**Supplement – Koutoukidis et al.**

**Procedures**

Participants underwent magnetic resonance imaging and elastography (MRI and MRE) scans at baseline and 24 weeks, and vibration-controlled transient elastography scans at baseline, 16 weeks, and 24 weeks. The scans were conducted by trained operators and participants were fasted for at least 4 hours before the scans. MRI scans were performed with a Siemens Prisma 3T scanner (Siemens Healthineers, Erlangen, Germany). MRI-proton density fat fraction (PDFF) and T2* maps were determined using multiple-echo gradient recalled echo sequences ($TR/TE_{min}$ = 15/1.1 ms, $\Delta TE$ = 1.1 ms, slice thickness 10 mm, FA = 3°, and bandwidth 1560 Hz/px). T1 maps were acquired using a standard shortened modified Look-Locker inversion recovery (shMOLLI) sequence. cT1 values were provided by Perspectum using the aforementioned sequences. The PDFF for two participants at baseline (36% each) was slightly above the usual upper threshold (≤35%) accepted for quantifying cT1. For these 2 scans, the measured cT1s were derived from 3 ROIs placed on a single slice (in contrast with the segmentation-based analysis performed for the rest of the data). Liver stiffness by MRE was determined using a spin echo sequence (4 slices, slice thickness 8 mm, TR/TE = 1000/47 ms, strong SPAIR fat suppression, matrix size 128 × 128, GRAPPA acceleration factor 2, bandwidth 2170 Hz/px, mechanical frequency 60 Hz). Liver stiffness maps were analysed as per the recommendations of the QIBA profile [1].

Blood samples were analysed using standard protocols in the hospital laboratory. Weight and fat-free mass were measured with bioelectrical impedance (TANITA SC-240MA, Tanita, Netherlands). After sitting for 5 minutes in a calm environment, blood pressure was measured 3 times with 1-minute intervals and the average of the last two measurements was used for analysis. Physical performance was measured with the objective modified physical performance test including 9 daily activities (e.g., performing a progressive Romberg test, climbing up and down four flights of 10 stairs). Each activity was scored 0-4

with the maximum score of 36 indicating high performance. Hand-grip strength was measured 3 times with a dynamometer (Takei 5401, Takei Scientific Instruments Co., Ltd, Tokyo, Japan) using the dominant hand. The grip strength measurements were combined with the chair stands, Romberg test, and sex, to calculate the Liver Frailty Index, for which higher scores indicate higher frailty [2]. Seven-day alcohol intake was assessed with an interview and heavy drinking was screened for with AUDIT-C. Participants filled in standardised demographic and feedback questionnaires. They also had a physical examination at baseline, 4, 16, and 24 weeks.

**Medication adjustment guidance**

| TYPE 2 DIABETES | | |
|---|---|---|
| **Patient currently takes:** | **Current dose** | **Recommendation** |
| Metformin | | HALF daily dose |
| Liraglutide | 0.6mg<br>1.2mg<br>1.8mg | STOP<br>REDUCE by 0.6mg<br>REDUCE by 0.6mg |
| Other Glucagon-like peptide-1 agonists | | HALF daily dose |
| SGLT2 inhibitors | | STOP |
| Sulphonylurea | | STOP |
| Glitazone | | STOP |
| Glinide | | STOP |
| DPP IV inhibitor | | STOP |
| Acarbose | | STOP |

**At the end of the weight loss phase, re-assess patients' requirements for oral diabetic therapies using HbA1c measurements or a finger prick blood glucose measurement.**

| HYPERTENSION | | |
|---|---|---|
| **Patient currently takes:** | **Current dose** | **Recommendation** |
| Loop Dieuretic:<br>*Furosemide* | ≤ 40 mg daily<br>80 — 120 mg daily<br>≥ 120 mg daily | STOP<br>REDUCE by 40 mg daily<br>REDUCE by 40 mg daily |
| *Bumetamide* | ≤ 1 mg daily<br>2-3 mg daily<br>≥ 3 mg daily | STOP<br>REDUCE to 1mg daily<br>REDUCE by 1mg daily |
| Thiazide Diuretic | | STOP |
| α Blocker | Used for hypertension<br>Other uses | STOP<br>CONTINUE |
| ß Blocker | | HALF daily dose |
| Ca channel blocker | | HALF daily dose |
| ACE inhibitors or ARBs | Used for hypertension<br>Used for heart failure | STOP<br>HALF daily dose |

| LIPID-LOWERING DRUGS | |
|---|---|
| **Patient currently takes:** | **Recommendation** |
| Fibrates | STOP |
| Statins | CONTINUE |
| Ezetimibe | CONTINUE |

**Table S1**: Demographic and clinical characteristics at baseline

| Characteristic | Intervention | Standard of Care |
|---|---|---|
| Total, N | 11 | 6 |
| Age, years, median (IQR) | 61.2 (7.5) | 54.8 (7.5) |
| Sex, female | 4 (36.4) | 4 (66.7) |
| Ethnicity | | |
| White | 11 (100) | 5 (83.3) |
| Asian | 0 (0) | 1 (16.7) |
| Education | | |
| None | 2 (18.2) | 0 (0) |
| Up to secondary | 2 (18.2) | 2 (33.3) |
| Tertiary | 6 (54.5) | 4 (66.7) |
| Undisclosed | 1 (9.1) | 0 (0) |
| Annual household income | | |
| <£15.5k | 2 (18.2) | 1 (16.7) |
| £15.5-25k | 3 (27.3) | 0 (0) |
| £26-39k | 3 (27.3) | 2 (33.3) |
| >=£40k | 2 (18.2) | 3 (50) |
| Undisclosed | 1 (9.1) | 0 (0) |
| Smoking status | | |
| Never | 4 (36.4) | 2 (33.3) |
| Previous | 6 (54.5) | 3 (50) |
| Current | 1 (9.1) | 1 (16.7) |
| Type 2 diabetes | 7 (63.6) | 3 (50) |
| Hypertension | 9 (81.8) | 3 (50) |
| BMI $\geq$ 35 kg/m$^2$ | 5 (45.5) | 5 (83.3) |
| BMI, kg/m$^2$, median (IQR) | 34.9 (9) | 37.5 (3.4) |
| AUDIT-C score, median (IQR) | 2 (2.5) | 2.5 (2.5) |
| Histological diagnosis | 9 (81.8) | 6 (100) |
| Time since diagnostic biopsy, months, median (IQR) | 17.3 (28.5) | 3.1 (28.5) |
| NAS score, median (IQR) | 5 (2.5) | 5 (2.5) |

**Figure S1:** NAFLD activity score of each of the 15 participants with biopsy-proven CC-MASLD

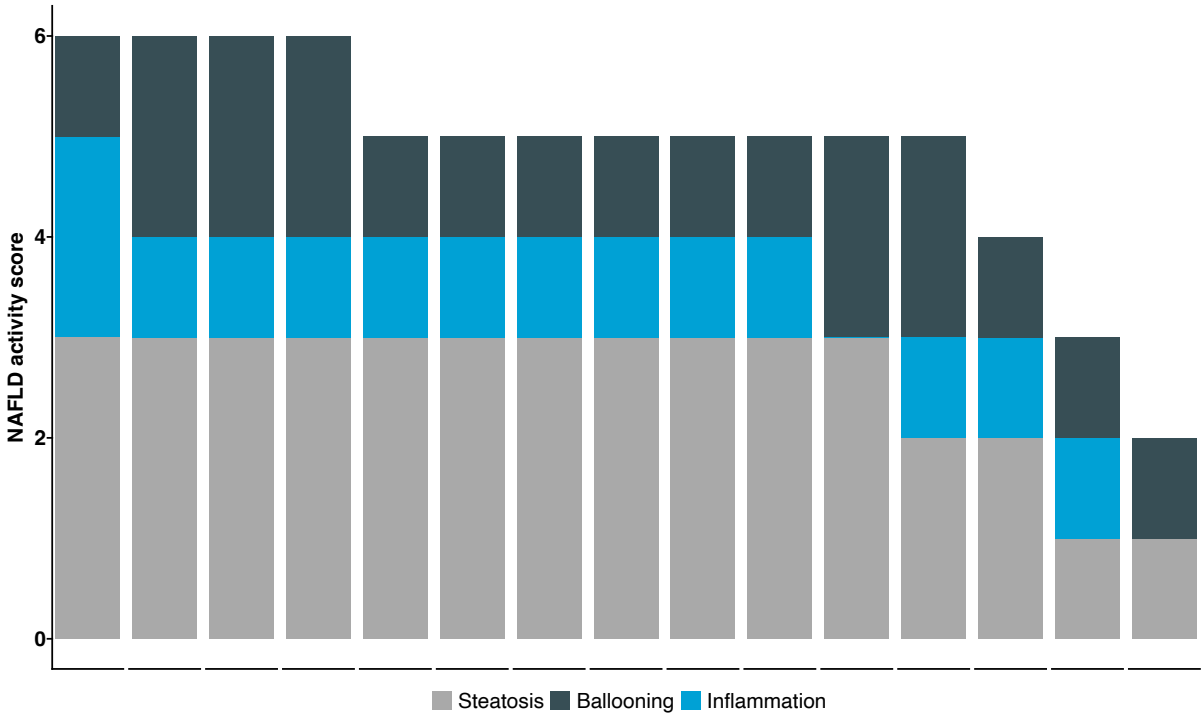


**Figure S2**: Individual (dotted) and average (solid) absolute changes by group in AST, UKELD, and Child-Pugh score.

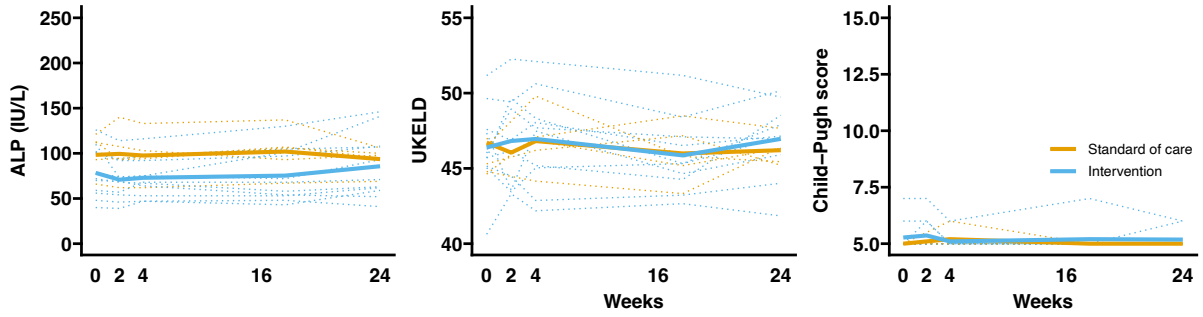

**Table S2: Per-protocol analysis**

| Marker | Adjusted difference (95% CI) |
|---|---|
| Weight, kg | -14.5 (-19.5 to -9.5) |
| Fat-free mass, kg | -3.4 (-6.1 to -0.7) |
| Fat-free mass, % | 6.9 (1.9 to 11.9) |
| Liver fat fraction, % | -7.5 (-11.7 to -3.3) |
| Controlled attenuation parameter, dB/m | -75 (-125.4 to -26.5) |
| corrected T1, ms | -153.4 (-273.8 to -33) |
| MRE-measured liver stiffness, kPa | 0.5 (-1.2 to 2.2) |
| VCTE-measured liver stiffness, kPa | -2 (-8.4 to 4.7) |
| Enhanced liver fibrosis score | 0.3 (-1.5 to 2.1) |
| ALT, IU/L | |
| AST, IU/L | |
| Bilirubin, µmol/L | |
| Conjugated bilirubin, µmol/L | |
| INR | |
| Prothrombin time | |
| Physical performance test | 1.8 (-1.2 to 4.8) |
| Liver frailty index | 1.6 (-8.7 to 11.8) |
| Grip strength, kg | 0.2 (-0.4 to 0.8) |
| UKELD | 0 (-1.8 to 1.9) |
| Child-Pugh score | -0.1 (-0.5 to 0.2) |
| Cholesterol to HDL ratio | -0.4 (-1.3 to 0.6) |
| Cholesterol, mmol/L | -0.2 (-1.2 to 0.8) |
| Haemoglobin A1c, % | -0.5 (-1.1 to 0.2) |
| Systolic blood pressure, mmHg | 0.8 (-12.6 to 14.2) |
| Diastolic blood pressure, mmHg | -4.6 (-11.9 to 2.9) |

**Table S3: Adverse events overview**

| | Intervention, n(%) | Standard of care, n(%) |
|---|---|---|
| Participants with ≥1 adverse event | 10 (91%) | 4 (80%) |
| Adverse events reported by at least 2 participants in each group | | |
| Headache | 4 (36%) | 0 (0%) |
| Constipation | 3 (27%) | 0 (0%) |
| COVID-19 | 3 (27%) | 2 (40%) |
| Insomnia | 2 (18%) | 0 (0%) |
| Dizziness | 2 (18%) | 1 (20%) |
| Participants with adverse event grade ≥3 | 0 (0%) | 0 (0%) |
| Adverse event leading to entering enhanced observation | 0 (0%) | 0 (0%) |
| Adverse event leading to discontinuation of the intervention | 0 (0%) | N/A |
| N of serious adverse events | 0 (0%) | 0 (0%) |
| Pre-specified serious adverse events | | |
| Hepatic decompensation | 0 (0%) | 0 (0%) |
| Liver transplantation | 0 (0%) | 0 (0%) |
| Hepatocellular carcinoma | 0 (0%) | 0 (0%) |
| Death | 0 (0%) | 0 (0%) |

**Table S4: Alcohol intake [median (IQR)] throughout the study based on 7-day self-reported intake at each time point.**

| | Intervention | | | | Standard of care | | | |
|---|---|---|---|---|---|---|---|---|
| | Baseline | 4 weeks | 16 weeks | 24 weeks | Baseline | 4 weeks | 16 weeks | 24 weeks |
| **Alcohol units/week** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (5) | 0 (4) | 0 (4) | 0 (0) |

## References


1. QIBA. Magnetic Resonance Elastography of the Liver. 2018 [11 July 2022]; Available from: https://qibawiki.rsna.org/images/a/a5/MRE-QIBAProfile-2018-05-02-CONSENSUS.pdf.
2. Wang CW, Lebsack A, Chau S, Lai JC. The Range and Reproducibility of the Liver Frailty Index. Liver Transpl. 2019;25(6):841-7. Epub 2019/03/19.