibroScan measurements, metabolic variables, inflammation markers, appetite measures and *ad libitum* food intake.

Results: Baseline characteristics (mean ± SD) were age 46 ± 14 years, hepatic fat content 12.2% ± 8.8% points, body mass index 38.8 ± 6.1 kg/m^2 and waist circumference 125.8 ± 12.3 cm. After 6 weeks of treatment with curcumin, hepatic fat content was changed by −0.86% points (95% CI −3.65; 1.94) compared with 0.71% points (95% CI − 2.08; 3.51) with placebo, thus resulting in a non-significant estimated treatment difference of −1.57% points (95% CI −5.36; 2.22, $P = .412$). Compared with placebo, curcumin treatment caused small reductions in fasting plasma glucose (estimated treatment difference [ETD] − 0.24 mmol/L [95% CI −0.45; −0.03]), triglycerides (ETD [percentage change] −20.22% [95% CI −33.21; −6.03]) and gamma glutamyltransferase (ETD [percentage change] −15.70% [95% CI −23.32; −7.32]), but except for gamma glutamyltransferase, none of these differences remained statistically significant after adjusting for multiple testing. Treatment was well tolerated.

Conclusions: Compared with placebo, curcumin treatment for 6 weeks had no significant effect on MRS-assessed hepatic fat content in obese individuals with primarily mild steatosis. Curcumin was well tolerated.

1 | INTRODUCTION

The growing prevalence of obesity is strongly associated with hepatic steatosis and, thus, an increase in the prevalence of non-alcoholic fatty liver disease (NAFLD). In the Western world, NAFLD affects 25%-30% of the general population.[1] Ultimately, NAFLD can result in non-alcoholic steatohepatitis, cirrhosis and hepatocellular carcinoma.[2] Despite the severe consequences of NAFLD, effective management is currently limited to lifestyle-induced weight loss. Few drugs have shown moderately positive effects on NAFLD,[3,4] but the side effects and questionable durability of these drugs call for more research.

Several medical plant-derived supplements have been explored for their potential beneficial effects in hepatic steatosis. Systematic reviews of the literature suggest that curcumin, a phenolic compound extracted from the turmeric root (*Curcuma longa*), reduces hepatic fat content (HFC) in NAFLD.[5,6] However, no studies have assessed HFC using magnetic resonance spectroscopy (MRS), which is regarded as the gold standard for non-invasive measurement of HFC,[7-9] and only one study has assessed liver stiffness with FibroScan,[10] a marker of fibrosis. Also, meta-analyses have shown that curcumin can improve several liver-related variables in individuals with NAFLD, including circulating levels of alanine transaminase, aspartate transaminase, total and low-density lipoprotein cholesterol, triglyceride as well as fasting plasma glucose, HbA1c, hyperinsulinaemia, insulin resistance (according to homeostatic model assessment [HOMA-IR]), body weight, body mass index (BMI) and waist circumference.[11-15] Furthermore, curcumin seems to have anti-inflammatory properties.[16-19]

As obesity-associated hepatic steatosis is strongly correlated with reduced glucose tolerance and the development of type 2 diabetes, it is worth mentioning that no studies have examined the effect of long-term curcumin treatment on oral glucose tolerance or insulin, glucagon and glucagon-like peptide-1 (GLP-1) responses during an oral glucose tolerance test (OGTT) in obese individuals.

Here, we used a randomized placebo-controlled parallel group design to investigate the effect of 6 weeks of curcumin treatment on MRS-assessed HFC in obese individuals. The majority of the individuals had mild steatosis. Also, the effects of curcumin on anthropometric measurements, hepatic biomarkers (including FibroScan measurements), metabolic variables, inflammation markers, appetite measures and *ad libitum* food intake were investigated.

2 | MATERIALS AND METHODS

2.1 | Trial design, approval and ethics

The study was a single-centre, randomized, double-blind, placebo-controlled, parallel-group trial investigating the effect of 6 weeks of curcumin treatment on HFC in individuals with obesity and was conducted from April 2019 to December 2020 at the Center for Clinical Metabolic Research, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark, in accordance with the Declaration of Helsinki (2013 edition) and Good Clinical Practice guidelines. The study was approved by the Scientific–Ethical Committee of the Capital Region of Denmark (ID no.: H-18045227) and the Danish Data Protection Agency (J. no.: VD-2018-385/ I-Suite no.: 6636) and was registered at www.clinicaltrials.gov (registration no.: NCT03864783). Written informed consent was obtained from all participants before screening.

2.2 | Eligibility criteria

Inclusion criteria were age above 20 years, BMI above 27 kg/m^2 and the participants should have a steatosis diagnosis within the last 3 years, without significant weight loss in the subsequent 3 years. If the participant had no diagnosis of steatosis, the participant should have a BMI above 30 kg/m^2 and meet two of the following criteria: steatosis on FibroScan (controlled attenuation parameter [CAP] value above 325 dB), waist circumference above 94 cm, HbA1c above 48 mmol/mol or fatty liver index score above 60%.[20,21] Key exclusion criteria were use of glucose-lowering, lipid-lowering or steatogenic drugs, known viral, inherited or alcoholic liver disease, history of alcohol abuse, adhering to a weight management programme and any condition or clinical or biochemical signs considered incompatible with participation by the investigator.

2.3 | Treatment and randomization

Included participants were randomized to curcumin or placebo (1:1). Curcumin was administered as tablets containing Meriva (Indena S.p.A. Milan, Italy) 1000 mg twice daily, corresponding to 400 mg of curcuminoids. All tablets were produced and sponsored by the manufacturers who otherwise had no role in the study design, data collection, data analysis, data interpretation or publication of this manuscript. Placebo and Meriva tablets contained the same ingredients except for curcuminoids. For simplicity, Meriva tablets are referred to as curcumin in the following. Compliance was considered acceptable if more than 75% of dosages were ingested. Participants reported missed dosages, concomitant medication and adverse events during the trial. The randomization was performed by a person not otherwise involved in the study by producing a sequence of random numbers using www.random.org referring to the number on a bag containing trial product. The participants, radiologist, laboratory technicians and investigators were blinded to treatment allocation until the primary analysis was finalized.
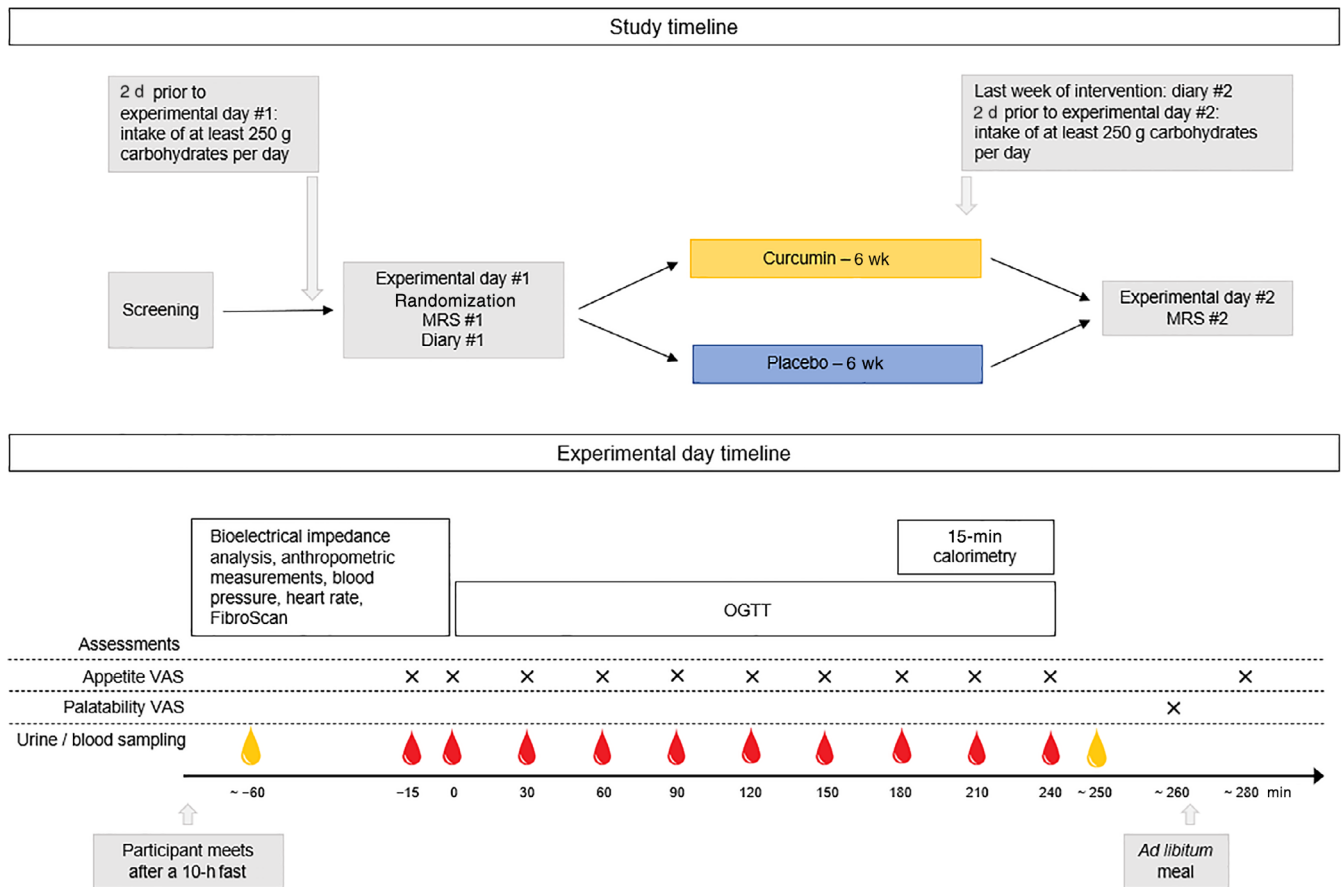
FIGURE 1 Timeline of the study and timeline of experimental days. Red drop indicates blood sampling, yellow drop indicates urine sampling. MRS, magnetic resonance spectroscopy; OGTT, oral glucose tolerance test; VAS, visual analogue scale

2.4 | Procedures

After inclusion, participants attended baseline MRS (including measurement of volume of visceral adipose tissue [VAT] and volume of subcutaneous adipose tissue [SAT]), experimental day #1 and filled out a 3-day diary of food consumption and physical activity. After this, they were randomized to 6 weeks of intervention. After intervention, the assessments were repeated (Figure 1). A detailed description of the study timeline and all procedures are found in Appendix S1. MRS was performed at the Department of Radiology, Herlev Hospital, University of Copenhagen, Herlev, Denmark, using a 3.0-T Ingenia magnetic resonance imaging (MRI) system (Philips Medical Systems, Best, The Netherlands) and the MRI protocol included planning scans and single-voxel spectroscopy for measuring HFC. Scans were evaluated by the same radiologist and HFC was calculated as previously described.[22] At each experimental day, participants met in the research facility after an overnight 10-hour fast. First, the participants were asked to void the urinary bladder and a urine sample was collected. Bioelectrical impedance analysis, waist circumference, hip circumference and body weight were assessed. Next, with participants positioned comfortably on a hospital bed, after at least 10 minutes of rest, blood pressure and heart rate were measured and transient elastography (FibroScan) was performed, and a cannula was inserted in a

cubital vein for blood sampling. The forearm was wrapped in a heating pad for arterialization of venous blood. At time point 0 minutes, 75 g of glucose dissolved in 300 ml of tap water was ingested over 5 minutes. Blood samples were collected at time points of −15, 0, 30, 60, 90, 120, 150, 180, 210 and 240 minutes. Appetite sensations were assessed by visual analogue scale (VAS) at time points 0, 30, 60, 90, 120, 150, 180, 210 and 240 minutes and 10 minutes after termination of a subsequent *ad libitum* meal (see below). Between 180 and 240 minutes, resting energy expenditure was assessed by indirect calorimetry. After blood sampling at time point 240 minutes, participants voided their bladder and urine was sampled. Lastly, participants were served an *ad libitum* meal consisting of minced meat, pasta, corn, carrots and green pepper (1.47 kcal/g: 36% of energy as fat, 15% as protein, 48% as carbohydrates and 1% as dietary fibre) (Figure 1). A detailed description of all methods including biochemical analyses can be found in Appendix S1.

2.5 | Calculations and statistical analysis

Calculations of fatty liver index score, FIB4 score, HOMA2-IR, urine albumin/creatinine ratio, composite appetite score and area under the curve (AUC) for variables measured during OGTT are described in

Appendix S1. Based on a previous study by Belfort et al.,[23] we expected that the SD of the change in hepatitis fat content would be 3.1% points. Thus, 18 participants in each arm were needed to detect a minimum clinically relevant reduction in HFC by 15% with 80% power. For all continuous variables, a constrained linear mixed model with inherent baseline adjustment[24] was used to estimate the effect of curcumin compared with placebo. An unstructured covariance pattern was assumed to account for repeated measurements on each study participant. Skewed data were log-transformed prior to analysis. P values for secondary and exploratory end points in turn were adjusted for multiple testing using the method of Benjamini–Hochberg,[25] which controls the false discovery rate. An adjusted P value of less than .05 was considered statistically significant. In Appendix S1, the endpoints are listed grouped as secondary and exploratory endpoints. R version 4.0.3 was used for statistical analyses. All graphs were made with GraphPad Prism v. 9.0.0. Figure 1 was created in Microsoft PowerPoint.

3 | RESULTS

3.1 | Participant characteristics and safety

We screened 86 persons after informed consent was given. Forty-seven were ineligible for participation. The investigator excluded two for practical reasons related to the severe acute respiratory syndrome coronavirus 2 pandemic causing national lockdown, and their results were excluded from all analyses. One participant could not cooperate with the second MRS at end-of-treatment (EOT) because of claustrophobia. Thirty-seven participants completed experimental day #2, and 36 participants completed the second MRS. All participants were Caucasian. No participants had an HbA1c above 48 mmol/mol at inclusion or a BMI below 30 kg/m². Three participants had a glucose value of 11.1 mmol/L or higher at time point 120 minutes during the first OGTT and 11 participants reached 11.1 mmol/L or higher at some point during the first OGTT. At the first OGTT, 22 individuals had a fasting glucose of 5.5 mmol/L or above and 17 individuals had plasma glucose of 7.8 mmol/L or higher at time point 120 minutes. Ten individuals had HFC below 5.5% and 17 individuals had mild steatosis in MRS #1 (the maximum HFC was 27.1%); however, all results were included in statistical analysis, regardless of the result being below or above 5.5% at baseline. Baseline characteristics for all participants are shown in Table 1. Compliance was satisfying (above 95% ingested dosages). Seven adverse events were reported in the placebo group versus nine in the curcumin group. No participants left the study because of side effects. A participant in the placebo group had a short visit to the emergency department with dyspnoea, presumably anxiety-related and not related to study product or procedures. One participant in the curcumin group experienced a decrease in leukocyte and erythrocyte counts at experimental day #2, but showed no symptoms related to this, and values were normalized at a follow-up visit. All other reported adverse events were mild and did not interfere with the daily life of the participants. We found no statistically significant effect of curcumin on safety measures (creatinine, urine albumin, urine creatinine, urine

TABLE 1 Participant baseline characteristics

	Placebo (mean ± SD)	Curcumin (mean ± SD)
Men/women (- / -)	14 / 5	13 / 5
Age (y)	47.7 ± 12.1	44.8 ± 15.8
BMI (kg/m²)	39.5 ± 6.8	38.0 ± 5.5
Waist circumference (cm)	127.0 ± 13.5	124.5 ± 11.5
HFC (%)†	14.7 ± 8.8	9.5 ± 8.4
Liver stiffness (kPa)†	6.0 ± 2.1	6.7 ± 3.5
HbA1c (mmol/Mol)	35.8 ± 4.0	34.2 ± 3.4
Body fat percentage (%)†	42.0 ± 7.8	42.3 ± 6.7

Abbreviations: BMI, body mass index; HFC, hepatic fat content.
†HFC measured by magnetic resonance spectroscopy; liver stiffness measured by FibroScan; body fat percentage measured by bioelectrical impedance analysis.
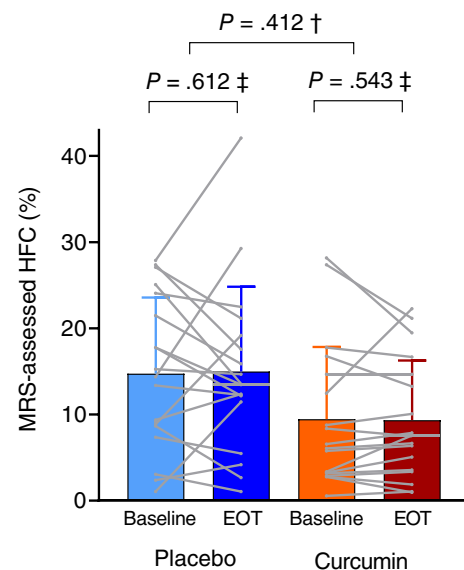

FIGURE 2 Hepatic fat content (HFC) measured by magnetic resonance spectroscopy (MRS) (mean ± SD) before and after intervention (baseline and end-of-treatment [EOT]) in 36 obese individuals randomized (1:1) to 6 weeks of placebo or curcumin treatment. Individual changes are shown in grey. Dagger (†) indicates P value from comparison of the estimated mean differences from baseline to EOT in the two groups, that is, estimated treatment difference. Double daggers (‡) indicate P value of the difference from baseline to EOT within each of the two groups

albumin/creatinine ratio, heart rate, systolic or diastolic blood pressure) (Table S1).

3.2 | Hepatic fat content

We found no effect of curcumin on changes in HFC from baseline to EOT (mean difference −0.86% points [95% CI −3.63; 1.94]; P = .543) or when comparing with placebo (ETD −1.57% points [95% CI −5.36; 2.22]; P = .412) (Figure 2).

TABLE 2 Baseline-adjusted effects of curcumin and placebo on anthropometric measurements, hepatic variables, metabolic variables and inflammation markers

	Baseline outcome (95% CI)[†]	Δ placebo (95% CI)[‡]	Δ curcumin (95% CI)[‡]	ETD curcumin versus placebo (95% CI)[‡]	P (unadjusted/ adjusted)
Anthropometric measurements					
BMI (kg/m^2)	38.31 (36.45; 40.28)	0.61 (2.22; 10.00)%	0.30 (−0.09; 0.70)%	−0.31 (−0.84; 0.23)%	0.262/ 0.550
Waist circumference (cm)	125.8 (121.7; 129.9)	−0.1 (−1.5; 1.3)	−1.4 (−2.8; 0.0)	−1.3 (−3.3; 0.6)	0.184/ 0.483
Waist−hip ratio	1.1 (1.0; 1.1)	−0.0 (−0.0; 0.0)	−0.0 (−0.0; −0.0)	−0.0 (−0.0; 0.0)	0.409 / 0.872
SAT (cm^3)	499.2 (436.0; 562.4)	−2.0 (−11.1; 7.15)	0.5 (−8.9; 9.9)	2.5 (−10.5; 15.4)	0.702 / 0.920
VAT (cm^3)	261.7 (224.9; 298.6)	−1.7 (−10.9; 7.60)	−4.8 (−14.1; 4.5)	−3.1 (−15.6; 9.3)	0.616 / 0.872
Hepatic biomarkers					
CAP (dB)	335.7 (321.2; 350.2)	4.5 (−13.8; 22.7)	8.0 (−11.0; 26.9)	3.5 (−21.9; 28.9)	0.784 / 0.920
Liver stiffness (kPa)	5.81 (5.07; 6.66)	4.84 (−10.14; 22.32)%	−11.28 (−24.49; 4.24)%	−15.37 (−31.78; 4.98)%	0.127 / 0.438
FIB4 score	0.7 (0.6; 0.8)	−1.7 (−13.4; 11.5)%	9.0 (−3.6; 23.1)%	10.9 (−6.9; 32.0)%	0.243 / 0.550
Alanine transaminase [§] (U/L)	43.11 (36.56; 49.66)	−2.67 (−8.20; 2.85)	−0.07 (−5.74; 5.61)	2.61 (−5.16; 10.38)	0.505 / 0.663
Aspartate transaminase [§] (U/L)	27.11 (24.22; 29.99)	−0.26 (−3.19; 2.67)	0.22 (−2.79; 3.22)	0.46 (−3.56; 4.51)	0.815 / 0.856
Lactate dehydrogenase [§] (U/L)	184 (175; 193)	13 (3; 22)	3 (−6;13)	−9 (−21; 3)	0.146 / 0.438
Alkalic phosphatase [§] (U/L)	83.8 (72.9; 94.7)	−1.0 (−4.0; 2.1)	−2.4 (−5.6; 0.7)	−1.5 (−5.5; 2.5)	0.463 / 0.648
GGT [§] (U/L)	28.33 (23.84; 33.66)	13.31 (6.02; 21.10)%	−4.48 (−10.78; 2.27)%	−15.70 (−23.32; −7.32)%	<0.001 / 0.013
Bilirubin [§] (μmol/L)	9.87 (8.19; 11.56)	−0.29 (−1.48; 0.89)	0.40 (−0.78; 1.59)	0.69 (−0.85; 2.23)	0.371 / 0.872
Ferritin [§] (μg/L)	128.0 (104.3; 151.7)	−11.5 (−23.9; 0.9)	−14.5 (−27.2; −1.8)	−3.0 (20.8; 14.8)	0.739 / 0.920
Albumin [§] (g/L)	39.29 (38.54; 40.04)	−0.02 (−0.84; 0.80)	−0.30 (−1.17; 0.57)	−0.28 (−1.40; 0.83)	0.613 / 0.872
Platelets [§] (number of platelets × 10^9/L)	258.8 (239.4; 278.2)	7.3 (−8.3; 22.8)	−8.6 (−23.6; 6.5)	−15.8 (−37.3; 5.8)	0.148 / 0.840
Estimated urea production (mmol/min)	0.30 (0.27;0.33)	0.02 (−0.02; 0.05)	0.01 (−0.03; 0.05)	−0.01 (−0.05;0.04)	0.822 / 0.939
FGF21 [§] (pg/ml)	154 (117; 203)	3 (−20; 32) %	−13 (−32; 13) %	−15 (−40; 20) %	0.352 / 0.872
Metabolic variables					
HOMA2-IR [§]	2.54 (2.10; 2.97)	0.24 (−0.09; 0.56)	−0.15 (−0.48; 0.19)	−0.38 (−0.84; 0.07)	0.098/ 0.438
HbA1c [§] (mmol/mol)	35.03 (33.78; 36.26)	0.20 (−0.52; 0.92)	−0.66 (−1.38; 0.07)	−0.86 (−1.82; 0.11)	0.080 / 0.438
Glucose					
Fasted state (mmol/L)	5.55 (5.38; 5.72)	0.11 (−0.04; 0.26)	−0.13 (−0.28; 0.02)	−0.24 (−0.45; −0.03)	0.027 / 0.284
AUC (0-240 min) (mmol/L × h)	29.2 (28.0; 30.5)	0.1 (-0.9; 1.1)	-0.2 (-1.2; 0.9)	-0.3 (-1.7; 1.2)	0.700 / 0.817

TABLE 2 (Continued)

	Baseline outcome (95% CI)[†]	Δ placebo (95% CI)[‡]	Δ curcumin (95% CI)[‡]	ETD curcumin versus placebo (95% CI)[‡]	P (unadjusted/ adjusted)
Insulin					
Fasted state (pmol/L)	136.9 (111.5; 162.2)	11.9 (−7.0; 30.8)	−8.6 (−28; 10.7)	−20.5 (−46.3; 5.2)	0.116/ 0.438
AUC (0-240 min) (pmol/L × h)	2312 (1808; 2816)	125 (-150; 399)	−42 (-323; 240)	-166 (-537; 205)	0.375/ 0.648
C-peptide					
Fasted state (pmol/L)	781.5 (693.8; 869.1)	20.8 (−34.2; 75.8)	−8.5 (−64.8; 47.9)	−29.2 (106.1; 47.6)	0.450/ 0.648
AUC (0-240 min) (pmol/L × h)	8312 (7502; 9120)	-326 (-774; 123)	-368 (-828; 92)	-42 (-669; 585)	0.894/ 0.894
Glucagon					
Fasted state (mmol/L)	10.4 (8.2; 12.2)	22.4 (−7.2; 61.5)%	1.5 (−23.6; 34.8)%	−17.1 (−42.9; 20.4)%	0.320 / 0.611
AUC (0-240 min) (mmol/L × h)	28.1 (22.3; 33.9)	-0.5 (-6.3; 5.3)	-1.8 (-7.7; 4.2)	-1.3 (-9.6; 7.0)	0.759 / 0.839
GLP-1					
Fasted state (mmol/L)	7.3 (5.7; 8.8)	0.4 (−1.7; 2.5)	−0.7 (−2.9; 1.4)	−1.1 (−4.0; 1.8)	0.440 / 0.648
AUC (0-240 min) (mmol/L × h)	36.5 (30.2; 42.9)	−5.1 (−11.3; 1.2)	−3.0 (−9.4; 3.3)	2.2 (−6.2; 10.6)	0.604 / 0.746
High-density lipoprotein [§] (mmol/L)	0.99 (0.93; 1.06)	3.03 (−1.23; 7.48)%	−0.59 (−2.26; 9.91)%	−3.52 (−9.02; 2.31)%	0.228 / 0.840
Total cholesterol [§] (mmol/L)	4.57 (4.35; 4.79)	0.04 (−0.13; 0.21)	−0.09 (−0.27; 0.08)	−0.13 (−0.37; 0.11)	0.284 / 0.840
Triglyceride [§] (mmol/L)	1.46 (1.30; 1.63)	10.82 (−1.90; 25.19)%	−12.14 (−22.48; −0.04)%	−20.22 (−33.21; −6.03)%	0.008 / 0.275
Resting energy expenditure (estimated kcal per day)	2108 (1959; 2257)	23 (−65; 112)	5 (−87; 96)	−19 (−145; 108)	0.769 / 0.917
Inflammation markers					
TNF-alpha [§] (pg/ml)	1.20 (1.10; 1.30)	−3.78 (−9.02;1.75)%	−1.24 (−6.75; 4.59)%	2.6 (−4.98; 10.86)%	0.502 / 0.872
IL-6 [§] (pg/ml)	1.31 (1.01; 1.07)	−0.19 (−11.32; 12.34)%	8.47 (−3.62; 22.09)%	8.67 (−7.31; 27.43)%	0.300 / 0.840
IL-8 [§] (pg/ml)	4.52 (4.05; 5.03)	−3.20 (−12.70; 7.34)%	−7.53 (−16.84; 2.81)%	−4.48 (−17.29; 10.32)%	0.528 / 0.872
IL-10 [§] (pg/ml)	0.30 (0.26; 0.34)	−6.41 (−15.61; 3.80)%	−1.72 (−11.37; 8.97)%	5.00 (−7.37; 19.03)%	0.440 / 0.872
IFN-gamma [§] (pg/ml)	6.01 (5.11;7.06)	−5.06 (−18.61; 10.74)%	−2.94 (−17.10; 13.65)%	2.24 (−17.09; 26.07)%	0.834 / 0.948
Hs-CRP [§] (mg/l)	2.27 (1.69; 3.04)	8.47 (−13.36; 35.80)%	8.84 (−13.10; 36.33)%	0.34 (−25.57; 35.27)%	0.982 / 0.989
YKL-40 [§] (ug/L)	51.60 (41.79; 61.40)	−0.20 (−8.45; 8.04)	−5.79 (−14.2; 2.66)	−5.58 (−16.76; 5.60)	0.232 / 0.840
Adiponectin [§] (pg × 10^5/ml)	166.90 (147.65; 186.15)	8.00 (−4.04; 20.03)	−1.50 (−14.24; 11.29)	-9.50 (−26.67; 7.66)	0.273 / 0.840

Note: In the last coloumn, the adjusted P value is written in italic.

Abbreviations: AUC, area under the curve; BMI, body mass index; CAP, controlled attenuation parameter; ETD, estimated treatment difference; FGF21, fibroblast growth factor 21; GGT, gamma glutamyltransferase; GLP-1, glucagon-like peptide-1; HOMA2-IR, homeostatic model assessment for insulin resistance; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; INF-gamma, interferon gamma; SAT, subcutaneous adipose tissue volume; TNF-alpha, tumour necrosis factor alpha; VAT, visceral adipose tissue volume.

[†]Baseline values are mean (95% CI) for normally distributed data and geometric mean (95% CI) for skewed data.

[‡]Delta values and ETD are differences in mean (95% CI) for normally distributed data and percentage difference in geometric mean for skewed data.

[§]Concentrations in the fasted state.

3.3 | Anthropometric measurements

Intervention with curcumin was not associated with significant changes in BMI, waist circumference, waist–hip ratio, VAT or SAT (Table 2), or measurements from bioelectrical impedance analysis, when compared with placebo (Table S2).

3.4 | Hepatic biomarkers

We found no effect of curcumin on FibroScan measurements of HFC (CAP value) or liver stiffness, or any biochemical hepatic variables (including urea production and FGF-21), when comparing with placebo, except for gamma glutamyltransferase (GGT). GGT exhibited a small but statistically significant decrease compared with placebo;

however, this difference was driven by a significant increase in the placebo group (Table 2).

3.5 | Metabolic measures

We found no statistically significant effect of curcumin on HOMA2-IR or HbA1c when comparing with placebo. Curcumin significantly decreased triglycerides compared with placebo, but we found no effect on HDL or total cholesterol (Table 2). LDL is not reported, as it would only be an estimate calculated from total cholesterol and HDL values. Curcumin significantly lowered fasting plasma glucose, but there was no effect on the AUC for plasma glucose, or on fasting plasma/serum concentrations or AUC for insulin, C-peptide, glucagon or GLP-1 when comparing with placebo (Figure 3).
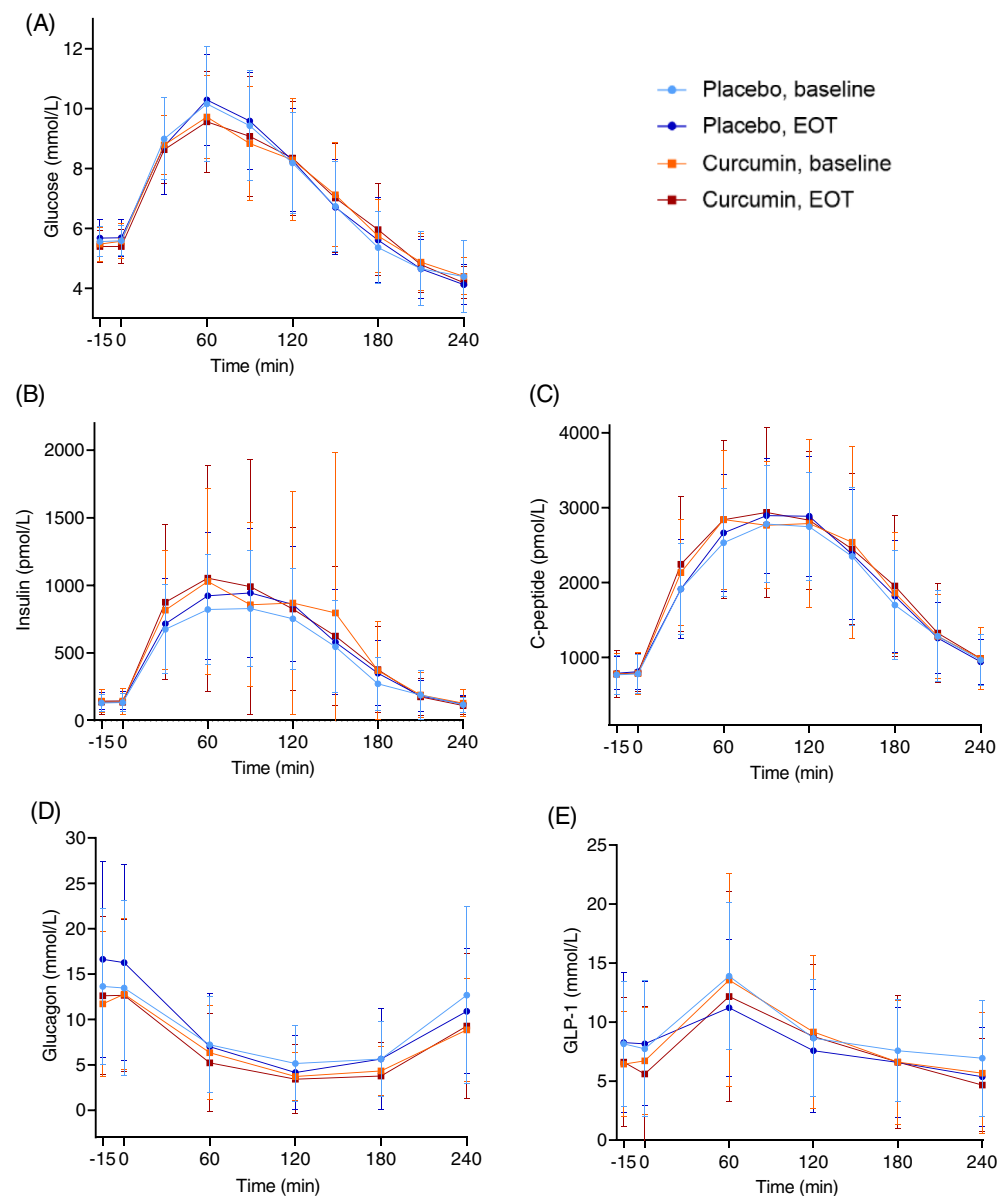

FIGURE 3 Plasma/serum concentrations of A, Glucose, B, Insulin, C, C-peptide, D, Glucagon, and E, Glucagon-like peptide-1 (GLP-1) during oral glucose tolerance test (OGTT) at baseline and at end-of-treatment (EOT) (mean ± SD) for all participants receiving placebo (n = 19) and curcumin (n = 18). For statistical comparisons, please refer to Table 2

3.6 | Inflammation markers and adiponectin

We found no effect of curcumin on any of the measured biomarkers of inflammation (tumour necrosis factor-alpha, interleukin [IL]-6, IL-8, IL-10, interferon-gamma, high-sensitivity C-reactive protein, YKL-40) or adiponectin (Table 2). YKL-40 is a 40 kDa glycoprotein named after its molecular weight and tyrosine (Y), lysine (K) and leucine (L).[26]

3.7 | Appetite measures, *ad libitum* meal measures and food and physical activity diaries

Curcumin appeared to decrease the sensation of prospective food intake and comfort, increase the sensation of nausea when comparing AUC with placebo AUC, and decrease the sensation of comfort 10 minutes after the *ad libitum* meal (Table S3). From data in the diaries, we found that participants in the curcumin group consumed a smaller amount of food and beverages compared with participants in the placebo group. However, none of these findings remained significant after adjusting for multiple testing. We found no effect of curcumin on the participants' experience of hunger, satiety, fullness or thirst, or when calculating composite appetite score. Furthermore, curcumin did not affect VAS scores on palatability sensations, meal duration or ingested kcal during the *ad libitum* meal. The ingested number of calories, calorie balance and ingested amount of the different constituents of the food and beverages were not affected by curcumin (Table S3).

4 | DISCUSSION

Compared with placebo, curcumin did not decrease HFC in obese participants, but it resulted in small reductions in circulating levels of triglyceride, glucose and GGT during fasting, and it reduced prospective food intake and comfort and increased nausea during OGTT and resulted in decreased self-reported amounts of ingested food and beverages. Except for the difference in GGT, which was driven by an increase in the placebo group, these differences were not statistically significant after correction for multiple comparisons.

Rodent studies have shown that curcumin supplementation can prevent diet-induced steatosis.[16,27-35] Only a few rodent studies have examined curcumin as a treatment for established steatosis, also with positive results.[36,37] Randomized controlled trials have been carried out showing a decrease in ultrasound-assessed HFC in patients diagnosed with steatosis when treating with curcumin.[38-42] Another study found a reduction in ultrasound-assessed HFC in the curcumin-treated group, but not when comparing with placebo.[43] Importantly, ultrasound is inferior to MRS[7-9] and considered sensitive only for HFC above 12.5%,[44] confounding the above-mentioned results. To our knowledge, the present study is the first to investigate curcumin's effect on MRS-assessed HFC. Curcumin is here tested in a selected cohort; thus, we cannot rule out that a cohort with steatosis but normal BMI or a cohort with

diabetes or a cohort with primarily moderate or severe steatosis would exhibit different outcomes.

Previously, van Werven et al. reported MRS to have acceptable reproducibility when scanning individuals in the fasted state (the coefficient of variance was 9.5% in liver tissue of non-obese and 4.1% in steatotic liver tissue; the repeatability coefficient was 1.3% in hepatic triglyceride content in both groups[45]). Recently, Kovar et al. showed that feeding state and composition of the last meal before MRS may affect HFC substantially.[46] We did not measure HFC with MRS in the fasted state, nor did we standardize feeding state or meal composition before the scan, and this might explain the missing reproducibility—especially in the placebo group—in our study. On the contrary, Colgan et al. performed a study where MRS-assessed HFC did not vary substantially with feeding state, and variation in HFC did not correlate with BMI.[47] Thus, our results reflect daily life variations, but taking the results from Kovar et al. and van Werven et al. into consideration, we cannot exclude that the lack of standardization of feeding state and meal composition prior to MRS in the present study may have contributed to the variation in MRS results and, thus, masked an effect of curcumin. Nevertheless, we performed FibroScan after 10-12 hours of fasting and CAP values showed no effect of curcumin compared with placebo, supporting our primary finding of no effect of curcumin on MRS-assessed HFC. In our study, post hoc analysis showed no significant correlation between changes in HFC and changes in variables known to correlate with HFC, that is, BMI, VAT, waist circumference and body fat percentage. The median percentage change for HFC was 6- to 15-fold greater than the percentage change for the other variables (data not shown). Study sample size calculation was carried out before inclusion; however, the substantial individual change in HFC over time might necessitate a bigger sample size to prove if curcumin affects HFC. The sample size in the present study may, thus, be considered a limitation. Our randomization resulted in a higher baseline HFC in the placebo group. However, the difference was not significant, and we found no correlation between baseline HFC and change in HFC over time (data not shown).

We found a significant effect of curcumin on GGT, but this was driven by a significant increase of GGT in the placebo group and a non-significant decrease in the curcumin group. Other studies have shown small reductions[43] or no effect of curcumin on GGT.[48,49] One study has shown a significant decrease in liver stiffness using FibroScan after curcumin treatment; however, when compared with placebo, the significance disappeared.[10] In the present study, no effects of curcumin on liver stiffness (assessed by FibroScan) or FIB4 score were observed.

Preclinical studies have shown that curcumin induces fibroblast growth factor 21 (FGF21) production via the PPAR-alpha route.[50,51] As FGF21 has been shown to have anti-steatogenic properties,[52] we included circulatory levels of FGF21 as an exploratory endpoint, but it was not affected by curcumin.

A previous study showed that 9 months of curcumin treatment significantly improved glucose tolerance (OGTT, 120 minutes) in overweight or obese prediabetic individuals[53] (an increase of ~0.7 mmol/L in the placebo group vs. a decrease of ~1.4 mmol/L in the curcumin group after 9 months of treatment). A meta-analysis[14] and several

additional studies[42,49,54-56] have shown curcumin-associated reductions in fasting plasma glucose in individuals with NAFLD, impaired glucose tolerance or diabetes. By contrast, the present data do not support clinically significant glucometabolic effects of curcumin in obese individuals, as we did not observe any effect on circulating levels of glucose, insulin, C-peptide, glucagon or GLP-1 during OGTT, and the small effect on fasting plasma glucose was not deemed clinically relevant, and significance disappeared when we adjusted for multiple comparisons. In line with our findings, no acute effect of oral administration of 6 g of *Curcuma longa* on plasma glucose levels during OGTT was observed in healthy subjects.[57] Also, we observed an effect of curcumin treatment in this study on HOMA2-IR, albeit not significant. Other studies have reported a significant decrease.[48,53,55] These studies investigated curcumin treatment of longer duration and included individuals with higher baseline HOMA-IR. In the present study, the tendency of curcumin-induced lowering of HbA1c, driven by a decrease in the curcumin group with no change in the placebo group, disappeared after adjustment for multiple comparisons. It is possible that a longer treatment duration would lead to a significant lowering effect of HbA1c, as seen in other studies.[14,40,53,55] Previous studies have shown small but significant reductions of circulating triglycerides during curcumin treatment.[40,55] In the present study, fasting triglyceride levels were reduced by curcumin, but the reduction was not clinically relevant, and statistical significance disappeared after adjustment for multiple comparisons.

We found a small effect of curcumin treatment on food ingestion reported in the diaries, prospective food intake, comfort and nausea levels (AUC), but significance disappeared when adjusting for multiple testing. Other studies have reported mild gastrointestinal side effects of curcumin.[40,42] We saw no effect of curcumin on plasma levels of GLP-1 during OGTT, contrasting to previous preclinical findings of curcumin-induced secretion of GLP-1.[58-60] We saw no effects of curcumin on anthropometric measures, confirming negative findings from most,[42,43,49,61-63] but not all, previous human studies.[64-66]

Obesity is associated with low-grade inflammation, which is often considered the culprit of the development of many obesity-related conditions and co-morbidities.[67,68] Curcumin has been reported to have anti-inflammatory properties in humans,[16-19,54] and curcumin-induced elevation of circulating adiponectin has been suggested as a mediator.[69] In the present study, we observed no effect of curcumin on several inflammation biomarkers or adiponectin.

High amounts of Meriva and non-formulated curcumin have been well-tolerated in human trials.[70,71] The formulation of curcumin in this trial was chosen because of the bioavailability being superior to unformulated curcumin.[72,73] We did not measure plasma levels of curcumin in our study. Another study found a significant reduction in HFC after 8 weeks of treatment with Meriva, which was well tolerated.[39] Therefore, we chose 6 weeks of treatment with Merivain double dose. Other formulations with acceptable bioavailability could have been considered, for example, nano-lipid-formulations[74] or curcumin derivatives or analogues.[75] An interesting theory is that curcumin exerts its effects by improving intestinal barrier function by increasing the number and quality of tight junctions between epithelial cells, and by decreasing inflammation in the intestinal wall. Supporters of this theory therefore claim that a higher concentration of non-formulated curcumin is the preferred treatment.[76-79]

In conclusion, we found no effect of curcumin on MRS-assessed HFC in our cohort (obese individuals with primarily mild steatosis), but we saw a small but statistically significant decrease in GGT. Statistical significance of the small and clinically insignificant reductions in fasting plasma glucose and triglycerides disappeared after correction for multiple comparisons. Thus, this randomized, double-blind, placebo-controlled, parallel-group trial showed no clinically relevant effects of 6 weeks of curcumin treatment on HFC, glucometabolic variables, hormonal responses during OGTT and exploratory metabolic endpoints in obese individuals. Furthermore, previous reported anti-inflammatory properties of curcumin were not evident. No safety issues related to curcumin treatment were observed.

CONFLICT OF INTEREST

All authors declare that there are no conflicts of interests associated with this manuscript.

PEER REVIEW

The peer review history for this article is available at https://publons. com/publon/10.1111/dom.14804.

DATA AVAILABILITY STATEMENT

Data is available on request by contacting corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.