Received: 16 November 2021 | Revised: 27 January 2022 | Accepted: 16 February 2022

DOI: 10.1002/oby.23425

Obesity A Research Journal | THE OBESITY SOCIETY | WILEY

ORIGINAL ARTICLE

Obesity Biology and Integrated Physiology

Greater ectopic fat deposition and liver fibroinflammation and lower skeletal muscle mass in people with type 2 diabetes

Tom Waddell[1,2] | Alexandre Bagur[1,2] | Diogo Cunha[2] | Helena Thomaides-Brears[2] | Rajarshi Banerjee[2] | Daniel J. Cuthbertson[3,4] | Emily Brown[3,4] | Kenneth Cusi[5] | Jean-Pierre Després[6] | Michael Brady[2]

[1]Department of Engineering Science, The University of Oxford, Oxford, UK

[2]Perspectum Ltd., Oxford, UK

[3]Department of Cardiovascular and Metabolic Medicine, Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, UK

[4]Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK

[5]The University of Florida, Gainesville, Florida, US

[6]Laval University, Quebec, Canada

Correspondence
Tom Waddell, Perspectum Ltd., Gemini One, 5520 John Smith Dr., Oxford, OX4 2LL, UK.
Email: tom.waddell@perspectum.com

Funding information
TW is funded by the Royal Commission for the Exhibition of 1851.

Abstract

Objective: Type 2 diabetes (T2D) is associated with significant end-organ damage and ectopic fat accumulation. Multiparametric magnetic resonance imaging (MRI) can provide a rapid, noninvasive assessment of multiorgan and body composition. The primary objective of this study was to investigate differences in visceral adiposity, ectopic fat accumulation, body composition, and relevant biomarkers between people with and without T2D.

Methods: Participant demographics, routine biochemistry, and multiparametric MRI scans of the liver, pancreas, visceral and subcutaneous adipose tissue, and skeletal muscle were analyzed from 266 participants (131 with T2D and 135 without T2D) who were matched for age, gender, and BMI. Wilcoxon and χ^2 tests were performed to calculate differences between groups.

Results: Participants with T2D had significantly elevated liver fat (7.4% vs. 5.3%, $p = 0.011$) and fibroinflammation (as assessed by corrected T1 [cT1]; 730 milliseconds vs. 709 milliseconds, $p = 0.019$), despite there being no differences in liver biochemistry, serum aspartate aminotransferase ($p = 0.35$), or alanine transaminase concentration ($p = 0.11$). Significantly lower measures of skeletal muscle index (45.2 cm^2/m^2 vs. 50.6 cm^2/m^2, $p = 0.003$) and high-density lipoprotein cholesterol (1.1 mmol/L vs. 1.3 mmol/L, $p < 0.0001$) were observed in participants with T2D.

Conclusions: Multiparametric MRI revealed significantly elevated liver fat and fibroinflammation in participants with T2D, despite normal liver biochemistry. This study corroborates findings of significantly lower measures of skeletal muscle and high-density lipoprotein cholesterol in participants with T2D versus those without T2D.

INTRODUCTION

In the UK and United States, an estimated 4.3 and 30 million people, respectively, are diagnosed with type 2 diabetes (T2D), and disease prevalence is projected to double by 2030 (1). T2D is often accompanied by comorbidities, is a major risk factor for coexisting liver, renal, and eye disease, and has been noted to be an important risk factor in COVID-19-related mortality (2). Irrespective of

age, individuals with T2D in England require twice as much hospital support, including inpatient costs and pharmacotherapy, as individuals without T2D, and the annual care costs for these patients is £3 billion, which is 8% of total secondary care costs (3). Although the pathophysiology of T2D is multifactorial, with risk factors that have been shown to include low socioeconomic status and specific ethnicities (4,5), obesity has been traditionally identified as a key contributing factor. Individuals with overweight (BMI = 25-30 kg/m^2) or obesity (BMI > 30) are three and seven times more likely, respectively, to develop T2D than individuals who are considered to have a normal body weight (BMI < 25) (6).

Compared with computed tomography, which has been used in the early studies on visceral and regional adiposity, multiparametric magnetic resonance imaging (MRI) has been a remarkable advance, as it allows for the study of the different facets of fat distribution and ectopic fat depot phenotypes associated with T2D (7,8). For example, South Asian individuals have been shown to accumulate greater visceral adipose tissue (VAT) and to be significantly more likely to develop T2D than White European individuals of a similar BMI (4,5). Furthermore, reduced skeletal muscle mass, accumulation of VAT, and elevated fat deposits within the liver and pancreas have all individually been significantly associated with T2D incidence (9,10). This highlights the need to combine multiorgan and body composition imaging for a comprehensive phenotypical assessment of individuals with T2D.

Multiparametric MRI has been used in the UK Biobank for detecting liver fat and fibrosis as indicators of potential liver damage/disease (10-13). T1 mapping provides an MRI indicator of regional tissue water by measuring longitudinal relaxation time, a measure of the time that it takes for protons to re-equilibrate their spins following excitation from a radio-frequency pulse. T1 lengthens with accordance to increases in extracellular fluid and reflects the degree of tissue inflammation and fibrosis. However, liver T1 is influenced by the presence of iron, which can be measured from the T2* relaxation time. Corrected T1 (cT1) is an algorithm developed by the imaging analysis company Perspectum (Oxford, UK) that removes the bias introduced by elevated iron on T1 (14).

cT1 and proton density fat fraction (PDFF), a measure of organ fat, have been shown to correlate well with the characteristic histological features of nonalcoholic fatty liver disease (NAFLD) (15,16) and to predict liver-related outcomes (17). Using MRI-derived measures of visceral, subcutaneous, and liver fat and machine-learning clustering techniques, Wagner et al. (18) reported six distinct subphenotypes of patients with T2D. Notably, the cluster with the highest risk of T2D, renal, and vascular disease included patients with obesity with associated insulin resistance, liver fat deposition, and low insulin secretion.

In this study, we collect MRI-derived measures of body composition and ectopic fat deposition within the liver and pancreas and compare them between individuals with and without T2D who were matched for age, gender, and BMI. Notably, we report on liver health using a novel T2*-corrected measure of liver T1 (cT1) as a measure of fibroinflammation, which has been shown to correlate well with features of NAFLD.

Study Importance

What is already known?

- Type 2 diabetes (T2D) is associated with end-organ damage and an increased risk of nonalcoholic fatty liver disease.
- People with T2D have higher relative volumes of visceral adipose tissue and greater ectopic fat deposition (including more liver fat) compared with age- and BMI-matched people without T2D.

What does this study add?

- We report significantly elevated magnetic resonance imaging (MRI)-derived measures of liver fat and a novel T2*-corrected measure of liver fibroinflammation (cT1) in people with T2D compared with age- and BMI-matched people without T2D, a difference not revealed by routine liver biochemistry.

How might these results change the direction of research or the focus of clinical practice?

- Our findings emphasize the utility of multiparametric MRI for investigating previously unrecognized liver disease in people with T2D that is not detectable by routine laboratory testing.
- We further corroborate findings of significantly lower skeletal muscle mass in people with T2D.

METHODS

Study population

MRI data and participant demographics were acquired retrospectively from the UK Biobank study (https://www.ukbiobank.ac.uk/), a general population-based cohort that conducted MRI scanning of the brain, heart, and abdomen in people aged 40 to 69 years from across the UK. Accompanying participant demographic data, collected through an online data access application (application number: 9914), included measures of age, gender, BMI, waist circumference, and routine biochemistry results, including serum/plasma high-density lipoprotein (HDL), triglycerides, aspartate aminotransferase (AST), alanine transaminase (ALT), and glycated hemoglobin (HbA1c) concentrations.

In total, there were 318 participants with self-reported T2D and accompanying MRI data enrolled in the UK Biobank study. Of these participants, 237 (162 male individuals, 75 female individuals) were selected, with an age range of 41 to 70 years and a BMI range of 18.5 to 45.9. Each participant with T2D was then paired with a participant with no self-reported diabetes of any type, matched for gender,

age (±5 years), and BMI (±1 kg/m^2). Data from 474 participants (237 with T2D and 237 without T2D) were collected for MRI analysis (Supporting Information Figure S1).

Image acquisition protocol

MRI scans were performed using a Siemens Aera 1.5-T scanner (Siemens AG, Munich, Germany). For the liver, a single transverse section positioned at the porta hepatis was selected. A Shortened Modified Look-Locker Inversion and a multiecho-spoiled gradient echo sequence was performed to quantify liver T1 and iron/fat, respectively. The full liver imaging protocol has been detailed elsewhere (13,19). Abdominal water- and fat-separated images were obtained from the two-point Dixon protocol. This imaging protocol results in a series of consecutive "slabs," each comprising a contiguous set of sections. The contrasts and brightness of the slabs were adjusted automatically prior to processing the entire acquired volume. PDFF maps of the pancreas were reconstructed from the dedicated pancreas gradient-recalled echo (GRE) 10-echo acquisition (echo time $[TE]_1 = 2.38$ milliseconds, $\Delta TE = 2.38$ milliseconds) using a magnitude-based multipoint water-fat separation algorithm (20).

Image analysis protocol

Liver

Liver MRI scans were analyzed using Perspectum's LiverMultiScan technology. This software automatically delineates the liver from cT1, T2*, and PDFF image maps, excluding major vessels within the image section using a previously published deep-learning approach (21). Manual analysis of pancreas and body composition images was completed by two trained analysts who were blinded to group allocation.

Pancreas

Pancreas images were analyzed by manually placing, on PDFF maps when possible, a single region of interest of 10 mm within the head, body, and tail of the pancreas, avoiding blood vessels and ducts.

Adipose tissue volumes and muscle mass

For delineation of subcutaneous adipose tissue (SAT), VAT, and skeletal muscle index (SMI), a single two-dimensional section positioned at the third lumbar (L3) vertebrae was extracted from whole-body Dixon MRI. The L3 section was selected because this region has been shown to be strongly associated with whole-body skeletal muscle distribution and to accurately estimate total SAT and VAT volumes (22-24). Cross-sectional areas of SAT, VAT, and skeletal muscle were manually segmented using ITK-SNAP software (version 3.8.0) (25), and these are reported as centimeters squared. SMI was calculated by indexing the centimers squared values of lean muscle to the squared height of the participant (centimeters squared/meters squared). Figure 1 shows sample MRI scans.

Assessment of organ dysfunction

NAFLD and nonalcoholic steatohepatitis (NASH) were defined based on the following liver biomarkers and thresholds (26,27): NAFLD = liver fat by PDFF > 5.56%; and NASH = liver fat by PDFF > 10% and cT1 > 825 milliseconds. Elevated pancreatic fat was defined based on a pancreatic fat value of >7%. Elevated AST and ALT were defined based on the following thresholds: AST > 37 IU/L for male individuals and >31 IU/L for female individuals; and ALT > 50 IU/L for male individuals and >35 IU/L for female individuals.

Statistical analysis

Statistical analysis was performed using the R software platform (version 3.6.1, the R Project for Statistical Computing, the R Foundation, Vienna, Austria). Three-dimensional modeling of participant features was completed using the Plotly open-source graphical library in R. Descriptive statistics, which report medians and interquartile ranges (IQR), are displayed in order to summarize participant characteristics. Wilcoxon and χ^2 tests were performed to calculate the significance (p value) of differences in biomarkers between participants with T2D and those without T2D. $P < 0.05$ was deemed significant following a Bonferroni correction. To calculate the associations between participant biomarkers and T2D, we performed univariate and stepwise multivariate logistic regression modeling using the brglm2 package in the R software platform (version 3.6.1). Model inputs included the following: pancreas fat, liver fat, liver cT1, VAT, SAT, SMI, HDL-cholesterol (HDL-C), triglycerides, AST, ALT, BMI, waist circumference, age, and gender. Risk scores and confidence intervals (CI) were calculated against the odds ratios of participants who had self-reported T2D. Spearman correlation tests were calculated to investigate the relationships between biomarkers.

RESULTS

Population characteristics

A total of 474 participants (237 with T2D and 237 without T2D) with accompanying MRI scans were selected from the UK Biobank online resource. Measures of MRI-derived body composition and pancreas fat were successfully obtained from 452 (224 with T2D and 228 without T2D) and 400 (197 with T2D and 203 without T2D) participants, respectively (Supporting Information Figure S1). The most common reason for pancreas MRI report failure was nonvisualization of the pancreas due to fat occlusion or image artifact. After excluding any participants with missing data, 266 remained (131 with T2D and 135 without T2D), and they

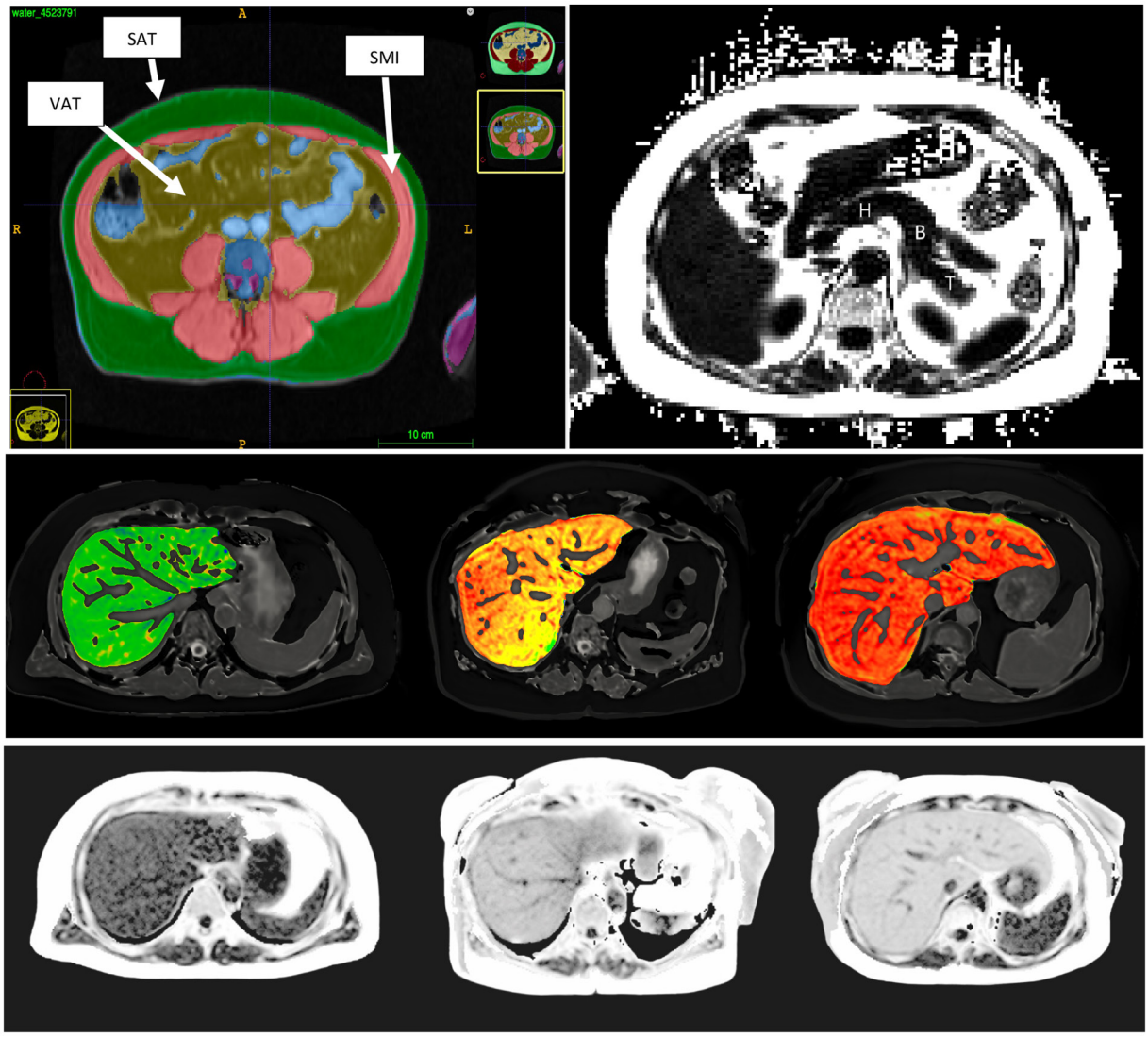

FIGURE 1 Example magnetic resonance images of body composition segmentation (top left), pancreas (with example of typical region of interest placement [H = head, B = body, T = tail; top right]), liver corrected T1 (cT1) (middle), and liver proton density fat fraction (bottom). SAT, subcutaneous adipose tissue; SMI, skeletal muscle index; VAT, visceral adipose tissue

were included in the final analysis. Overall, participants in both groups were well matched for BMI, waist circumference, gender, and age (Table 1).

Analysis of participants with T2D versus those without T2D

Biochemistry

As anticipated, participants in the group with T2D reported significantly higher HbA1c values ($p < 0.001$) but significantly lower HDL-C ($p < 0.001$) compared with participants without T2D. We observed no significant differences in triglycerides ($p = 0.26$), AST ($p = 0.35$), or ALT ($p = 0.11$). Prevalence of elevated AST and ALT was similar between the groups with T2D and without T2D ($p = 0.71$, $p = 0.23$, respectively; Table 2).

MRI-derived measurements: liver, pancreas, and body composition metrics

Participants in the group with T2D reported significantly higher MRI-measured liver fat ($p = 0.011$) and liver cT1 ($p = 0.019$).

We observed no significant differences in MRI-measured pancreas fat ($p = 0.22$), VAT ($p = 0.35$), or SAT ($p = 0.43$; Table 2). Prevalence of significant pancreas steatosis and liver steatosis was high but not significantly different between participants with or without T2D (38% vs. 40%, 64% vs. 47%, respectively; Table 3). However, we observed that prevalence of NASH was significantly greater in participants with T2D and obesity compared with participants without T2D (Supporting Information Figures S2 and S3).

Furthermore, significantly lower SMI values were observed in the group with T2D ($p = 0.003$).

TABLE 1 Anthropometrics and demographic characteristics of study population

	Participants with T2D	Participants without T2D	*p* value
n	131	135	–
Age (y)	56 (52-63)	57 (53-63)	0.66
Ethnicity (% White British)	84%	96%	0.37
Gender (% male)	68%	73%	0.67
BMI (kg/m^2)	29.4 (27-33.9)	29.7 (26.8-33.5)	0.97
WC (cm)	99 (91-106)	97 (91-109)	0.56
DBP (mm Hg)	84 (77-90)	85 (78-92)	0.34
SBP (mm Hg)	142 (129-151)	142 (131-155)	0.42
Self-reported hypertension (%)	50	42	0.40

Note: Data are median (IQR).

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure; T2D, type 2 diabetes; WC, waist circumference.

TABLE 2 Biochemical and imaging characteristics

	Participants with T2D	Participants without T2D	*p* value
Biochemical			
HbA1c (mmol/L)	42.9 (38.6-51.3)	36.1 (32.9-38.3)	**<0.001**
HDL (mmol/L)	1.1 (1-1.3)	1.3 (1.1-1.5)	**<0.001**
Triglycerides (mmol/L)	1.8 (1.3-2.6)	1.7 (1.2-2.4)	0.26
ALT (IU/L)	29.9 (20.6-36.6)	25.9 (19.3-34.6)	0.11
AST (IU/L)	25.3 (21.6-30.7)	26.6 (22.9-32.5)	0.35
Imaging			
VAT (cm^2)	219.2 (170.9-297.4)	215.1 (149.4-278.8)	0.35
SAT (cm^2)	244.3 (185.5-322.9)	271.4 (181.3-366.1)	0.43
SMI (cm^2/m^2)	45.2 (38.1-52.9)	50.6 (42.6-55.9)	**0.003**
Liver cT1 (ms)	730 (685-786)	709 (671-753)	**0.019**
Liver fat (%)	7.4 (4.1-13.8)	5.3 (2.7-10.6)	**0.01**
Pancreas fat (%)	6.1 (4.2-9.6)	5.8 (3.1-8.9)	0.22

Note: Data are median (IQR). Significant *p* values are in bold.

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; cT1, corrected T1; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; SAT, subcutaneous adipose tissue; SMI, skeletal muscle index; T2D, type 2 diabetes; VAT, visceral adipose tissue.

Correlation analysis

cT1 showed moderate positive correlations with BMI and VAT (ρ: 0.41, $p < 0.001$; ρ: 0.41, $p < 0.001$, respectively; Table 4). BMI showed moderate positive correlations with all MRI-measured metrics of fat, except for pancreas fat, which correlated weakly. VAT positively correlated with MRI-measured liver fat but correlated only weakly with pancreas fat.

Univariate and multivariate analysis

Univariate modeling revealed that either liver fat > 5% ($p = 0.01$) or >10% ($p = 0.01$) and elevated liver cT1 ($p = 0.01$) were associated with a diagnosis of T2D. We observed a significant reduction in SMI ($p = 0.01$) and HDL-C ($p < 0.001$) with a diagnosis of T2D. Stepwise multivariate analysis, including the significant variables listed earlier, revealed that reduced SMI ($p \leq 0.001$) and HDL-C ($p < 0.001$) remained significantly associated with T2D, with an odds ratio of 0.94 (95% CI: 0.91-0.97) and 0.15 (95% CI: 0.06-0.40), respectively.

TABLE 3 Abnormalities of organ structure/function

	People with T2D	Control individuals	*p* value
NAFLD (%)	64	47	0.10
NASH (%)	11	7	0.35
Elevated pancreatic fat (%)	38	40	0.34
Elevated AST (%)	16	14	0.71
Elevated ALT (%)	16	10	0.23

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; T2D, type 2 diabetes.

TABLE 4 Spearman correlation analysis

Biomarker interaction	ρ	p value
BMI: VAT	0.52	**<0.001**
BMI: SAT	0.69	**<0.001**
BMI: SMI	0.34	**<0.001**
BMI: liver fat	0.42	**<0.001**
BMI: liver cT1	0.41	**<0.001**
BMI: pancreas fat	0.25	**<0.001**
VAT: liver fat	0.54	**<0.001**
VAT: liver cT1	0.41	**<0.001**
VAT: pancreas fat	0.28	**<0.001**
VAT: SAT	0.27	**<0.001**
SAT: liver fat	0.33	**<0.001**
SAT: liver cT1	0.30	**<0.001**
SAT: pancreas fat	0.19	**0.001**
HbA1c: liver fat	0.19	**0.001**
HbA1c: liver cT1	0.24	**<0.001**
HbA1c: pancreas fat	0.19	**0.001**
HbA1c: BMI	0.19	**0.001**
HbA1c: VAT	0.15	**0.016**
HbA1c: SAT	0.04	0.47
HbA1c SMI	−0.08	0.21
HbA1c: HDL	−0.23	**<0.001**
AST: liver cT1	0.16	**0.005**
ALT: liver cT1	0.28	**<0.001**

Note: Significant p values are in bold.

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; cT1, corrected T1; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; SAT, subcutaneous adipose tissue; SMI, skeletal muscle index; VAT, visceral adipose tissue.

DISCUSSION

We report MRI-derived measures of the liver, pancreas, and body composition in participants with and without T2D from the UK Biobank. We highlight that participants with self-reported T2D have evidence of significantly greater liver damage, as measured by significantly greater levels of liver fibroinflammation and determined by MRI-derived measures of liver fat and cT1, with significantly reduced skeletal muscle mass, as determined by MRI-derived measures of SMI, compared with BMI-, age-, and gender-matched participants.

Notably, in the group with T2D, we report evidence of significantly greater liver damage in participants with obesity versus those with normal weight, despite similar HbA1c levels, which suggests that weight has a greater contribution than glycemia to NAFLD. This is consistent with Pavlides et al. (17), who also showed this finding in patients with T2D and obesity versus those with T2D and a normal weight with a similar age and BMI to those in the present analysis. Monitoring HbA1c is a key component in the management of T2D and is one of the decision-making tools in pharmacological intensification and setting patient targets (National Institute for Health & Care Excellence [NICE] guideline: NG28). However, our findings emphasize the need for a multimodality approach to T2D care that extends beyond considering glycemic control and cardiorenal complications to additionally consider liver health aside from the conventional screening approaches that focus predominantly on the cardiometabolic renal axes. Furthermore, we observed significantly greater liver fat and cT1 in the group with T2D, despite no differences in ALT or AST, biomarkers frequently used for the assessment of liver health. This has been reported previously in BMI-matched patients with and without T2D with a similar BMI to those in the present analysis (28). This highlights potential limitations of biochemical tests for the assessment of coexisting liver disease in patients with T2D, and more sophisticated tools are needed to assess and stage accurately.

We observed no significant differences in measures of pancreas fat or VAT between participants with and without T2D. This is in contrast to findings by Nadarajah et al. (29), who reported significantly greater pancreatic fat in patients with T2D versus control patients with a similar BMI to those in the present study. However, patients were not matched for age, and those in the group with T2D were significantly older (mean difference of 7.5 years), which may have been a confounding factor. Elevated pancreatic fat and VAT, but not SAT, is associated with a significant increase in circulating insulin and glucose in BMI-matched individuals (30,31). Although our findings do not corroborate this, existing literature has highlighted the role of ectopic fat in the liver, pancreas, and VAT in driving T2D and, therefore, the need to phenotype patients beyond BMI alone.

NAFLD is present (when assessed for properly) in 55.5% of patients with T2D worldwide, with 37.3% demonstrating coexisting NASH and 17.3% having biopsy-confirmed advanced fibrosis (32). However, the presence of NASH is often overlooked. There are implications to its diagnosis with NAFLD in the context of coexisting T2D, which significantly increases the likelihood of disease progression to NASH than to NAFLD alone (32,33), and having a synergistic risk (concomitant NAFLD and T2D mellitus) of nonliver comorbidities, both cardiovascular and renal (34-36). Providing priority referrals for the assessment of liver health in high-risk patients with T2D may allow for the early detection of disease and delivery of personalized care. Excess liver fat can be significantly reduced through lifestyle modifications such as physical activity and dietary modification (37). However, in a select number of patients with advanced disease, lifestyle modifications alone may not be sufficient, and these patients will require more-intensive treatment strategies.

Our work demonstrates that participants with T2D had significantly lower measures of SMI, which is consistent with previous work (38). Skeletal muscle plays a critical role in postprandial glucose disposal through insulin-stimulated recruitment of the glucose transporter protein 4 (GLUT-4), allowing for uptake of glucose into the skeletal muscle cells (myocytes) (39). Insulin resistance in skeletal muscle, as typically observed in T2D, results in impaired insulin-stimulated glucose disposal and has been shown

to manifest long before evident hyperglycaemia (40). Skeletal muscle insulin resistance also occurs during normal aging processes, with a ~5% to 10% loss of skeletal muscle mass per year and a 4% decline in basal metabolic rate reported after the age of 50 years (41,42). Resistance training is an effective method for ameliorating age-related declines in insulin sensitivity, with benefits regarding GLUT-4 translocation and insulin sensitivity being reported (43,44). Importantly, a review by Mesinovic et al. (45) highlighted that the effect of common glucose-lowering medications on muscle mass remains unclear, and they particularly considered such agents as glucagon-like peptide 1 (GLP-1) receptor agonists that can be associated with significant weight loss. Understanding these effects is of great clinical importance to ensure that high-risk patients with T2D are not receiving therapies that may exacerbate further loss of skeletal muscle.

The association between HDL-C and T2D has been well-established, and our finding of significantly lower HDL-C levels in participants with T2D is in agreement with previous work (46). Although research investigating the role of HDL-C in T2D pathophysiology has been conflicting, HDL-C is reported to directly alter glucose metabolism (47), skeletal muscle glucose uptake, and β-cell insulin secretion (48).

We acknowledge limitations in our analysis and those of the UK Biobank. The large majority of UK Biobank participants are of White ethnicity and are less likely to live in socioeconomically deprived areas, and there is evidence of a "healthy-volunteer" selection bias (49). Therefore, it may be unsuitable to generalize our findings to the general population. Additionally, the number of patients per group is small.

CONCLUSION

This study combines MRI-derived measures of organ health and body composition with biochemical measures to study phenotypic differences in participants with and without T2D. We show that participants with T2D have evidence of significantly greater liver damage combined with reduced skeletal muscle mass. We highlight the limitations of routine biochemical tests and the need to screen for coexisting NAFLD in patients with T2D. As the burden of T2D and, in parallel, NAFLD and associated hepatic and extrahepatic complications continues to grow, it is imperative to stratify high-risk patients with coexisting diseases and multiorgan abnormalities and provide more personalized care before irreversible complications develop.O

CONFLICT OF INTEREST

TW: shareholder and employee at Perspectum; AB: option shareholder and employee at Perspectum; DC: previous employee at Perspectum; HTB: shareholder and employee at Perspectum; RB: shareholder and executive at Perspectum; MB: shareholder and executive at Perspectum; DJC: investigator-initiated research funding from AstraZeneca plc and Novo Nordisk A/S; KC: has received research support toward the University of Florida as principal investigator from Cirius Therapeutics; Echosens; Inventiva; Novo Nordisk A/S; Poxel SA; and Zydus Pharmaceuticals. KC is also a consultant for Allergan plc; Altimmune; Arrowhead Pharmaceuticals; AstraZeneca plc; Bristol Myers Squibb; Boehringer Ingelheim; Coherus BioSciences; Eli Lilly and Co.; Fractyl Health, Inc.; Hanmi Pharmaceuticals; Genentech, Inc.; Intercept Pharmaceuticals, Inc.; Janssen Pharmaceuticals; Madrigal Pharmaceuticals; Novo Nordisk A/S; Sonic Incytes Medical Corp.; and Terns Pharmaceuticals. JPD is the Scientific Director at the Centre for Sustainable Health Research University, Quebec, Canada. The other authors declared no conflict of interest.

ORCID

Tom Waddell https://orcid.org/0000-0001-9101-7905
Daniel J. Cuthbertson https://orcid.org/0000-0002-6128-0822
Kenneth Cusi https://orcid.org/0000-0002-8629-418X

REFERENCES

1. Rowley WR, Bezold C, Arikan Y, et al. Diabetes 2030: insights from yesterday, today, and future trends. *Popul Health Manag*. 2017;20:6-12.
2. Yu BO, Li C, Sun Y, et al. Insulin treatment is associated with increased mortality in patients with COVID-19 and type 2 diabetes. *Cell Metab*. 2021;33:65-77.e2.
3. Stedman M, Lunt M, Davies M, et al. Cost of hospital treatment of type 1 diabetes (T1DM) and type 2 diabetes (T2DM) compared to the non-diabetes population: a detailed economic evaluation. *BMJ Open*. 2020;10:e033231. doi:10.1136/bmjopen-2019-033231
4. Karastergiou K. The interplay between sex, ethnicity, and adipose tissue characteristics. *Curr Obes Rep*. 2015;4:269-278.
5. Goff LM. Ethnicity and type 2 diabetes in the UK. *Diabet Med*. 2019;36:927-938.
6. Abdullah A, Peeters A, de Courten M, et al. The magnitude of association between overweight and obesity and the risk of diabetes: a meta-analysis of prospective cohort studies. *Diabetes Res Clin Pract*. 2010;89:309-319.
7. Levelt E, Pavlides M, Banerjee R, et al. Ectopic and visceral fat deposition in lean and obese patients with type 2 diabetes. *J Am Coll Cardiol*. 2016;68:53-63.
8. Linge J, Borga M, West J, et al. Body composition profiling in the UK Biobank imaging study. *Obesity (Silver Spring)*. 2018;26:1785-1795.
9. Gupta P, Lanca C, Gan AT, et al. The association between body composition using dual energy x-ray absorptiometry and type-2 diabetes: a systematic review and meta-analysis of observational studies. *Sci Rep*. 2019;9:12634. doi:10.1038/s41598-019-49162-5
10. Taylor R. Type 2 diabetes: etiology and reversibility. *Diabetes Care*. 2013;36:1047-1055.
11. Wilman HR, Kelly M, Garratt S, et al. Characterisation of liver fat in the UK Biobank cohort. *PLoS One*. 2017;12:e0172921. doi:10.1371/journal.pone.0172921
12. McKay A, Wilman HR, Dennis A, et al. Measurement of liver iron by magnetic resonance imaging in the UK Biobank population. *PLoS One*. 2018;13:e0209340. doi:10.1371/journal.pone.0209340
13. Mojtahed A, Kelly CJ, Herlihy AH, et al. Reference range of liver corrected T1 values in a population at low risk for fatty liver disease-a UK Biobank sub-study, with an appendix of interesting cases. *Abdom Radiol (NY)*. 2019;44:72-84.
14. Pavlides M, Banerjee R, Tunnicliffe EM, et al. Multiparametric magnetic resonance imaging for the assessment of non-alcoholic fatty liver disease severity. *Liver Int*. 2017;37:1065-1073.
15. Banerjee R, Pavlides M, Tunnicliffe EM, et al. Multiparametric magnetic resonance for the non-invasive diagnosis of liver disease. *J Hepatol*. 2014;60:69-77.

16. Eddowes PJ, McDonald N, Davies N, et al. Utility and cost evaluation of multiparametric magnetic resonance imaging for the assessment of non-alcoholic fatty liver disease. *Aliment Pharmacol Ther*. 2018;47:631-644.
17. Pavlides M, Banerjee R, Sellwood J, et al. Multiparametric magnetic resonance imaging predicts clinical outcomes in patients with chronic liver disease. *J Hepatol*. 2016;64:308-315.
18. Wagner R, Heni M, Tabák AG, et al. Pathophysiology-based subphenotyping of individuals at elevated risk for type 2 diabetes. *Nat Med*. 2021;27:49-57.
19. Thomaides-Brears HB, Lepe R, Banerjee R, Duncker C. Multiparametric MR mapping in clinical decision making for diffuse liver disease. *Abdom Radiol (NY)*. 2020;45:3507-3522.
20. Triay Bagur A, Hutton C, Irving B, et al. Magnitude-intrinsic water–fat ambiguity can be resolved with multipeak fat modeling and a multipoint search method. *Magn Reson Med*. 2019;82:460-475.
21. Irving B, Hutton C, Dennis A, et al. Deep quantitative liver segmentation and vessel exclusion to assist in liver assessment. In: *Medical Image Understanding and Analysis: 21st Conference, MIUA 2017, Edinburgh, UK, July 11-13, 2017, Proceedings*. Springer International Publishing; 2017: 663-673.
22. Demerath EW, Shen W, Lee M, et al. Approximation of total visceral adipose tissue with a single magnetic resonance image. *Am J Clin Nutr*. 2007;85:362-368.
23. Shen W, Punyanitya M, Wang Z, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *J Appl Physiol (1985)*. 2004;97:2333-2338.
24. Schweitzer L, Geisler C, Pourhassan M, et al. What is the best reference site for a single MRI slice to assess whole-body skeletal muscle and adipose tissue volumes in healthy adults? *Am J Clin Nutr*. 2015;102:58-65.
25. Yushkevich PA, Piven J, Hazlett HC, et al. User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. *NeuroImage*. 2006;31:1116-1128.
26. Jayaswal ANA, Levick C, Selvaraj EA, et al. Prognostic value of multiparametric magnetic resonance imaging, transient elastography and blood-based fibrosis markers in patients with chronic liver disease. *Liver Int*. 2020;40:3071-3082.
27. Szczepaniak LS, Nurenberg P, Leonard D, et al. Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population. *Am J Physiol Endocrinol Metab*. 2005;288:E462-E468.
28. Kotronen A, Juurinen L, Hakkarainen A, et al. Liver fat is increased in type 2 diabetic patients and underestimated by serum alanine aminotransferase compared with equally obese nondiabetic subjects. *Diabetes Care*. 2008;31:165-169.
29. Nadarajah C, Fananapazir G, Cui E, et al. Association of pancreatic fat content with type II diabetes mellitus. *Clin Radiol*. 2020;75:51-56. doi:10.1016/j.crad.2019.05.027
30. Shah R, Murthy VL, Abbasi SA, et al. Visceral adiposity and the risk of metabolic syndrome across body mass index: the MESA study. *JACC Cardiovasc Imaging*. 2014;7:1221-1235.
31. Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. *J Hepatol*. 2019;71:793-801.
32. Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver versus nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. *Clin Gastroenterol Hepatol*. 2015;13:643-654.
33. Bertot LC, Adams LA. The natural course of non-alcoholic fatty liver disease. *Int J Mol Sci*. 2016;17:774. doi:10.3390/ijms17050774
34. Musso G, Gambino R, Tabibian JH, et al. Association of non-alcoholic fatty liver disease with chronic kidney disease: a systematic review and meta-analysis. *PLoS Med*. 2014;11:e1001680. doi:10.1371/journal.pmed.1001680
35. Mantovani A, Zaza G, Byrne CD, et al. Nonalcoholic fatty liver disease increases risk of incident chronic kidney disease: a systematic review and meta-analysis. *Metabolism*. 2018;79:64-76.
36. Khalid YS, Dasu NR, Suga H, et al. Increased cardiovascular events and mortality in females with NAFLD: a meta-analysis. *Am J Cardiovasc Dis*. 2020;10:258-271.
37. Chakravarthy MV, Waddell T, Banerjee R, et al. Nutrition and nonalcoholic fatty liver disease: current perspectives. *Gastroenterol Clin North Am*. 2020;49:63-94.
38. Wang T, Feng X, Zhou J, et al. Type 2 diabetes mellitus is associated with increased risks of sarcopenia and pre-sarcopenia in Chinese elderly. *Sci Rep*. 2016;6:38937. doi:10.1038/srep38937
39. Honka M-J, Latva-Rasku A, Bucci M, et al. Insulin-stimulated glucose uptake in skeletal muscle, adipose tissue and liver: a positron emission tomography study. *Eur J Endocrinol*. 2018;178:523-531.
40. Abdul-Ghani MA, Defronzo RA. Pathogenesis of insulin resistance in skeletal muscle. *J Biomed Biotechnol*. 2010;2010:476279. doi:10.1155/2010/476279
41. Conley KE, Jubrias SA, Esselman PC. Oxidative capacity and ageing in human muscle. *J Physiol*. 2000;526:203-210.
42. Marcell TJ. Sarcopenia: causes, consequences, and preventions. *J Gerontol A Biol Sci Med Sci*. 2003;58:911-916.
43. Phillips S, Winett R. Uncomplicated resistance training and health-related. *Curr Sports Med Rep*. 2010;9:208-213.
44. Westcott WL. Resistance training is medicine: effects of strength training on health. *Curr Sports Med Rep*. 2012;11:209-216.
45. Mesinovic J, Zengin A, De Courten B, Ebeling PR, Scott D. Sarcopenia and type 2 diabetes mellitus: a bidirectional relationship. *Diabetes Metab Syndr Obes*. 2019;12:1057-1072.
46. Al-Mrabeh A, Zhyzhneuskaya SV, Peters C, et al. Hepatic lipoprotein export and remission of human type 2 diabetes after weight loss. *Cell Metab*. 2020;31:233-249.e4.
47. Drew BG, Duffy SJ, Formosa MF, et al. High-density lipoprotein modulates glucose metabolism in patients with type 2 diabetes mellitus. *Circulation*. 2009;119:2103-2111.
48. Femlak M, Gluba-Brzózka A, Ciałkowska-Rysz A, et al. The role and function of HDL in patients with diabetes mellitus and the related cardiovascular risk. *Lipids Health Dis*. 2017;16:207. doi:10.1186/s12944-017-0594-3
49. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. *Am J Epidemiol*. 2017;186:1026-1034.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Waddell T, Bagur A, Cunha D, et al. Greater ectopic fat deposition and liver fibroinflammation, and lower skeletal muscle mass in people with type 2 diabetes. *Obesity (Silver Spring)*. 2022;30:1231–1238. doi:10.1002/oby.23425