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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Chapter 8

A fasting-mimicking diet programme reduces abdominal adipose tissue while preserving abdominal muscle mass in persons with type 2 diabetes

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Abstract

Background and Aim

This study evaluated the effects of a fasting-mimicking diet (FMD) programme alongside usual care on abdominal visceral- (aVAT) and subcutaneous (aSAT) adipose tissue, and abdominal muscle area (aMA) in persons with type 2 diabetes in primary care.

Methods and Results

100 persons with type 2 diabetes using metformin and/or diet alone for glycemic control were randomly assigned to receive an FMD for 5 consecutive days each month plus usual care or usual care only for 12 months. The treatment effect of the FMD on aVAT, aSAT and aMA as well as associations between changes in aVAT, aSAT or aMA, and changes in metabolic parameters were assessed. 89 participants completed baseline visits including MRI. The adjusted estimated treatment effect after 12 months in the FMD group was a loss of 37.9 cm^2 (95% CI -54.7, to -21.0) in aVAT, 20.9 cm^2 (95%CI -34.5 to -7.3) in aSAT and 1.6 cm^2 (95% CI -4.6 to 1.4) in aMA compared to the control group. Changes in aVAT and aSAT were strongly associated with change in HbA1c and moderately with other metabolic parameters.

Conclusions

A 12-month FMD programme reduced both aVAT and aSAT, while aMA remained unaffected compared to controls in persons with type 2 diabetes. The decline in aVAT and aSAT was associated with a reduction of several metabolic parameters, including HbA1c. A monthly FMD programme yields various health benefits in type 2 diabetes and appears to be a valuable treatment option as adjunct to usual care.

Trial registration

ClinicalTrials.gov: NCT03811587

Introduction

The distribution of adipose tissue and the functionality of different fat depots contribute to insulin resistance and cardiovascular disease risk(1-7). An excess of total body fat, subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) is associated with both prediabetes and type 2 diabetes(1-3). Among these, VAT shows the strongest association, particularly in men(8). Therefore, treatment options for type 2 diabetes should ideally not only target glucose metabolism, but also decrease total body fat, SAT and VAT.

Lifestyle interventions, including caloric restriction, can effectively reduce excessive adipose tissue and lower cardiometabolic disease risk(9, 10). However, caloric restriction can also lead to a reduction of fat free mass, which consists predominantly of muscle tissue(11-14). The loss of muscle is detrimental, as it can promote weight regain by reducing energy requirements and basal metabolic rate(15, 16). Reduced muscle mass, especially when combined with obesity (a condition known as sarcopenic obesity), is also associated with an increased risk of developing hypertension, dyslipidaemia and diabetes, as well as an increased risk of disability and overall mortality(17, 18). Optimal treatment for persons with type 2 diabetes should therefore reduce VAT and SAT while preserving muscle mass.

While periodic or intermittent fasting programmes have benefits in persons with type 2 diabetes with respect to glucose metabolism, bodyweight and overall fat mass, their effect on muscle mass remains unclear, as some studies report a reduction in fat-free mass, while others do not observe such an effect(19-21). Periodic and intermittent fasting programmes are characterized by alternating periods of rigorous caloric restriction (fasting) and unrestricted intake. To alleviate the burden of fasting, fasting-mimicking diet (FMD) programmes were developed that mimic the physiological effects of fasting, while still permitting the consumption of light meals on fasting days(22). The few studies evaluating the effect of an FMD on fat mass and fat free mass found a reduction of fat mass while fat free mass and metabolic rate were preserved(22, 23). However, these studies included healthy participants and did not specify VAT and SAT as outcome measures. Thus, the effect of an FMD programme on adipose tissue structure and muscle mass in persons with type 2 diabetes remains unclear, while these anthropometric measures are potentially of major importance for metabolic control.

In this study, secondary outcomes from the Fasting In diabetes Treatment (FIT) trial were assessed to determine whether the use of an FMD programme as an adjunct to usual care affects visceral and subcutaneous adipose tissue and muscle mass in persons with type 2 diabetes. Additionally, associations between changes in abdominal VAT

(aVAT), abdominal SAT (aSAT) or abdominal muscle area (aMA) and changes in metabolic parameters were explored in all participants as well as in men and women separately.

Methods

Study design

The FIT trial was a randomized, controlled, assessor-blinded intervention trial, conducted in the Leiden University Medical Center (LUMC) in the Netherlands. The trial was performed according to the principles of the Declaration of Helsinki, in accordance with the Medical Research Involving Human Subjects Act (WMO), and to the standards of Good Clinical Practice (GCP). The protocol and amendments were approved by the Medical Research Ethics Committee of the LUMC before start of the trial, and the study protocol was published(24). The trial was prospectively registered on ClinicalTrials.gov, NCT03811587.

One hundred participants with type 2 diabetes under regular primary care surveillance were recruited in collaboration with general practice centers in the area around Leiden and The Hague. Inclusion criteria were the diagnosis of type 2 diabetes, a BMI≥ 27 kg/m^2 and age >18 years and <75 years. Participants had to be treated with lifestyle advice only and have a glycated hemoglobin (HbA1c) above 48 mmol/mol, or lifestyle advice plus metformin as only glucose-lowering drug, irrespective of their HbA1c. Exclusion criteria were a recent myocardial infarction (<6 months), creatinine clearance <30 ml/min/1.73m^2 (MDRD), pregnancy, contraindications for MRI, allergy for one of the ingredients of the diet, history of syncope during caloric restriction in the past or any significant other disease (at the discretion of the investigator). All participants provided written informed consent. 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 <100 kg and >100 kg was applied.

Both the FMD group and the control group were provided with usual care via their own general practitioner's office. Usual care entailed regular clinical and biochemical evaluation and eventual adaptation of medication use according to Dutch guidelines for general practitioners(25), usually carried out by a practice nurse dedicated to chronic disease management. The control group received usual care only, and was not given any instructions to modify their lifestyle, including diet or physical activity. The FMD group received twelve 5-consecutive day FMD cycles in one year, consisting

of complete meal replacement products every month as an adjunct to usual care. Caloric content and macronutrient composition were as follows; day 1 contained ~ 1100 kcal (10% protein, 56% fat and 34% complex carbohydrate); day 2–5 was identical and provided ~ 750 kcal (9% protein, 44% fat, 47% complex carbohydrate). Persons weighing more than 100 kg received one additional bar a day (90 kcal) with similar macronutrient composition. Participants of the FMD group were contacted by telephone every month during the FMD period. Adherence to the trial regimen was assessed verbally during these telephone calls. Apart from the FMD instructions, they were not given any guidance to modify their lifestyle between FMD periods. Self-initiated change in physical activity and diet quality were monitored(26).

Data collection

Data on anthropometrics, laboratory measurements and MRI measurements at baseline, 6 months and 12 months was used, with a three-week period between the last FMD cycle and the measurements at 6 and 12 months. Blinded research nurses collected data, and blood samples and MRI data were analysed by distinct blinded teams, while unblinded staff handled diet concerns and distribution. Standard blood tests were performed in the hospital's laboratory following venipuncture of the antecubital vein. Blood samples were collected in tubes containing ethylenediaminetetraacetic acid (EDTA), sodium fluoride (NaF), serum-separating technology (SST), and lithium heparin (LiHep). Further details of assessments during follow-up can be found in the published protocol of the FIT trial(24).

Abdominal subcutaneous- and visceral fat depots and abdominal muscle were quantified using MRI. Participants were asked to come after at least 6h 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 using a turbo spin echo imaging protocol. The multiple overlapping fat- and water- separated abdominal image volumes were resampled into a new single volume with slice thickness 2 mm and in-plane resolution of 0.9091 × 0.9091 mm. From this, a single axial slice at the center of the third lumbar vertebra was manually selected. Image segmentation was performed using a semi-automated process using Atlas™ (Perspectum Ltd, Oxford, UK). The slice was automatically segmented using a previously trained 2D U-Net model to delineate the axial cross sections of visceral adipose tissue, subcutaneous adipose tissue, and skeletal muscle. The automatic segmentation was manually corrected in ITK-SNAP(27) using anatomical definitions described by Shen et al.(28) and Wang et al.(29) The bowel and other abdominal organs, the larger vasculature, and renal fat were excluded. Cross-sectional areas (cm^2) of each compartment were calculated by multiplying in-plane voxel resolution by the number of voxels and is regarded as

representative of abdominal muscle mass. Abdominal muscle mass serves as an estimate of fat-free mass and lean tissue mass and correlates well with measurements obtained through dual-energy X-ray absorptiometry(30).

Statistical analyses

An intention-to-treat (ITT) analysis was conducted. Data are summarized using mean and standard deviation, or in case of a skewed distribution median and interquartile range. The differences in aVAT, aSAT and aMA between the FMD group and control group using all available data at baseline, 6 months and 12 months were estimated using linear mixed models with an α-level of 0.05 for statistical significance. These included fixed effects for time and time-by-arm interaction terms with random effects for individual participants. The models were adjusted for randomization stratifiers (sex and weight > 100 kg) and for the baseline value of the outcome. As a sensitivity analysis, the same linear mixed models were computed using an unstructured covariance matrix. Linear mixed models were also stratified by sex.

Linear regression models including both FMD and control participants were used to evaluate the association of change in weight (independent variable) and change of aVAT, aSAT or aMA (dependent variables) between baseline and twelve months follow-up. These associations were also assessed stratified by sex. Associations for all participants were calculated correcting for the confounders age and sex and were corrected for baseline levels of the dependent and independent variables(31-34). Furthermore, linear regression models were used to evaluate the association between change in aVAT, aSAT and aMA (independent variables) and several anthropometric- and metabolic parameters (dependent variables), using all participants. These associations were also assessed stratified by sex. Associations are noted as strong with an adjusted R^2 of > 0.6, moderate with an adjusted R^2 of 0.3 to 0.6 and weak with an adjusted R^2 < 0.3). The metabolic parameters Matsuda index (reflecting insulin sensitivity) and disposition index (reflecting endogenous insulin secretion) were calculated using plasma glucose and insulin concentrations in response to an oral glucose tolerance test(35-37). Statistical analyses were computed using Rstudio version 4.1.0 for Windows.

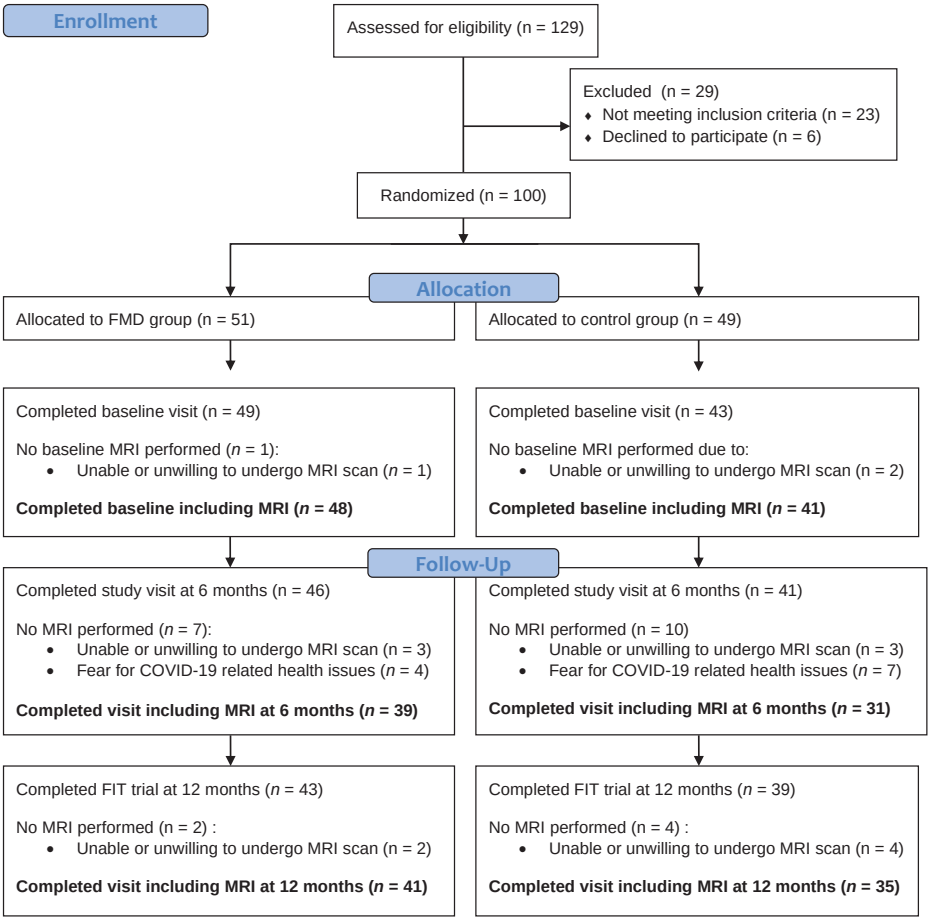

Figure 1. Flow diagram of participant inclusion and follow-up of the FIT trial.

COVID-19 = coronavirus disease 2019. FMD = fasting-mimicking diet. n = number of participants.
n* = number of participants for whom this was reason for being lost to follow-up or discontinuing FMD, there may be several reasons per participant.

Results

Inclusion and baseline characteristics

Between November 20, 2018, and July 1, 2020, 129 individuals were assessed for eligibility, of whom 29 were excluded (Figure1). 100 participants were randomly assigned to the FMD group (n=51) or control group (n=49). The follow-up ended on the 5th of August, 2021. In the FMD group, participants were lost to follow up before completing baseline measurements due to scheduling issues (n=1), health issues (n=1)

or unwillingness to undergo the MRI (n=1). In the control group, participants were lost to follow due to dissatisfaction with randomization (n=2), scheduling issues (n=2), fear of COVID-19 related health issues (n=1), unable or unwilling to undergo the MRI scan (n=2) or reason unknown (n=1). Therefore, data were available of 48 participants of the FMD group and 41 of the control group who completed the baseline visits of the FIT trial, including MRI (**Table 1**). Detailed information on participant inclusion, follow-up and reasons for drop-out is described elsewhere(38).

	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)
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
Body fat (%), mean ± SD	38.0 ± 7.8	37.6 ± 7.5
Fat free mass (kg), mean ± SD	62.2 ± 11.2	61.6 ± 11.8
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
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 [b]	1.2 ± 0.3	1.3 ± 0.3

	FMD group (*n* = 48)	Control group (*n* = 41)
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
hsCRP (mg/L, median (IQR)	1.6 (0.9 – 3.4)	2.0 (1.2 – 4.9)
MRI		
Abdominal visceral adipose tissue area (cm^2), mean ± SD	307.6 ± 105.6	283.4 ± 91.3
Abdominal subcutaneous adipose tissue area (cm^2), mean ± SD [c]	297.3 ± 120.0	326.9 ± 111.8
Abdominal muscle area (cm^2), mean ± SD	147.0 ± 24.5	146.4 ± 31.5

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.
b) Missing data control group n=1 due to invalid measurement
c) Missing data FMD group n=7 and control group n=3, due to technical issues
BMI = Body Mass Index. FMD = fasting-mimicking diet. HbA1c = glycated haemoglobin. HDL = high-density lipoprotein. hsCRP = high sensitivity C-reactive protein. IQR = interquartile range. LDL = low-density lipoprotein. n = number. SD = standard deviation. T2D = type 2 diabetes.

Effect of FMD on abdominal fat and muscle

Changes in mean aVAT, aSAT, and aMA over time in both the FMD and control group are presented for all participants, as well as stratified for sex (**Table 2**). Between baseline and 12 months, the adjusted estimated treatment effect of the FMD intervention compared to the control group on aVAT was -37.9 cm^2 (95% CI -54.7 to -21.0 cm^2), and on aSAT it was -20.9 cm^2 (95% CI -34.5 to -7.3 cm^2). The adjusted estimated treatment effect on aMA was -1.6 cm^2 (95% CI -4.6 to 1.4 cm^2). In men, the adjusted estimated treatment effect on aVAT was -48.8 cm^2 (95% CI -76.1 to -21.3), on aSAT -2.45 cm^2 (95% CI -14.3 to 9.4 cm^2) and on aMA -1.4 cm^2 (95% CI -5.8 to 2.9 cm^2) as compared to -28.0 cm^2 (95% CI -46.1 to -9.7 cm^2), -20.9 cm^2 (95% CI -34.6 to -7.3 cm^2), and -3.9 cm^2 (95% CI -8.0 to 0.2 cm^2) in women. Sensitivity analyses show similar results (**Table S1**). As an example, MRI imaging of abdominal aVAT, aSAT and aMA of one individual FMD participant is shown (**Figure 2**).

		FMD group		Control group			
	Months	n	Mean (SD)	n	Mean (SD)	Adjusted* estimated treatment effect (95% CI)	p-value
All							
aVAT (cm^2)	0	48	307.6 (105.6)	41	283.4 (91.3)		
	6	40	269.8 (89.8)	31	286.8 (104.1)	-30.8 (-48.1 to -13.4)	<0.01
	12	41	259.5 (84.1)	35	288.4 (92.4)	-37.9 (-54.7 to -21.0)	<0.01
aSAT (cm^2)	0	41	297.3 (120.0)	38	326.9 (111.8)		
	6	34	280.1 (106.4)	27	280.5 (82.2)	-17.5 (-31.4 to -3.6)	0.016
	12	36	282.7 (117.4)	30	306.5 (104.5)	-20.9 (-34.5 to -7.3)	<0.01
aMA (cm^2)	0	48	147.0 (24.5)	41	146.4 (31.5)		
	6	40	143.5 (24.4)	31	150.9 (31.3)	-2.2 (-5.3 to 0.9)	0.17
	12	41	140.5 (21.6)	35	147.0 (30.9)	-1.6 (-4.6 to 1.4)	0.31
Men							
aVAT (cm^2)	0	25	365.8 (94.6)	20	336.1 (79.0)		
	6	22	317.6 (78.7)	17	346.0 (96.9)	-36.5 (-63.6 to -9.2)	0.011
	12	20	304.3 (80.1)	18	340.1 (89.9)	-48.8 (-76.1 to -21.3)	<0.01
aSAT (cm^2)	0	22	228.4 (71.4)	19	269.7 (86.0)		
	6	19	225.0 (73.4)	16	249.5 (72.3)	-0.85 (-12.5 to 10.8)	0.89
	12	19	230.4 (96.9)	16	255.8 (81.5)	-2.45 (-14.3 to 9.4)	0.69
aMA (cm^2)	0	25	164.1 (19.5)	20	171.7 (20.8)		
	6	22	160.8 (18.0)	17	172.8 (22.0)	-1.4 (-5.8 to 2.9)	0.53
	12	20	158.8 (11.1)	18	170.0 (22.3)	1.0 (-3.5 to 5.4)	0.66
Women							
aVAT (cm^2)	0	23	244.4 (77.7)	21	233.3 (73.0)		
	6	18	211.3 (65.3)	14	215.0 (57.3)	-25.4 (-44.8 to -5.85)	0.014
	12	21	216.7 (64.1)	17	233.7 (58.1)	-28.0 (-46.1 to -9.7)	<0.01
aSAT (cm^2)	0	19	377.1 (116.3)	19	384.1 (106.7)		
	6	15	349.9 (102.2)	11	325.7 (77.1)	-17.2 (-31.2 to -3.2)	0.018
	12	17	341.1 (112.7)	14	364.4 (99.5)	-20.9 (-34.6 to -7.3)	<0.01
aMA (cm^2)	0	23	128.4 (13.3)	21	122.3 (18.1)		
	6	18	122.4 (10.2)	14	124.3 (16.4)	-2.7 (-7.1 to 1.6)	0.23
	12	21	123.0 (12.6)	17	122.6 (16.4)	-3.9 (-8.0 to 0.2)	0.065

Table 2. Changes in aVAT, aSAT and aMA with Adjusted Treatment Effects of FMD vs control group in all participants and men and women separately.

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. FMD = fasting-mimicking diet. SAT = subcutaneous adipose tissue. SD = standard deviation. VAT = visceral adipose tissue.

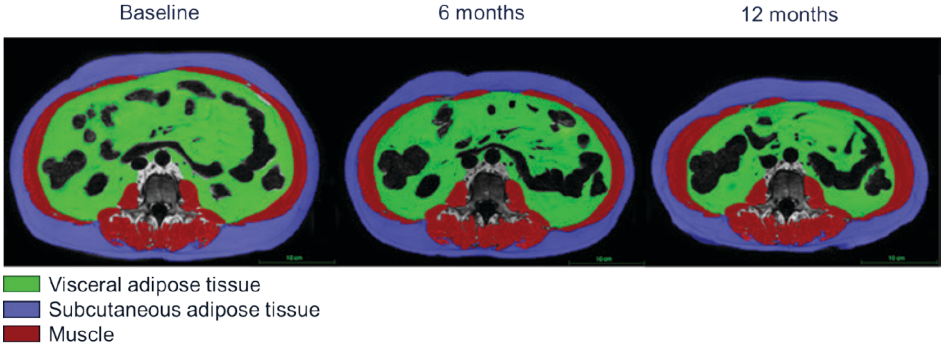

Figure 2. Distribution of aVAT, aSAT and aMA at the level of the third lumbar vertebra by MRI of an individual FMD participant at baseline, 6 months and 12 months.

At baseline: aVAT 340.9 cm^2, aSAT 239.8 and aMA 152.2. After 6 months: aVAT 257.0 cm^2, aSAT 198.2 cm^2, aMA 148.4 cm^2. After 12 months: aVAT 183.1 cm^2, aSAT 198.1 cm^2, aMA 146.6 cm^2.
aVAT=abdominal visceral adipose tissue; aSAT=abdominal subcutaneous adipose tissue; aMA=abdominal muscle area.

Associations between change in weight, BMI or waist circumference vs change in aVAT, aSAT or aMA

Analyses performed in all participants showed that change in weight from baseline to twelve months was strongly associated with changes in aVAT and moderately associated with aSAT and aMA (**Table 3**). Change in weight was associated with aVAT with an adjusted R^2 of 0.75 in men and of 0.64 in women and associated with aSAT with an adjusted R^2 of 0.51 in men and 0.66 in women. Comparable associations were seen for BMI and waist circumference (**Table 3)**.

Each kilogram of weight loss was associated with a decrease of 8.1 cm^2 (95% CI: 6.6 to 9.5 cm^2) in aVAT, 4.1 cm^2 (95% CI: 3.1 to 5.0 cm^2) in aSAT, and 0.81 cm^2 (95% CI: 0.52 to 1.11 cm^2) in aMA. In men, each kilogram of weight lost was associated with a reduction of aVAT of 11.0 cm^2 (95% CI 8.6 to 13.3 cm^2) and of aSAT of 2.8 cm^2 (95% CI 1.8 to 3.7 cm^2). In women, each kilogram of weight lost was associated with a reduction of aVAT of 5.6 cm^2 (95% CI 4.0 to 7.2 cm^2) and of aSAT of 5.8 cm^2 (95% CI 3.9 to 7.6). Similar results were observed for BMI and waist circumference (**Table 3**)**.**

Dependent variable		n	Independent variables β (95% CI)	p-value	Adjusted R^2
			Δ weight (kg)		
Δ aVAT (cm^2)	All	76	8.1 (6.6 to 9.5)	<0.01	0.68
	Men	38	11.0 (8.6 to 13.3)	<0.01	0.75
	Women	38	5.6 (4.0 to 7.2)	<0.01	0.64
Δ aSAT (cm^2)	All	62	4.1 (3.1 to 5.0)	<0.01	0.59
	Men	32	2.8 (1.8 to 3.7)	<0.01	0.51
	Women	30	5.8 (3.9 to 7.6)	<0.01	0.66
Δ aMA (cm^2)	All	76	0.81 (0.52 to 1.1)	<0.01	0.35
	Men	38	0.90 (0.47 to 1.3)	<0.01	0.40
	Women	38	0.62 (0.21 to 1.0)	<0.01	0.44
			Δ BMI (kg/m^2)		
Δ aVAT (cm^2)	All	76	23.1 (18.5 to 27.6)	<0.01	0.64
	Men	38	35.0 (27.0 to 43.0)	<0.01	0.74
	Women	38	15.5 (10.9 to 20.1)	<0.01	0.63
Δ aSAT (cm^2)	All	62	13.1 (10.3 to 15.9)	<0.01	0.64
	Men	32	9.2 (6.1 to 12.3)	<0.01	0.53
	Women	30	16.4 (11.7 to 21.2)	<0.01	0.69
Δ aMA (cm^2)	All	76	2.5 (1.6 to 3.3)	<0.01	0.36
	Men	38	3.1 (1.6 to 4.6)	<0.01	0.35
	Women	38	1.8 (0.6 to 2.9)	<0.01	0.44
			Δ waist circumference (cm)		
Δ aVAT (cm^2)	All	76	5.7 (4.2 to 7.2)	<0.01	0.51
	Men	38	7.5 (5.3 to 9.7)	<0.01	0.64
	Women	38	3.6 (1.7 to 5.5)	<0.01	0.37
Δ aSAT (cm^2)	All	62	3.3 (2.4 to 4.2)	<0.01	0.53
	Men	32	2.1 (1.2 to 3.1)	<0.01	0.35
	Women	30	4.8 (3.2 to 6.4)	<0.01	0.63
Δ aMA (cm^2)	All	76	0.58 (0.30 to 0.87)	<0.01	0.24
	Men	38	0.79 (0.38 to 1.2)	<0.01	0.34
	Women	38	0.42 (-0.033 to 0.87)	0.068	0.29

Table 3. Associations between changes in weight, BMI or waist and changes in aVAT, aSAT and aMA between baseline and 12 months.

Results represent regression coefficients with 95% confidence intervals. The adjusted R^2 of the model is given. These models are adjusted for age, sex (when looking at all participants) and baseline values of the dependent and independent variables. Adj. R^2 = adjusted R^2. aMA = abdominal muscle area. aSAT = subcutaneous adipose tissue. aVAT = visceral adipose tissue. β = regression coefficient. BMI = body mass index. CI = confidence interval.

Associations between change in aVAT and change in metabolic parameters

Change in aVAT after twelve months was strongly associated with change in HbA1c, moderately associated with changes in diastolic blood pressure, disposition index, HDL cholesterol, and triglycerides, and weakly associated with changes in fasting glucose, fasting insulin, and the Matsuda index (**Table 4**). No association was observed between changes in aVAT and changes in systolic blood pressure, total cholesterol, LDL cholesterol, or hsCRP.

Stratified by sex the associations of change in aVAT with change in diastolic blood pressure and fasting insulin were no longer present in men (**Table S2**). In women, the association with fasting insulin was also no longer observed. Several parameters appear to be more strongly associated with changes in aVAT in women than in men, including HbA1c (adj. R^2: 0.75 in women vs 0.58 in men) and the disposition index (adj. R^2: 0.65 in women vs 0.16 in men).

		Δ aVAT (cm^2) (Independent variable)		
Dependent variable	**n**	**β (95% CI)**	**p-value**	**Adj. R^2**
Δ systolic RR (mm Hg)	76	0.047 (-0.013 to 0.11)	0.12	0.28
Δ diastolic RR (mm Hg)	76	0.027 (0.0024 to 0.052)	0.032	0.48
Δ HbA1c (mmol/mol)	76	0.080 (0.054 to 0.11)	<0.01	0.67
Δ HbA1c (%)	76	0.0073 (0.0050 to 0.0097)	<0.01	0.67
Δ Fasting glucose (mmol/L)	75	0.012 (0.0048 to 0.020)	<0.01	0.29
Δ Fasting insulin (mmol/L)	74	0.052 (0.0055 to 0.099)	0.029	0.14
Δ Matsuda index	73	-0.0081 (-0.012 to -0.0047)	<0.01	0.26
Δ Disposition Index	73	-0.069 (-0.11 to -0.028)	<0.01	0.40
Δ Total cholesterol (mmol/L)	75	<0.001 (-0.0020 to 0.0035)	0.59	0.022
Δ HDL Cholesterol (mmol/L)	76	-0.0018 (-0.0026 to -0.0011)	<0.01	0.36
Δ LDL Cholesterol (mmol/L)	74	<0.001 (-0.0021 to 0.0025)	0.85	-0.034
Δ Triglycerides (mmol/L)	75	0.0050 (0.0022 to 0.0077)	<0.01	0.38
Δ hsCRP (mg/L)	76	0.0024 (-0.011 to 0.016)	0.72	0.34

Table 4. Associations between changes in aVAT and several metabolic parameters between baseline and 12 months.

Results represent regression coefficients with 95% confidence intervals. The adjusted R^2 of the model is given. These models are adjusted for age, sex, and baseline values of the dependent and independent variables. Adj. R^2 = adjusted R^2. aVAT = visceral adipose tissue. β = regression coefficient. BMI = body mass index. CI = confidence interval.

Associations between change in aSAT and change in metabolic parameters

Analyses performed in all participants showed that change in aSAT from baseline to twelve months was associated with change in several metabolic parameters (**Table 5**). Change in aSAT was strongly associated with and HbA1c, moderately associated with fasting glucose, Disposition index, HDL cholesterol and triglycerides and weakly associated with change in Matsuda index and HDL cholesterol. There was no association between change in aSAT and change in systolic RR, diastolic RR, fasting insulin, total cholesterol, LDL cholesterol and hsCRP.

Stratified by sex (**Table S3**), in men the associations of change in aSAT with change in disposition index and HDL cholesterol the were no longer present but an association with change in insulin was observed. In women, the association with change in Matsuda index and triglycerides was also no longer observed. HbA1c seems to be more strongly associated with changes in aSAT in women than in men (adjusted R^2: 0.71 in women vs. 0.48 in men).

		Δ aSAT (cm^2) (Independent variable)		
Dependent variable	**n**	**β (95% CI)**	**p-value**	**Adj. R^2**
Δ systolic RR (mm Hg)	62	0.041 (-0.080 to 0.16)	0.50	0.28
Δ diastolic RR (mm Hg)	62	0.032 (-0.019 to 0.082)	0.21	0.49
Δ HbA1c (mmol/mol)	62	0.12 (0.068 to 0.18)	<0.01	0.60
Δ HbA1c (%)	62	0.011 (0.0062 to 0.016)	<0.01	0.60
Δ Fasting glucose (mmol/L)	61	0.022 (0.0082 to 0.035)	<0.01	0.41
Δ Fasting insulin (mmol/L)	60	0.076 (-0.026 to 0.18)	0.14	0.021
Δ Matsuda index	59	-0.013 (-0.021 to -0.0047)	<0.01	0.15
Δ Disposition Index	59	-0.10 (-0.19 to -0.019)	0.017	0.38
Δ Total cholesterol (mmol/L)	61	0.0041 (<0.001 to 0.0090)	0.10	0.076
Δ HDL Cholesterol (mmol/L)	62	-0.0025 (-0.0042 to <0.001)	<0.01	0.21
Δ LDL Cholesterol (mmol/L)	60	0.0033 (<0.001 to 0.0075)	0.12	-0.018
Δ Triglycerides (mmol/L)	61	0.0074 (0.0022 to 0.013)	<0.01	0.42
Δ hsCRP (mg/L)	62	-0.0035 (-0.031 to 0.024)	0.80	0.34

Table 5. Associations between changes in aSAT and several metabolic parameters between baseline and 12 months.

Results represent regression coefficients with 95% confidence intervals. The adjusted R^2 of the model is given. These models are adjusted for age, sex (when looking at all participants) and baseline values of the dependent and independent variables. Adj. R^2 = adjusted R^2. aSAT = subcutaneous adipose tissue. β = regression coefficient. BMI = body mass index. CI = confidence interval.

Associations between change in aMA and change in metabolic parameters

Analyses of all participants showed that, while changes in most metabolic parameters from baseline to twelve months were not associated with changes in aMA (**Table 6**), change in aMA was moderately associated with change in systolic blood pressure, HbA1c and triglycerides. There was no association between change in aMA and other metabolic parameters.

Stratified by sex (**Table S4**), in men the association of change in aMA with change in systolic blood pressure was no longer present and an association between change in aMA and change in fasting glucose appeared. In women, the association with change waist circumference, systolic blood pressure, HbA1c and triglycerides was no longer observed and an association between change in aMA and change in disposition index and HDL cholesterol appeared. There were no clear differences in associations with change in aMA and metabolic parameters between men and women.

		Δ aMA (cm^2) (Independent variable)		
Dependent variable	**n**	**β (95% CI)**	**p-value**	**Adj. R^2**
Δ systolic RR (mm Hg)	76	0.45 (0.063 to 0.84)	0.023	0.30
Δ diastolic RR (mm Hg)	76	0.13 (-0.034 to 0.30)	0.12	0.46
Δ HbA1c (mmol/mol)	76	0.32 (0.13 to 0.52)	<0.01	0.58
Δ HbA1c (%)	76	0.030 (0.012 to 0.048)	<0.01	0.58
Δ Fasting glucose (mmol/L)	75	0.043 (-0.0060 to 0.093)	0.084	0.26
Δ Fasting insulin (mmol/L)	74	0.15 (-0.17 to 0.47)	0.36	0.036
Δ Matsuda index	73	-0.020 (-0.045 to 0.0042)	0.10	0.054
Δ Disposition Index	73	-0.25 (-0.53 to 0.020)	0.069	0.34
Δ Total cholesterol (mmol/L)	75	0.017 (-0.0011 to 0.035)	0.065	0.070
Δ HDL Cholesterol (mmol/L)	76	-0.0030 (-0.0087 to 0.0028)	0.31	0.13
Δ LDL Cholesterol (mmol/L)	74	0.0088 (-0.0060 to 0.024)	0.24	-0.013
Δ Triglycerides (mmol/L)	75	0.025 (0.0066 to 0.044)	<0.01	0.33
Δ hsCRP (mg/L)	76	-0.015 (-0.10 to 0.071)	0.73	0.34

Table 6. Associations between changes in aMA and several metabolic parameters between baseline and 12 months.

Results represent regression coefficients with 95% confidence intervals. The adjusted R^2 of the model is given. These models are adjusted for age, sex (when looking at all participants) and baseline values of the dependent and independent variables. Adj. R^2 = adjusted R^2. aMA = abdominal muscle area. β = regression coefficient. BMI = body mass index. CI = confidence interval.

Discussion

Within the FIT trial, we assessed whether the use of an FMD programme as adjunct to regular care was associated with changes in adipose tissue mass and muscle mass in persons with type 2 diabetes. The adjusted estimated treatment effect indicated that the FMD group experienced a significant mean loss of aVAT and aSAT compared to the control group, while the effect on aMA was non-significant between groups. Weight loss was strongly associated with reductions in aVAT and moderately associated with reductions in aSAT and aMA. Each kilogram of weight loss was associated with an overall greater amount of aVAT loss than aSAT loss. When stratified by sex, the amount of aVAT loss was even greater in men, while in women aVAT and aSAT loss was similar. Changes in aVAT and aSAT between baseline and 12 months were strongly associated with change in HbA1c and moderately associated with change in Disposition index, HDL cholesterol and triglycerides. aVAT was additionally moderately associated with diastolic blood pressure and aSAT with fasting glucose. Change in aMA was moderately associated with change in systolic blood pressure, HbA1c and triglycerides. Change in HbA1c seems to be more strongly associated with changes of both aVAT and aSAT in women than in men.

Research has shown that reductions in both visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) can be achieved in individuals with obesity through various lifestyle interventions, such as low-calorie or low-carbohydrate diets(39-44). In terms of adipose tissue loss, two reviews, encompassing 89 and 65 studies respectively, demonstrate that multiple interventions including a variety in dietary changes including low- and very low-calorie diets(9, 45), exercise(9, 45), bariatric surgery(9) or drugs including liraglutide and orlistat(9, 45), result in a more pronounced absolute reduction in SAT compared to VAT in obese individuals. Another systematic review including 61 studies of obese individuals undergoing a range of weight-loss interventions like very-low calorie diet, low-calorie diet plus exercise or exercise alone, found that while several studies reported a preferential loss of VAT over SAT, this effect was not sustained beyond 12-14 weeks(46). Studies on the effects of the Mediterranean diet on VAT and SAT have shown inconsistent results. One study reported a reduction in SAT but not VAT(47), while another found the opposite(48). Other studies observed a decrease in VAT but did not assess SAT(49-51). In the current study in participants with type 2 diabetes, the adjusted estimated treatment effect of an FMD programme compared to controls showed that loss of aVAT (-37.9 cm^2) was greater than aSAT (-20.9 cm^2) after 12 months.

Weight loss interventions can lead to a decrease in muscle mass, which may promote frailty, disability, and loss of independence in older adults(21, 52). A systematic review and meta-analysis involving 4785 participants assessed the impact of severe caloric restriction (up to 900 kilocalories per day) on muscle mass in individuals with type 2 diabetes. The findings indicated significant reductions in muscle mass in individuals with T2D, which constituted approximately a quarter of the total weight loss observed(52). Another systematic review evaluating the effects of intermittent fasting on fat-free mass, found a decrease in nine out of 17 studies(21). Also glucose-lowering medication including semaglutide, dapagliflozin and canagliflozin were found to significantly decrease fat-free mass compared with placebo in a network meta-analysis of 18 RCTs involving 1363 subjects(53). In our study, FMD induced weight-loss did not seem to exacerbate loss of muscle mass.

Given the metabolic benefits associated with loss of VAT(8), the lack of FMD induced muscle mass loss, and previously described reduction in liver fat and inflammation/fibrosis(54) and improvement of overall glycaemic management(38) the findings highlight the potential value of the FMD as a therapeutic strategy for managing type 2 diabetes.

Increased VAT has been linked to detrimental effects on metabolic parameters(8), and decrease in VAT is correlated with improvements in metabolic parameters including insulin sensitivity and plasma triglycerides(55, 56). This is in accordance with the results of the current study, where change in VAT was strongly associated with HbA1c, moderately associated with changes in diastolic blood pressure, disposition index, HDL cholesterol, and triglycerides, and weakly associated with fasting glucose, fasting insulin, and the Matsuda index.

The relationship between SAT and metabolic parameters remains unclear in the literature. On one hand, protective effects of SAT have been suggested. For instance, each unit increase in SAT has been associated with a reduced risk of insulin resistance(57), and individuals with type 2 diabetes tend to have relatively less SAT mass compared to non-diabetic controls(58). Conversely, other studies have reported no significant association between SAT and metabolic parameters(56). Also, reductions in SAT have not consistently been correlated with improvements in metabolic outcomes(58). Interestingly, in the current study involving persons with type 2 diabetes, a reduction in aSAT was associated with favourable metabolic changes, including a decrease in HbA1c and fasting glucose alongside an improvement in insulin sensitivity (measured by the Matsuda index) and β-cell function (measured by the disposition index). These findings suggest that loss of SAT, particularly in the abdominal region, may contribute to improved metabolic profiles in individuals with type 2 diabetes.

Moreover, this supports the hypothesis that SAT may play a role in the pathogenesis of insulin resistance, as suggested by a study examining the relationship between SAT and insulin resistance(3). The contradictory findings may arise from differences in the impact of SAT across anatomical regions (abdominal vs. peripheral)(59), variations in the effects of adipose tissue volume versus adipocyte size reduction(55), and sex-specific differences in the association between aSAT and metabolic outcomes(3).

The current study highlights notable sex differences in the change of aVAT and aSAT in response to the FMD, where the adjusted estimated treatment effect in men showed a greater reduction in aVAT then aSAT, while in women the reductions were more balanced. Furthermore, the association in change of aVAT and aSAT in relation to weight loss aligns with previous findings that men tend to lose more VAT and less SAT than women for a given reduction in body weight or waist circumference(60, 61). However, the relationships between VAT, SAT, and metabolic parameters across sexes remain unclear in the literature. Some studies suggest that VAT is more strongly associated with insulin resistance in men than in women(8), while others report that the relationship varies, with VAT and SAT having similar effects on insulin resistance in men, whereas in women, VAT appears more closely linked to both insulin resistance and insulin secretion(3). In the present study, changes in both aVAT and aSAT in men were weakly associated with changes in insulin sensitivity, and moderately with HbA1c, and fasting glucose levels. In women, also both reductions in aVAT and aSAT were strongly associated with changes in insulin secretion and HbA1c, and moderately associated with fasting glucose. These findings highlight sex-specific relationships between distinct adipose tissue depots and various metabolic parameters. Further research is needed to clarify the underlying mechanisms and establish causal relationships.

Several limitations should be considered, including missing values. Missing values of aSAT were most numerous. aSAT could not be measured when the complete aSAT area was not included in the field of view of the MRI. We assumed that the data are missing at random, as the aSAT missings were technical and not person related. There were also missing values due to drop-out (5 participants) during the COVID-19 period, as some participants were concerned about COVID-19-related health risks when visiting the hospital, despite the implementation of preventive measures. Although we tried to minimize bias by encouraging participants to complete follow-up visits, even when they decided to discontinue the FMD, missings from loss-to follow up can have created selection bias. Although MRI-measured muscle cross-sectional area appears to correlate significantly with muscle function(62), we did not conduct functional strength assessments and therefore cannot evaluate muscle performance. Furthermore, power calculations were done for the primary outcome measures of the

FIT trial - improvement on HbA1c levels and/or glucose-lowering medication use(38) - however not for the outcomes described in this paper, which in combination with the missing values probably resulted in lower power.

Conclusion

Following a monthly 5-day fasting-mimicking diet programme for 12 months as an adjunct to usual care reduced both aVAT and aSAT, while aMA remained unaffected compared to controls in persons with type 2 diabetes. The decline in aVAT and aSAT was associated with a reduction of several metabolic parameters, including HbA1c. A monthly 5-day FMD programme in primary care yields important health benefits in type 2 diabetes and therefore seems a valuable treatment option as an adjunct to usual care.

Declarations

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Conflict of interest

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: financial support was received from Health~Holland, Top Sector Life Sciences & Health, the Dutch Diabetes Foundation, and L-Nutra for the project; no other relationships or activities that could appear to have influenced the submitted work.

Author contributors and Guarantor Statement

MS, EB, PP, ME, HP and HL contributed to the study design. MS and EB conducted the trial and performed MRI acquisition. EP performed the image segmentation and measurements. MS performed the data analysis and prepared the first draft of the manuscript. All authors participated in data interpretation, critical review and revision of the manuscript, and had final responsibility for the decision to submit for publication. HL is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical approval

The Fasting In diabetes Treatment (FIT) trial protocol and amendments were approved by the Medical Research Ethics Committee of the LUMC.

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.

QR-code to article and supplementary information

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