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Less is more: effectiveness and feasibility of a fasting-mimicking diet programme in persons with type 2 diabetes in primary care

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Citation
Schoonakker, M. P., & Burg, E. L. van den. (2026, February 12). *Less is more: effectiveness and feasibility of a fasting-mimicking diet programme in persons with type 2 diabetes in primary care*. Retrieved from https://hdl.handle.net/1887/4290087

Version:	Publisher's Version
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Downloaded from:	https://hdl.handle.net/1887/4290087

Note: To cite this publication please use the final published version (if applicable).

Chapter 7

A fasting-mimicking diet programme reduces liver fat and liver inflammation/fibrosis measured by magnetic resonance imaging in patients with type 2 diabetes

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Clinical Nutrition. 2025; 47:136-145.

Abstract

Background & Aims

This study aimed to assess whether a fasting-mimicking diet (FMD) programme as an adjunct to usual care can reduce liver fat and liver inflammation/fibrosis as measured by Magnetic Resonance Imaging (MRI) in patients with type 2 diabetes.

Methods

This study analyses secondary outcomes of the Fasting In diabetes Treatment (FIT) trial, which was a randomised, controlled, assessor-blinded trial in which people with type 2 diabetes using metformin only and/or diet alone for glycaemic control were randomised to receive 5-consecutive day cycles of FMD monthly as adjunct to usual care or usual care only for twelve months. Laboratory measurements, anthropometric measurements and MRI were performed at baseline, 6 and 12 months. Two MRI-derived biomarkers were measured: proton density fat-fraction (PDFF), a biomarker for liver fat, and iron content corrected T1 (cT1), a biomarker for liver inflammation/fibrosis.

Results

Data were available of 89 participants who completed baseline visits including MRI (n=48 in the FMD group and n=41 in the control group). Intention-to-treat analyses, using linear mixed models, revealed significant adjusted estimated treatment effects of the FMD on PDFF (-2.8%, 95% CI -4.7 to -0.8, $p<0.01$) and cT1 (-29.9 ms, 95% CI -51.8 to -8.0, $p<0.01$) at 12 months. In a post-hoc analysis, more participants in the FMD group compared to the control group transitioned from high to low risk for liver disease and cardiovascular disease based on PDFF ≥ 5.6%. In the FMD and control group combined, every percent decrease in PDFF was associated with a decrease in HbA1c of 0.75 mmol/mol (95% CI 0.51 to 0.99), fasting glucose of 0.14 mmol/L (95% CI 0.08 to 0.20), triglycerides of 0.04 mmol/L (95% CI 0.02 to 0.07), total cholesterol of 0.03 mmol/L (95% CI 0.01 to 0.05) and weight of 0.52 kg (CI 0.33 to 0.70). Every millisecond decrease in cT1 was associated with a decrease in HbA1c of 0.05 mmol/mol (95% CI 0.02 to 0.08), fasting glucose of 0.01 mmol/L (95% CI 0.00 to 0.02) and weight of 0.04 kg (CI 0.01 to 0.06).

Conclusion

Following an FMD programme for 5-consecutive days per month for twelve months reduces both liver PDFF and cT1 MRI-derived biomarkers in patients with type 2 diabetes, indicating a reduction in liver fat and liver inflammation/fibrosis. Decreases in PDFF and cT1 are associated with decreases in HbA1c, fasting glucose, triglycerides and weight. Decrease in PDFF was also associated with a decrease in total cholesterol.

Monthly cycles of an FMD appear to be a valuable adjunct to regular treatment of type 2 diabetes.

Trial registration

ClinicalTrials.gov: NCT03811587

Introduction

Type 2 diabetes is strongly linked to metabolic dysfunction-associated steatotic liver disease (MASLD; formerly known as non-alcoholic fatty liver disease (NAFLD))(1-3). Global prevalence of both diseases is rising, with MASLD affecting around 25%(4, 5) and type 2 diabetes affecting around 11%(6) of the adult population. The prevalence of MASLD in patients with type 2 diabetes is even higher reaching up to 69%(5, 7). Similar pathophysiologic mechanisms, including insulin resistance and low-grade inflammation, play a role in both type 2 diabetes and MASLD(1, 2, 8), and there is an overlap in risk factors like an unhealthy lifestyle and obesity(8, 9). MASLD can lead to metabolic dysfunction-associated steatohepatitis (MASH; formerly known as non-alcoholic steatohepatitis (NASH)), fibrosis, cirrhosis, liver failure and hepatocellular carcinoma(8), and cardiovascular disease (CVD) is the most important cause of morbidity and mortality in patients with both type 2 diabetes and MASLD(10, 11).

Lifestyle interventions, including changes in diet and physical activity, are the cornerstone of treatment for MASLD and MASH treatment (8, 12). Guidelines highlight the importance of weight loss, with a target of 5-10% reduction in body weight(8, 12, 13). At the moment, there is limited evidence to recommend a specific dietary composition(8, 12, 13). Continuous dieting for long periods of time can be very challenging for patients. Studies on intermittent and periodic fasting in patients with MASLD are scarce, but some studies suggest that these diets might be promising in reducing body weight, improving liver enzymes and reducing liver steatosis in patients with MASLD(12, 14, 15). As far as we know, there are no studies on the effects of following a fasting-mimicking diet (FMD) in patients with MASLD. An FMD is a specific form of periodic fasting, which mimics the effects of water-only fasting because of its macronutrient composition being low in sugar and protein, and primarily comprising complex carbohydrates and healthy fats(16). An FMD usually involves dietary adjustments for five consecutive days per month(17). Zhao et al.(18) found in a study with MASLD mouse models (induced by high-fat high-sucrose diet) that administration of an FMD reduced the lipid accumulation in the liver.

In the Fasting In diabetes Treatment (FIT) trial, patients with type 2 diabetes were randomised to follow a monthly 5-day FMD programme for twelve months next to usual care, or usual care alone. Use of glucose-lowering medication, glycated haemoglobin (HbA1c), bodyweight, waist circumference and body fat percentage were reduced and HDL-cholesterol increased(19). Since it is known that the prevalence of MASLD is higher in patients with type 2 diabetes(5, 7), Magnetic Resonance Imaging (MRI) was performed in the FIT trial to evaluate change in MRI-derived biomarkers of the liver. Both proton density fat-fraction (PDFF) and liver iron content corrected T1 mapping

(cT1) can be used as indices for liver pathology. PDFF is an accurate MRI-derived biomarker for liver fat quantification that is routinely used in clinical research(8, 20-22). cT1 has been found to correlate with histopathological features of MASH, and can be used as a MRI-derived biomarker for inflammation/fibrosis(21-23). cT1 is associated with a higher risk of incident CVD and all-cause mortality, independent of pre-existing metabolic syndrome, liver fibrosis or liver fat(24). The aim of the present study is to assess whether following an FMD programme for 5-consecutive days per month for twelve months as an adjunct to usual care reduces PDFF, an MRI-derived biomarker for liver fat, and reduces cT1, an MRI-derived biomarker for liver inflammation/fibrosis, in patients with type 2 diabetes as compared to usual care only. Furthermore, we assess whether changes in PDFF are associated with changes in cT1 and vice versa, and whether changes in PDFF or cT1 are associated with changes in metabolic parameters.

Methods

Study design

The FIT trial is a randomised, controlled, assessor-blinded intervention trial conducted between November 2018 and August 2021 at the Leiden University Medical Centre in the Netherlands(25). The Medical Research Ethics Committee of the LUMC approved the protocol. The trial was conducted according to the principles of the Declaration of Helsinki, with the Medical Research Involving Human Subjects Act, and to the standards of Good Clinical Practice. The trial was prospectively registered on ClinicalTrials.gov, NCT03811587.

Patients with type 2 diabetes were eligible to participate when they had a BMI ≥ 27 kg/m^2, were aged >18 years and <75 years, were treated in primary care with lifestyle advice alone (HbA1c > 48 mmol/mol) or treated with lifestyle advice plus metformin as the only glucose-lowering drug (regardless of HbA1c). All participants gave written informed consent before inclusion. Included participants were allocated to the FMD or control group in computer-generated random sequence via the electronic trial database Castor EDC, which assured allocation concealment. Permuted block randomization with block sizes 2 and 4 was performed, and stratification for gender and weight <100kg or >100 kg was applied. After randomization, participants in the FMD group received twelve monthly 5-consecutive day FMD cycles for one year as adjunct to usual care, while the control group received usual care only. The FMD, which is commercially available, comprised complete meal replacement products (**Supplementary Material Table 1**). The FMD contained ~1100 kcal (10% protein, 56% fat and 34% complex carbohydrate) on day one and ~750 kcal (9% protein, 44% fat, 47% complex carbohydrate) on days

two to five. For patients with a body weight >100 kg, the FMD was supplemented with one bar a day with similar macronutrient composition (90 kcal). Ingredients were all plant-based. Usual care entailed regular clinical evaluation in general practice, laboratory measurements and (if necessary) adaptation of medication use according to the Dutch guidelines for general practitioners(26). Further details of the study design and exclusion criteria can be found in the study protocol(25). Enrolment allocation, follow-up and primary outcomes (HbA1c and glucose-lowering medication use) are described elsewhere(19).

Data collection

This study analyses secondary outcomes of the FIT trial. Data were collected at baseline including demographics, patient history, medication use, anthropometric measurements, laboratory measurements and MRI(25). Follow-up was performed at six and twelve months, and included anthropometric measurements, laboratory measurements and MRI(25). For the FMD group, this entailed a three week period between the last FMD cycle and the follow-up measurements. MRI-derived biomarkers can be used as indices for liver pathology. In this study, the MRI-derived biomarkers included PDFF (marker for liver fat content), T2* (marker for liver iron content) to correct liver T1 resulting in cT1 (marker for liver inflammation/fibrosis)(20). Laboratory measurements in fasting condition included HbA1c, glucose and lipid profiles. Results on changes in anthropometric and laboratory measurements were published previously(19).

For MRI, participants were asked to come after at least six hours of water-only fasting. All MR images were obtained on a Philips Ingenia 3T scanner (Philips, Amsterdam, Netherlands) using an abdominal MRI scan without contrast following the LiverMultiScan (Perspectum Ltd., Oxford, United Kingdom) image acquisition protocol(27). Four transverse slices obtained at the porta hepatis location in the liver were acquired using a shortened modified look-locker inversion (shMOLLI) and a multi-echo spoiled gradient-echo sequence to quantify T1, T2* and PDFF. After image acquisition, pseudonymized data were analysed off-site using LiverMultiScan software (Perspectum Ltd., Oxford, United Kingdom) by specialized imaging analysts trained in abdominal anatomy and artefact detection, who were blinded to group allocation. Using a semi-automatic method, iron-corrected T1 (cT1) and PDFF maps on the liver were delineated into whole liver segmentation maps. Three circular regions of interest (15-mm diameter) were placed on the transverse T2* maps for each slice to cover a representative sample of the liver, and then used to calculate average T2* values for T1-correction. Non-parenchyma structures such as bile ducts and large blood vessels as well as image artifacts were excluded from image analysis.

Statistical analyses

Data are summarized using mean and standard deviation or median and interquartile range in case of a skewed distribution. An intention-to-treat (ITT) analysis was conducted. The differences in PDFF, cT1 and T2* between the FMD group and control group were estimated with linear mixed models using all available data at baseline, six months and twelve months. The linear mixed models included fixed effects for time and time-by-arm interaction terms with random effects for individual participants. The models were adjusted for the baseline value of the outcome and for randomisation stratifiers (sex and weight > 100 kg). As a sensitivity analysis, we computed the same linear mixed models using an unstructured covariance matrix. The analysis was also performed for the outcome 'weight', which was published previously(19).

As a post-hoc analysis of the treatment effect, we analysed PDFF and cT1 categorically. PDFF values above 5.6% are commonly used as threshold for hepatic steatosis, which can progress to liver disease like MASH, fibrosis, cirrhosis and hepatocellular carcinoma. Therefore we categorized PDFF < 5.6% as 'low risk' and PDFF ≥ 5.6% as 'high risk'(20, 28) for liver disease. cT1 was categorized as follows: cT1 < 800 ms is 'low risk', cT1 between 800-875 ms is 'intermediate risk', and cT1 > 875 ms is 'high risk'(20, 29). A higher level of cT1 correlates with histopathologic features of MASH, and is associated with a higher risk of progressive liver disease or CVD(21, 22, 24, 30). Then, we followed the risk assessment proposed by Schaapman et al.(20) that combines PDFF with cT1. First, PDFF is assessed, and if this is <5.6% the risk is classified as 'low'. If PDFF is ≥ 5.6%, the three previously described categories of cT1 are used to determine if the risk is low, intermediate or high. The Fisher's exact test was used to determine if the number of participants that changed from one category to another when comparing baseline to twelve months, differed between the FMD group and the control group.

In the complete group, the associations between changes in PDFF and cT1 from baseline to twelve months were evaluated using linear regression, in which PDFF was the independent variable and cT1 the dependent variable, and vice versa. Furthermore, the associations between changes from baseline to twelve months in PDFF or cT1 (independent variables) and changes in metabolic parameters, including HbA1c, fasting glucose, total cholesterol, triglycerides and weight (dependent variables) were evaluated, also from baseline to twelve months. Crude associations were calculated using linear regression (model 1), independent from randomization. In model 2, we adjusted for possible confounders: age, sex and alcohol consumption. Baseline levels possibly influence the potential to change, therefore in model 3 we additionally adjusted for the baseline measurements of the independent and dependent variables. To assess

whether associations were different between the FMD group and the control group, we calculated the same associations and models in the separate groups. Furthermore, we run the models without outliers (values of the dependent variable above the *third quartile + 1.5*IQR* (interquartile range) or below the *first quartile – 1.5*IQR*).

Statistical analyses were performed using Rstudio version 4.3.1 for Windows. Figures were created in GraphPad Prism version 9.0.1 for Windows.

Results

In the FIT trial, 129 individuals were assessed for eligibility, of whom 29 were excluded (**Figure 1**). 100 participants were randomly assigned to the FMD group (n=51) or the control group (n=49). For this study, data were available of 89 participants who completed the baseline visits of the FIT trial, including MRI (**Figure 1**). In the FMD group, two participants were lost to follow-up before completing baseline measurements due to scheduling issues (n=1) and health issues unrelated to the intervention (n=1). One participants was unable or unwilling to undergo the MRI scan. In the control group, six participants were lost to follow-up before completing baseline measurements, due to dissatisfaction with randomisation (n=2), scheduling issues (n=2), fear of COVID-19 related health issues (n=1) and reason unknown (n=1). Two participants were unable or unwilling to undergo the MRI scan. The FMD group (n=48) and the control group (n=41) were similar regarding baseline characteristics (**Table 1**).

The number of participants who completed follow-up including MRI scan at 12 months was n=41 in the FMD group versus n=35 in the control group. Loss to follow-up was primarily due to the inability to complete study visits, and was unlikely to be related to treatment issues. Drop outs did not differ between groups. For these reasons, missing data were assumed to be at random. At various time points, 11 of the 41 participants discontinued the FMD but agreed to complete follow-up visits. These participants were included in the intention-to-treat analysis. Detailed information on participant inclusion, follow-up and reasons for drop-out is described elsewhere(19).

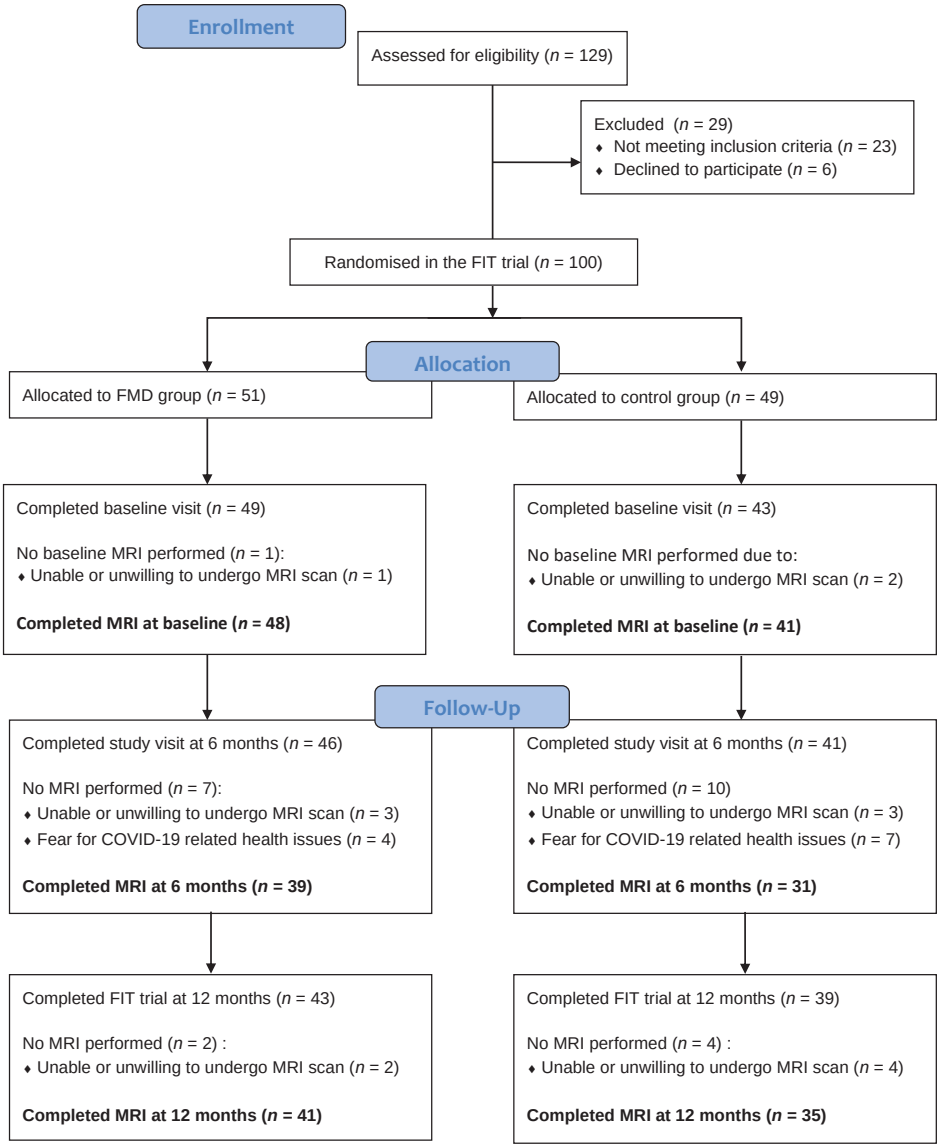

Figure 1. Flow chart of participant inclusion and follow-up in the FIT trial, including the number of completed MRI scans.

The flow-chart shows reasons for missing MRI data. Detailed information on participant inclusion, follow-up and reasons for drop-out is described elsewhere(19).

	FMD group (*n* = 48)	Control group (*n* = 41)
Demographics		
Age (years), mean ± SD	63.6 ± 8.2	62.1 ± 8.7
Sex, *n* (%)		
Male	25 (52)	21 (51)
Female	23 (48)	20 (49)
Alcohol use (units per week), median (IQR)	0.3 (0-4.3)	0 (0-6.0)
Medical History		
Time since diagnosis T2D (years), median (IQR)	4 (3-11)	6 (3-10)
T2D complications, *n* (%)	7 (15)	6 (15)
Hypertension, *n* (%)	34 (71)	27 (66)
Hypercholesterolemia, *n* (%)	38 (79)	24 (59)
History of cardiovascular disease, *n* (%)	8 (17)	4 (10)
Use of glucose-lowering medication		
Metformin, *n* (%)	45 (94)	35 (85)
Metformin dose, median (IQR)	1000 (500 – 1700)	1000 (500 – 1000)
Anthropometrics		
BMI (kg/m^2), mean ± SD	33.1 ± 4.9	32.5 ± 3.5
Weight (kg), mean ± SD	100.6 ± 15.4	98.6 ± 13.1
Waist circumference (cm), mean ± SD	112.2 ± 11.8	110.5 ± 8.5
Laboratory measurements		
HbA1c (mmol/mol), mean ± SD	52.4 ± 9.2	53.6 ± 12.4
Fasting glucose (mmol/L), mean ± SD [a]	8.3 ± 1.9	8.9 ± 1.9
ASAT (U/l), mean ± SD	26.0 ± 10.3	24.9 ± 9.1
ALAT (U/l), mean ± SD	33.5 ± 17.5	33.1 ± 15.2
Lipid spectrum		
Cholesterol (mmol/L), mean ± SD	4.7 ± 1.0	4.8 ± 1.0
LDL (mmol/L), mean ± SD	2.6 ± 0.9	2.7 ± 0.9
HDL (mmol/L), mean ± SD	1.2 ± 0.3	1.3 ± 0.3
Cholesterol/HDL ratio, mean ± SD	4.0 ± 1.1	3.7 ± 0.9
Triglycerides (mmol/L), mean ± SD	1.8 ± 0.8	1.6 ± 0.6
MRI		
PDFF (%), mean (SD)	11.2 (7.8)	12.5 (7.6)
PDFF ≥ 5.6%, n (%)	32 (66.7)	32 (78.0)
cT1 (ms), mean ± SD	833.8 ± 99.9	825.6 ± 84.2
cT1 < 800 ms, n%	19 (39.6)	16 (39.0)
cT1 800-875 ms, n%	14 (29.2)	13 (31.7)
cT1 > 875 ms, n%	15 (31.3)	12 (29.3)
T2* (ms), mean ± SD	15.7 ± 3.9	14.9 ± 3.6

Table 1. Baseline characteristics of the participants of the FIT trial who completed baseline visits including MRI (n=89).

Data are presented as mean ± SD, median (IQR) or number (n) with percentage (%).
a) Missing data FMD group n=1 and control group n=1, because participants did not arrive in fasting condition.
ALAT = alanine aminotransferase. ASAT = aspartate aminotransferase. BMI = Body Mass Index. cT1 = iron-corrected T1. FMD = fasting-mimicking diet. HbA1c = glycated haemoglobin. HDL = high-density lipoprotein. IQR = interquartile range. LDL = low-density lipoprotein. n = number. PDFF = proton density fat-fraction. SD = standard deviation. T2D = type 2 diabetes.

	FMD group		Control group		Adjusted* estimated treatment effect (95% CI)	*p*-value
	n	Mean (SD)	*n*	Mean (SD)		
PDFF (%)						
Baseline	48	11.2 (7.8)	41	12.5 (7.6)		
6 months	39	7.2 (6.5)	31	12.6 (8.4)	-3.4 (-5.4 to -1.4)	<0.01
12 months	41	8.8 (7.4)	35	13.2 (9.2)	-2.8 (-4.7 to -0.8)	<0.01
cT1 (ms)						
Baseline	48	833.8 (99.9)	41	825.6 (84.2)		
6 months	38	805.0 (89.4)	31	846.9 (91.0)	-33.6 (-56.3 to -11.0)	<0.01
12 months	41	807.4 (87.0)	34	841.1 (97.7)	-29.9 (-51.8 to -8.0)	<0.01
T2* (ms)						
Baseline	48	15.7 (3.9)	41	14.9 (3.6)		
6 months	39	16.6 (4.0)	31	15.4 (4.0)	0.5 (-0.5 to 1.5)	0.37
12 months	41	16.7 (4.0)	35	15.1 (4.2)	0.7 (-0.3 to 1.7)	0.16
Weight (kg)						
Baseline	48	100.6 (15.4)	41	98.6 (13.1)		
6 months	44	95.5 (14.9)	36	97.9 (13.7)	-3.8 (-5.4 to -2.2)	<0.0001
12 months	43	95.3 (14.5)	37	98.8 (13.9)	-3.7 (-5.3 to -2.1)	<0.0001

Table 2. Analyses over time using linear mixed models.

The linear mixed models were computed with fixed effects for time and time-by-arm interaction terms and with random effects for individual participants.
* The models were adjusted for the baseline value of the outcome and for randomization stratifiers (sex and weight > 100 kg).
CI = confidence interval. cT1 = iron-corrected T1. FMD = fasting-mimicking diet. PDFF = proton density fat-fraction. SD = standard deviation.

Treatment effect

Effect of following an FMD diet on MRI-derived biomarkers over time

Mean PDFF changed from 11.2% (SD 7.8%) at baseline to 8.8% (SD 7.4%) at twelve months in the FMD group, while it changed from 12.5% (SD 7.6%) to 13.2% (SD 9.2%) in the control group, yielding an adjusted estimated treatment effect of -2.8% (95% CI -4.7 to -0.8, p<0.01, **Table 2**, **Figure 2**, **Figure 3**). Mean cT1 changed from 833.8 ms (SD 99.9 ms) at baseline to 807.4 ms (SD 87.0 ms) at twelve months in the FMD group, while it changed from 825.6 ms (SD 84.2) to 841.1 ms (SD 97.7 ms) in the control group, yielding an adjusted estimated treatment effect of -29.9 ms (95% CI -51.8 to -8.0, p<0.01, **Table 2**, **Figure 2**, **Figure 3**). T2* remained stable, with in the FMD group 15.7 ms (SD 3.9 ms) at baseline and 16.7 ms (SD 4.0 ms) at twelve months, and in the control group 14.9 ms (SD 3.6 ms) at baseline and 15.1 ms (SD 4.2 ms) at twelve months (adjusted estimated treatment effect of 0.7 ms, 95% CI -0.3 to 1.7, p=0.16, **Table 2**, **Figure 2**, **Figure 3**). Sensitivity analyses showed similar results (**Supplementary Material Table 2**).

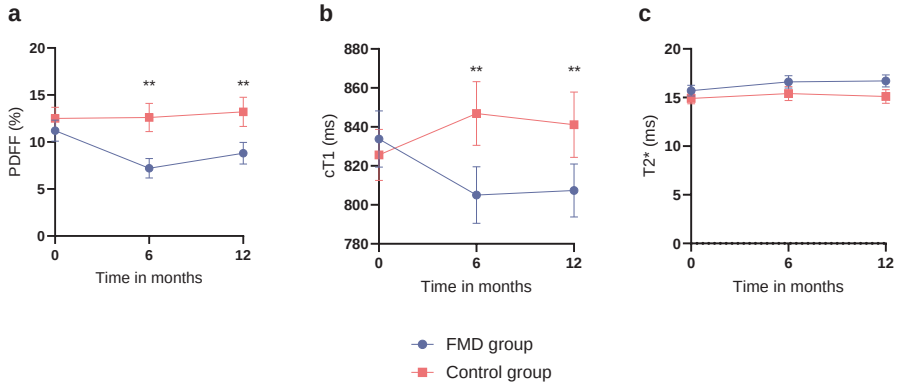

Figure 2. Observed changes in MRI-derived biomarkers over time: PDFF (liver fat), cT1 (liver inflammation/fibrosis) and T2* (iron).

Values are presented as mean ± standard error of the mean. (a) Change in PDFF over time. (b) Change in cT1 over time. (c) Change in T2* over time.
cT1 = iron-corrected T1. FMD = fasting-mimicking diet. PDFF = proton density fat-fraction. **p<0.01.

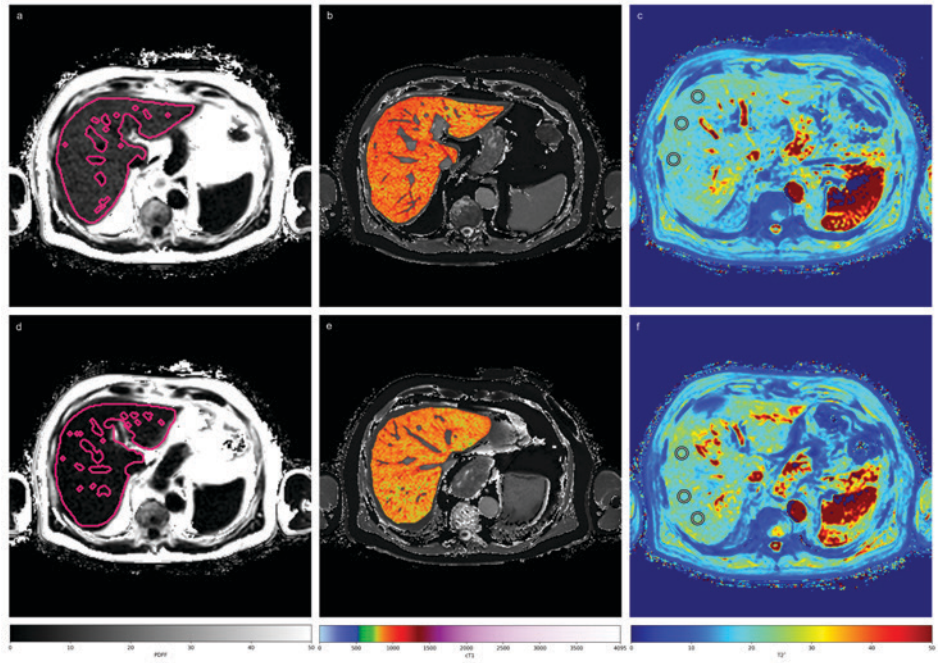

Figure 3. Example of MRI images after analysis with LiverMultiScan software (Perspectum Ltd., Oxford, United Kingdom).

Panels A and D show PDFF maps, panels B and E show iron-corrected T1 maps, and panels C and F show T2* maps, all acquired from the same participant in the FMD group. The first row illustrates baseline images with the following values: PDFF = 9.9% (A), cT1 = 920 ms (B) and T2* = 19.7 ms (C). The second row shows images obtained at 12 months: PDFF = 3.2% (D), cT1 = 867 ms (E) and T2* = 21.4 ms (F).
Using a semi-automatic method, PDFF and iron-corrected T1 (cT1) maps on the liver were delineated into whole liver segmentation maps. Three circular regions of interest (15-mm diameter) were placed on the transverse T2* maps for each slice to cover a representative sample of the liver, and then used to calculate average T2* values for T1-correction. Non-parenchyma structures such as bile ducts and large blood vessels as well as image artifacts were excluded from image analysis.

Post-hoc analysis

In a post-hoc analysis, we calculated disease risk (regarding progressive liver disease and CVD) based on PDFF and cT1 values at baseline and at twelve months (**Supplementary Material Table 3**). When analysing the changes in risk based on PDFF values from baseline to twelve months, more participants (16.2%) improved in the FMD group compared to the control group (**Table 3**). However, also more participants deteriorated in the FMD group compared to the control group (3 versus 1). When analysing the changes in risk based on cT1 values or the combination of PDFF and cT1 values, there were no significant differences between the two groups.

	FMD group	Control group	p-value
Risk based on PDFF values	n=41	n=35	0.05
Improved, n (%)	11 (26.8)	3 (8.6)	
Stable, n (%)	27 (65.9)	31 (88.6)	
Deteriorated, n (%)	3 (7.3)	1 (2.9)	
Risk based on cT1 values	n=41	n=34	0.27
Improved, n (%)	9 (22.0)	4 (11.8)	
Stable, n (%)	29 (70.7)	24 (70.6)	
Deteriorated, n (%)	3 (7.3)	6 (17.6)	
Risk based on the combination of PDFF and cT1 values	n=41	n=34	0.50
Improved, n (%)	9 (22.0)	4 (11.8)	
Stable, n (%)	28 (68.3)	25 (73.5)	
Deteriorated, n (%)	4 (9.8)	5 (14.7)	

Table 3. Changes in risk based on MRI-derived biomarkers.

This table shows the number of participants that improved, remained stable, or deteriorated according to their risk category comparing baseline to 12 months. The Fisher's exact test was used to determine if the number of participants that changed from one category to another (improved, stable or deteriorated), differed between the FMD group and the control group.
Participants were categorized as follows (Supplementary Material Table 3): PDFF < 5.6% was categorized as 'low risk' and PDFF ≥ 5.6% was categorized as 'high risk' for progressive liver disease and CVD. cT1 was categorized as follows: cT1 < 800 ms is 'low risk', cT1 between 800-875 ms is 'intermediate risk', and cT1 > 875 ms is 'high risk' for progressive liver disease and CVD. For the risk based on the combination of PDFF and cT1 values: PDFF is assessed first, and if this is <5.6% the risk is classified as 'low'; if PDFF is ≥ 5.6%, the three previously described categories of cT1 are used to determine if the risk is low, intermediate or high. cT1 = iron-corrected T1. CVD = cardiovascular disease. FMD = fasting-mimicking diet. PDFF = proton density fat-fraction.

Associations in total population

Associations between changes in PDFF versus changes in cT1

Analyses performed in all participants (n=75) showed that changes in PDFF were associated with changes in cT1 and vice versa, both with and without correction for confounders (**Table 4**, **Supplementary Material Figure 1**). Every percent decrease in PDFF from baseline to twelve months was associated with a decrease in cT1 by 5.67 ms (95% CI 3.95 to 7.39 ms) when corrected for confounders (age, sex, alcohol use, baseline PDFF and baseline cT1). Every millisecond decrease in cT1 from baseline to twelve months was associated with a decrease in PDFF of 0.07% (95% CI 0.05 to 0.09%), both with and without correction for confounders.

		Δ PDFF (independent variable)		
Dependent variable	**N**	**β (95% CI)**	**p-value**	**Adj. R^2**
Δ cT1				
Model 1	75	6.56 (4.89 to 8.26)	<0.0001	0.44
Model 2	75	5.90 (4.23 to 7.57)	<0.0001	0.50
Model 3	75	5.67 (3.95 to 7.39)	<0.0001	0.53

		Δ cT1 (independent variable)		
Dependent variable	**N**	**β (95% CI)**	**p-value**	**Adj. R^2**
Δ PDFF				
Model 1	75	0.07 (0.05 to 0.09)	<0.0001	0.44
Model 2	75	0.07 (0.05 to 0.09)	<0.0001	0.43
Model 3	75	0.07 (0.05 to 0.09)	<0.0001	0.45

Table 4. Associations between changes in PDFF versus changes in cT1 and vice versa.

Results represent regression coefficients with 95% confidence intervals. The adjusted R^2 of the model is given. Model 1: crude association. Model 2: model 1 adjusted for age, sex and alcohol use. Model 3: Model 2 adjusted for baseline measurements of the dependent and independent variables.
Adj. R^2 = adjusted R^2. β = regression coefficient. CI = confidence interval. cT1 = iron-corrected T1. PDFF = proton density fat-fraction.

Associations between changes in PDFF and changes in metabolic parameters

Analyses performed in all participants showed that changes in PDFF from baseline to twelve months were associated with changes in HbA1c, fasting glucose, triglycerides, cholesterol and weight from baseline to twelve months, both with and without correction for confounders (**Table 5**, **Supplementary Material Figure 2**). Every percent decrease in PDFF was associated with a decrease in HbA1c of 0.75 mmol/mol (95% CI 0.51 to 0.99), fasting glucose of 0.14 mmol/L (95% CI 0.08 to 0.20), triglycerides of 0.04 mmol/L (95% CI 0.02 to 0.07), cholesterol of 0.03 mmol/L (95% CI 0.01 to 0.05) and weight of 0.52 kg (95% CI 0.33 to 0.70). In general, when comparing the FMD group and the control group, and in the analysis without outliers, similar associations were found (**Supplementary Material Table 4, 5 and 6**).

	Δ PDFF (independent variable)				Δ cT1 (independent variable)			
Dependent variable	**n**	**β (95% CI)**	**p-value**	**Adj. R^2**	**n**	**β (95% CI)**	**p-value**	**Adj. R^2**
Δ HbA1c (mmol/mol)								
Model 1	76	0.95 (0.64 to 1.27)	<0.0001	0.32	75	0.07 (0.03 to 0.11)	<0.001	0.16
Model 2	76	0.98 (0.65 to 1.31)	<0.0001	0.31	75	0.08 (0.03 to 0.12)	<0.001	0.13
Model 3	76	0.75 (0.51 to 0.99)	<0.0001	0.68	75	0.05 (0.02 to 0.08)	<0.01	0.56
Δ Fasting glucose (mmol/L)								
Model 1	75	0.15 (0.08 to 0.21)	<0.0001	0.21	74	0.01 (0.00 to 0.02)	<0.01	0.12
Model 2	75	0.15 (0.08 to 0.22)	<0.0001	0.19	74	0.01 (0.00 to 0.02)	<0.01	0.09
Model 3	75	0.14 (0.08 to 0.20)	<0.0001	0.38	74	0.01 (0.00 to 0.02)	<0.01	0.26
Δ Cholesterol (mmol/L)								
Model 1	75	0.04 (0.01 to 0.06)	<0.01	0.11	74	0.00 (-0.00 to 0.00)	0.45	-0.00
Model 2	75	0.04 (0.01 to 0.06)	<0.01	0.12	74	0.00 (-0.00 to 0.00)	0.47	-0.01
Model 3	75	0.03 (0.01 to 0.05)	0.01	0.14	74	0.00 (-0.00 to 0.00)	0.46	0.03
Δ Triglycerides (mmol/L)								
Model 1	75	0.06 (0.03 to 0.08)	<0.0001	0.20	74	0.00 (0.00 to 0.01)	<0.01	0.12
Model 2	75	0.05 (0.03 to 0.08)	<0.001	0.23	74	0.00 (0.00 to 0.01)	<0.01	0.16
Model 3	75	0.04 (0.02 to 0.07)	<0.01	0.35	74	0.00 (0.00 to 0.01)	0.01	0.33
Δ Weight (kg)								
Model 1	76	0.49 (0.31 to 0.67)	<0.0001	0.27	75	0.04 (0.02 to 0.06)	<0.001	0.14
Model 2	76	0.45 (0.27 to 0.64)	<0.0001	0.29	75	0.03 (0.02 to 0.06)	<0.01	0.17
Model 3	76	0.52 (0.33 to 0.70)	<0.0001	0.34	75	0.04 (0.01 to 0.06)	<0.01	0.16

Table 5. Associations between changes in PDFF or cT1 between baseline and 12 months and changes in metabolic parameters.

Results represent regression coefficients with 95% confidence intervals. The adjusted R^2 of the model is given. Model 1: crude association. Model 2: model 1 adjusted for age, sex and alcohol consumption. Model 3: Model 2 adjusted for baseline values of the dependent and independent variables.
Adj. R^2 = adjusted R^2. β = regression coefficient. CI = confidence interval. cT1 = iron-corrected T1. HbA1c = glycated haemoglobin. PDFF = proton density fat-fraction.

Associations between changes in cT1 and changes in metabolic parameters

Analyses performed in all participants showed that changes in cT1 from baseline to twelve months were associated with changes in HbA1c, fasting glucose, triglycerides and weight from baseline to twelve months, both with and without correction for confounders (**Table 5**, **Supplementary Material Figure 3**). Every millisecond decrease in cT1, was associated with a decrease in HbA1c of 0.05 mmol/mol (95% CI 0.02 to 0.08), fasting glucose of 0.01 mmol/L (95% CI 0.00 to 0.02), triglycerides of 0.00 mmol/L (95% CI 0.00 to 0.01) and weight of 0.04 (95% CI 0.01 to 0.06). No association was found between changes in cT1 and changes in cholesterol. In general, when comparing the FMD group and the control group, similar associations were found (**Supplementary Material Table 4 and 5**). However, there was no association between change in cT1 and changes in fasting glucose and triglycerides in the control group (all models), which were seen in the total group and in the FMD group. Additionally, in the analysis without outliers (**Supplementary Material Table 6**), an association is found in all models between change in cT1 and change in cholesterol.

Discussion

In patients with type 2 diabetes, following an FMD programme for 5-consecutive days per month for twelve months in addition to usual care reduces PDFF and cT1 values compared to usual care alone, while there are no changes in T2*, indicating a reduction in liver fat and liver inflammation/fibrosis. In the post-hoc analysis, when analysing changes in risk of progressive liver disease and CVD based on PDFF ≥ 5.6%, we found a difference between the FMD group and the control group as more participants in the FMD group improved and changed from the high risk to the low risk category. When calculating disease risk based on cT1 alone or combined with PDFF, we did not find significant differences between groups, indicating that changes in cT1 values during follow up were not large enough to induce a difference in disease risk. This may have to do with the fact that a relatively high proportion of participants (approximately 70%) exhibited normal cT1 values at baseline, thereby limiting the potential for risk reduction through further decline of cT1. Changes in PDFF were associated with changes in cT1 and vice versa, and we found that a decrease in PDFF or cT1 was associated with a decrease in HbA1c, fasting glucose, triglycerides and weight. In addition, a decrease in PDFF was also associated with a decrease in total cholesterol. This suggests a relationship between metabolic changes and changes in liver fat and liver inflammation/fibrosis.

In line with earlier studies into the prevalence of an elevated liver fat percentage in patients with type 2 diabetes(5, 7), we found that 66.7% of the FMD group and 78.0% of the control group had a PDFF ≥ 5.6%. Our finding that following an FMD programme

can reduce PDFF, is in line with an earlier study which found that administration of an FMD can ameliorate lipid accumulation in mouse models in which fatty liver formation was induced(18). As far as we know, our study is the first to assess the effects of following an FMD on liver fat and liver inflammation/fibrosis in patients. There is a limited number of studies on intermittent energy restriction (IER) and liver fat or liver inflammation/fibrosis(31-33). In a clinical trial including patients with NAFLD, the 5:2 diet, a form of IER, has also been found effective in reducing liver fat(31). Furthermore, an alternate-day energy restriction study (also IER) including patients with NAFLD, found a reduction in liver steatosis grades and fibrosis scores measured by ultrasonography(32). A third study in patients with NAFLD, comparing alternate-day energy restriction to time restricted feeding and to usual care, did not find a difference in liver stiffness between the groups in a trial lasting 12 weeks, which may have been relatively short to find an effect on liver stiffness(33). The largest effects on PDFF and cT1 were observed at 6 months of follow-up, remaining relatively stable thereafter at 12 months. This can be attributed partly to the intention-to-treat nature of the analysis, as a higher proportion of participants were actively adhering to the FMD programme at 6 months compared to 12 months. Furthermore, this pattern aligns with the observed changes in weight over the year (**Table 2**), and it is known that weight loss is an important factor in improving liver fat and liver inflammation/fibrosis(8, 12).

In this study, we found that changes in PDFF are associated with changes in cT1. This is likely since liver steatosis and MASH are part of a disease spectrum and accumulation of fat in the liver is an important factor in the complex pathophysiology of MASH(34, 35). Hepatic triglyceride accumulation is one of the first steps in the pathogenesis of MASLD(36), and the association we found between changes in PDFF or cT1 and changes in triglycerides aligns with this. It is known that there is overlap in the pathogenic mechanism that can lead to MASLD and to type 2 diabetes, and that even though the exact mechanisms are not fully known yet, insulin resistance plays a key role(2). Ectopic fat in the liver is associated with insulin resistance, also in persons without type 2 diabetes(37, 38). This is in line with the associations we observed between changes in PDFF and cT1 versus changes in HbA1c and fasting glucose. Furthermore, we observed an association between changes in PDFF and cT1 and changes in weight, consistent with the well-established effects of weight loss on liver fat and liver inflammation/fibrosis(39, 40). This is further supported by clinical guidelines, which recommend a 5-10% weight reduction to improve liver health in patients with MASLD or MASH(8, 12, 13).

Strengths, limitations and future research

Strengths of this study include the measurement of MRI-derived biomarkers at different timepoints, in combination with laboratory measurements. In earlier studies, the MRI-derived biomarkers PDFF and cT1 correlated strongly with the degree of steatosis or fibrosis in histopathology(22, 41), which indicates that these biomarkers are valuable non-invasive outcome measures for clinical research. Another strength of this study is that even though not all included participants had an elevated liver fat content, we found a decrease in PDFF. In a population with patients who are diagnosed with both type 2 diabetes and MASLD, the effect might even be larger. The same accounts for the small change in cT1, this effect could be larger in a steatohepatitis cohort, since cT1 was 833.8 ms in the FMD group and 825.6 ms in the control group at baseline. The large variability in PDFF and cT1 can also be explained by the relatively high number of participants with non-elevated levels of PDFF or cT1 at baseline. Therefore, that not all participants were formerly screened for MASLD is also one of the limitations of this study. Consequently, other potential causes of liver disease were not routinely assessed. Only information on alcohol use was available and was used in our models. Another limitation is the relatively high number of missing outcome data in the analysis, which may have caused selection bias. We have assumed that the data are missing at random, but we cannot be sure. However, participants were encouraged to complete follow-up visits when they decided to discontinue the FMD. Another limitation is that there were no specific markers for liver disease available at the end of follow-up (e.g. ASAT and ALAT). For future research, a broader panel for laboratory markers of liver disease should be taken into account at all timepoints. In addition, further research on long-term effects including cardiovascular events is necessary, since follow-up was limited to twelve months. Furthermore, clinical trials investigating the effects of following an FMD programme specifically in patients with MASLD and MASH are warranted, as larger effects on PDFF and cT1 may be expected in these populations.

Clinical implications

This study shows that following an FMD programme for 5 days per month for twelve months has a positive effect on both PDFF and cT1, which indicates that an FMD programme can reduce liver fat and liver inflammation/fibrosis in patients with type 2 diabetes in primary care. In our post-hoc analysis of risk categories based on PDFF, we found that compared to participants in the control group, more participants from the FMD group improved from a high risk to a low risk category. A PDFF ≥ 5.6% is associated with progression of liver disease into MASH, fibrosis, cirrhosis and hepatocellular carcinoma(20, 28), and following an FMD programme can potentially reduce this risk. Even though we did not find significant differences between risk categories based on cT1, we did find an absolute decrease in cT1, and cT1 is associated

with a higher risk of incident CVD and all-cause mortality(24). The associations we found between changes in PDFF and cT1, and changes in several of the metabolic parameters, emphasize the relationship between liver fat and type 2 diabetes. This underscores the importance of focussing on lifestyle treatment such as following an FMD programme, which targets the entire metabolism, as an alternative to targeting specific diseases or disease symptoms with medication. For future research, it would be valuable to investigate the effects of an FMD programme on liver fat and inflammation/fibrosis in patients with MASLD, regardless of type 2 diabetes.

Conclusion

Following an FMD programme for 5-consecutive days per month for twelve months reduces both liver PDFF and cT1 MRI-derived biomarkers in patients with type 2 diabetes, indicating a reduction in liver fat and liver inflammation/fibrosis. Decreases in PDFF and cT1 are associated with decreases in HbA1c, fasting glucose, triglycerides and weight. The decrease in PDFF was also associated with a decrease in total cholesterol. Monthly cycles of an FMD appear to be a valuable adjunct to regular treatment of type 2 diabetes.

Declarations

Acknowledgements

The authors thank Pieter van den Boogaard, MRI technician of the Leiden University Medical Centre, for his expertise in training the researchers in MRI scanning, as well as optimizing the scan protocol. Furthermore, we gratefully acknowledge the contribution of all participants, the trial steering committee, the general practice centres, supporting staff and research nurses involved in the trial.

Data availability

The datasets generated during and/or analysed in the current study are available upon reasonable request. Requests should be sent to the FIT trial corresponding email (fit@lumc.nl). All proposals requesting data access will need to specify how the data will be used, and all proposals will need approval of the trial co-investigator team before data release.

Funding statement

The project was co-funded by Health~Holland, Top Sector Life Sciences & Health, and the Dutch Diabetes Foundation (project LSHM17040-PTO). L-Nutra contributed the formula diet and a small part of the funding. External peer-review took place during the funding process and was performed by ZonMw (The Netherlands Organisation for Health Research and Development). The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, approval of the manuscript or the decision to submit the manuscript for publication.

Conflict of Interest

All authors declare: financial support was received from Health~Holland, Top Sector Life Sciences & Health, the Dutch Diabetes Foundation, and L-Nutra for the project; HL has received consulting fees from Royal Philips and was member of the board of trustees of the SCMR and UEMS section Radiology without payment; no other relationships or activities that could appear to have influenced the submitted work.

Author Contribution

Elske L. van den Burg: Conceptualization, Methodology, Formal analysis, Investigation, Project administration, Writing – Original Draft, Visualization. Marjolein P. Schoonakker: Conceptualization, Methodology, Investigation, Project administration, Writing – Review & Editing. Petra G. van Peet: Conceptualization, Methodology, Formal analysis, Writing – Review & Editing, Supervision. Saska le Cessie: Methodology, Formal analysis, Writing – Review & Editing, Supervision. Mattijs E. Numans: Conceptualization, Writing – Review & Editing, Supervision. Hanno Pijl: Conceptualization, Writing – Review & Editing, Supervision, Funding acquisition. Hildo J. Lamb: Conceptualization, Methodology, Writing – Review & Editing, Supervision.

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QR-code to article and supplementary information

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