Fasting-mimicking diet in type 2 diabetes reduces myocardial triglyceride content: a 12-month randomised controlled trial

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Fasting-mimicking diet in type 2 diabetes reduces myocardial triglyceride content: A 12-month randomised controlled trial

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ABSTRACT

Background and aims: Type 2 diabetes is associated with a heightened risk of cardiovascular complications, including myocardial steatosis. Fasting-mimicking diets (FMDs) may mimic the metabolic benefits of fasting, while being less intensive than fasting. This study aims to investigate the effect of following an FMD program on myocardial triglyceride content (MTGC), as assessed by Magnetic Resonance Spectroscopy (MRS), in patients with type 2 diabetes.

Methods and results: 100 patients with type 2 diabetes, who used metformin as the only glucose-lowering drug or no medication were randomly assigned to either an FMD group or a control group. The FMD group received the FMD program for 5 consecutive days a month alongside usual care, while the control group received usual care only. Both groups underwent baseline, 6-months and 12-months examinations, including single voxel cardiac 1H-MRS to assess MTGC. N = 13 participants of the FMD and n = 13 of the control group had complete data at baseline and twelve month follow-up. The FMD group exhibited a significant reduction in MTGC over the twelve month period (−0.235 % MTGC, p = 0.027), while the control group saw no significant change (0.143 % MTGC, p = 0.236). The decrease of MTGC in the FMD group was statistically different (p = 0.018) from control.

Conclusion: Following an FMD program reduces MTGC, which indicates a favorable effect on cardiac metabolism and thereby may be an effective strategy to reduce the cardiovascular risk in patients with type 2 diabetes.

Clinical trials registration number: NCT03811587.

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Abbreviations

BMI	Body mass index
CI	Confidence interval
FMD	Fasting-mimicking diet
IQR	Interquartile range
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MTGC	Myocardial triglyceride content
PRESS	Point resolved spectroscopy
SD	Standard deviation

1Introduction

Prevalence of type 2 diabetes is rising globally, due to unhealthy dietary habits and decreased physical activity [1,2]. It is well-established that type 2 diabetes significantly increases the risk of cardiovascular complications, including heart failure, myocardial infarction, and cardiac remodeling, causing cardiovascular disease to be the leading cause of morbidity and mortality in patients with type 2 diabetes [3,4]. Lifestyle interventions, including changes in diet and increased physical activity, can help manage or even reverse diabetes and thereby decrease cardiovascular risks [5]. Several continuous dietary interventions are effective in the management of type 2 diabetes, however many patients with type 2 diabetes find it hard to adhere to these diets in the long-term [6,7]. Recently, studies have shown that

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intermittent and periodic fasting can have beneficial metabolic effects in patients with type 2 diabetes [8,9].

A dietary strategy that has gained recent attention is the implementation of periodic fasting-mimicking diets (FMD), which mimic water-only fasting by reducing total caloric intake while relatively increasing plant-based complex carbohydrates and healthy fats [10]. Lifestyle intervention and especially dietary changes are very hard to adhere to for most people. A fasting mimicking diet could potentially improve adherence, since it is a less intensive program with only 5-consecutive days of dietary intervention per month for twelve months [10]. Recent studies show similar health benefits as other dietary interventions, such as improving glucose metabolism, lipid profile and inflammation markers, thus potentially mitigating the cardiovascular risk associated with type 2 diabetes [10–12].

In both obesity and type 2 diabetes, myocardial steatosis, characterized as the accumulation of excess fat within the heart muscle, has emerged as an important contributor to cardiac dysfunction and the development of cardiovascular complications [13–15]. Excessive circulating free fatty acids and impaired insulin signaling in adipose tissue contribute to increased delivery of these fatty acids to the heart, resulting in deposition of triglycerides within cardiomyocytes [13,16,17].

Magnetic Resonance Spectroscopy (MRS) is a non-invasive imaging technique that allows for the quantitative assessment of tissue composition by measuring the concentrations of specific metabolites [18]. MRS has emerged as a powerful tool in the investigation of cardiac metabolism and has been shown to accurately and precisely assess the triglyceride content in the myocardium (MTGC) [18–20].

While the effects of following an FMD program on systemic metabolic parameters have been investigated to some extent, the impact of these diets on cardiac metabolism in patients with type 2 diabetes remains largely unexplored. Our hypothesis is that FMDs can lower myocardial triglyceride content in patients with type 2 diabetes. In this study, we aim to assess this by comparing MTGC measurements with noninvasive MRS in patients with type 2 diabetes who were randomized between following an FMD for a year in addition to usual care, or usual care only. The findings of this study might enhance our understanding of the potential therapeutic benefits of FMDs in improving cardiac function in this population.

2. Methods

2.1. Study design

100 patients with type 2 diabetes from general practices in the area around Leiden and The Hague were randomized into an FMD group and a control group. The trial was conducted at the Leiden University Medical Centre (LUMC) in the Netherlands. The Medical Research Ethics Committee of the LUMC approved the protocol. Participants were included after written informed consent. Patients were aged between 18 and 75 years old, had a BMI of 27 kg/m2 or higher, and received lifestyle advice only (with glycated hemoglobin (HbA1c) $>$ 48 mmol/mol) or lifestyle advice plus metformin (irrespective of HbA1c). Exclusion criteria included recent myocardial infarction ($<$6 months), impaired creatinine clearance, pregnancy, MRI contraindications, allergy to ingredients of the diet, history of syncope with calorie restriction, and any significant other disease.

The FMD group received the FMD alongside usual care and the control group received usual care only. Both groups underwent magnetic resonance imaging at baseline and at 6-months and 12-months follow-up. Randomization was combined with pseudonymization and blinded to assessors such as research nurses during data collection, and to investigators during image analysis. Further details of the study design can be found in the study protocol, and detailed information on enrolment, allocation, follow-up and informed consent are described elsewhere [21,22].

2.2. Patient characteristics and blood tests

General patient characteristics were gathered and blood tests were performed at baseline [21]. Sex, age, weight, height, BMI and cholesterol levels were assessed. Cholesterol levels were specified using a conversion of the 2018 US guidelines to mmol/L [23]. Total cholesterol, LDL and cholesterol/HDL-ratio were viewed as increased when above 3.88 mmol/L, 2.59 mmol/L or 3.37, respectively [24]. HDL was considered to be decreased when below 1.03 mmol/L [24]. Patient characteristics and blood tests were repeated at 6 months and 12 months.

2.3. Fasting-mimicking diet

The FMD is a 5-day program that replaces meals with bars, soups and snacks of plant-based origin to achieve a short-term calorie restriction, while providing sufficient micronutrients. The diet is high in complex carbohydrates and polyunsaturated fatty acids, and low in protein and sugar content, to limit the caloric intake and create the fasting-mimicking effect [21]. For patients with a weight under 100 kg, day one has around 4600 kJ (1100 kcal), while the other four days are identical and provide around 3140 kJ (750 kcal). For patients with a weight over 100 kg, the diet is supplemented daily with a bar with similar macronutrient composition, providing around 375 kJ (90 kcal).

2.4. MRS acquisition

Patients underwent MRS at baseline, 6 months and 12 months using an Ingenia Elition (X) 3.0T MRI scanner by Philips Healthcare (Best, The Netherlands) after at least 4 h of fasting. MRS was performed using a point-resolved spectroscopy (PRESS) sequence in a single voxel (15 x 25 $\times$ 40 mm) in the interventricular septum without water-suppression, and with selective excitation water suppression (Multiple Optimizations Insensitive Suppression Train, MOIST) [25,26]. An echo time of 35 ms and repetition time of 9 s was used for the unsuppressed signal, and a repetition time of 3.5 s was used for the water-suppressed spectra to ensure full relaxation of the water and lipid signals. The unsuppressed water signal was used as reference for triglyceride quantification. Spectral acquisitions were respiratory navigator gated and acquired with an NSA of 64. Based on previous research, a post R-wave electrocardiographical triggering delay of 200 ms was chosen [20].

2.5. Spectral analysis

The acquired spectra were analyzed using Java-Based Magnetic Resonance User Interface (jMRUI v5.0; jMRUI Project) (Supplemental Fig. 1) [27,28]. The spectra were fitted in the time domain to a Gaussian line shape using the AMARES algorithm [29]. A peak filter was used on the suppressed spectra to remove the remaining water peak if it remained. The myocardial triglyceride content (MTGC) was calculated using the following equation:

$$MTGC = \frac{triglyceride\ methyl\ (CH_3) + tryglyceride\ methyline\ (CH_2)^n}{water + triglyceride\ methyl\ (CH_3) + tryglyceride\ methyline\ (CH_2)^n} * 100\%$$

Spectra with an insufficient fit were excluded from further analysis. MTGC was categorized as normal (<0.7 %), increased (≥0.7 % and <1.0 %) or high (>1.0 %) based on values found in literature [20,30].

2.6. Statistical analysis

Differences in heart fat fraction between baseline and 6 months and between baseline and 12 months follow-up were calculated and subsequent statistical analysis was performed in RStudio (v.2023.09.0; Posit Software PBC., Boston, MA) using R (v4.3.1; R Foundation for Statistical Computing, Vienna, Austria) [31,32]. For baseline measurements, differences in means were calculated with t-tests, while differences in medians were calculated with Mann-Whitney U tests. Associations between changes in heart fat fraction (for all time points) and dieting was assessed with multiple linear regression and progressively corrected for age, sex weight at baseline, and change in weight between measurements. Means, medians, standard deviations (SD), confidence intervals (CI), interquartile ranges (IQR), regression coefficients, t-values and p-values are given where relevant. A significance level of 0.05 was used.

3. Results

3.1. Inclusion and baseline characteristics

Of the 100 patients with type 2 diabetes that were included in the study, MRS was acquired and successfully analyzed in 59 patients during baseline visit (Fig. 1). The participant baseline characteristics were not significantly different between the diet and control group, as shown in Table 1. Overall, 53 % of participants belonged to the FMD group. Study participants that were excluded or included due to the success of MRS acquisition or analysis were comparable, besides excluded participants

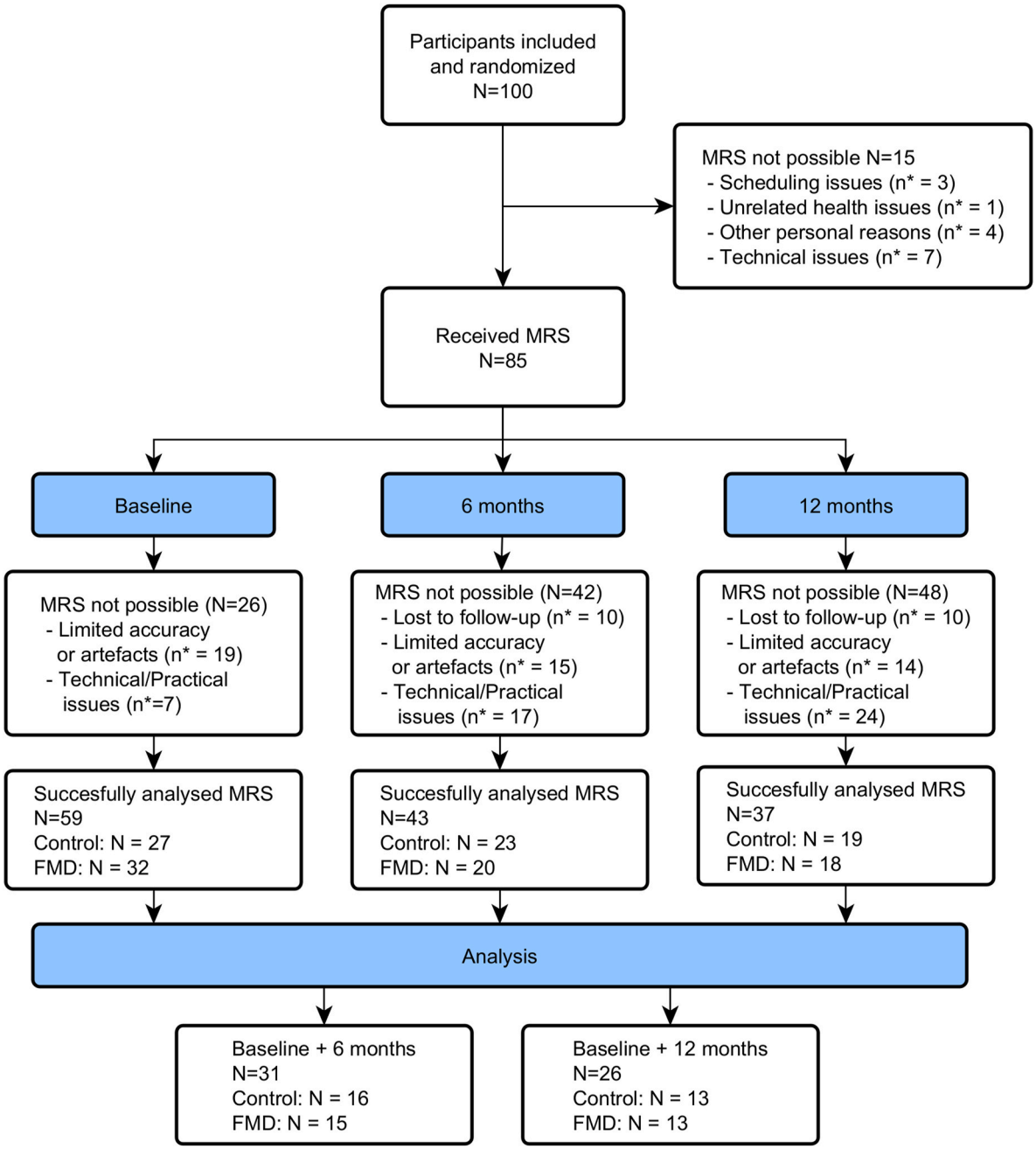

Fig. 1. Flow chart of included participants. MRS = Magnetic Resonance Spectroscopy; FMD = Fasting Mimicking Diet. *n is a subsample of N.

Table 1
Baseline characteristics of the FMD group and controls.

	FMD group	Control group	p
N	32	27	
Male	13 (41 %)	14 (52 %)	0.40
Age, median years (IQR)	67 (58–70)	66 (56–69)	0.25
Height, mean cm (SD)	172 (9)	173 (8)	0.86
Weight, mean kg (SD)	97 (14)	98 (11)	0.80
BMI, median kg/m^2 (IQR)	31 (29–35)	32 (31–34)	0.50
Time since diagnosis T2D, median years (IQR)	6 (3–12)	6 (3–10)	0.61
HbA1c, mean mmol/mol (SD)	52.7 (8.4)	53.4 (12.3)	0.83
HbA1c, mean % (SD)	7.0 (0.8)	7.0 (1.1)	0.83
Cholesterol, mmol/L (SD)	4.78 (1.02)	4.72 (0.88)	0.80
HDL	1.28 (0.30)	1.32 (0.33)	0.68
LDL	2.70 (0.94)	2.63 (0.81)	0.77
Chol./HDL	3.94 (1.16)	3.69 (0.90)	0.44
MTGC, % (IQR)	1.30 (0.95–1.64)	1.12 (0.76–1.66)	0.68

having larger height (p = 0.03) and weight (p = 0.01) but similar BMI (Supplemental Table 1).

At baseline, the median body mass index (BMI) of the patients with type 2 diabetes was 31.3 kg/m2 (IQR = 4.7). 70 % of patients were obese with a BMI above 30kg/m2. Overall, total cholesterol, LDL and cholesterol/HDL ratio were increased. Cholesterol levels were not statistically different between groups. Intracardiac fat fraction was increased or high (>0.7 % MTGC) in 48 patients (81 %).

MRS was performed successfully at baseline and after 12 months in 26 patients (13 in FMD group, 13 controls). Intracardiac fat fraction at baseline for these patients was also increased or high with a median myocardial triglyceride content of 1.26 % (IQR = 0.85 %) [30]. MTGC was high in 64 %, and increased in 85 % of these participants. Patient characteristics of these patients were comparable between groups (Table 2).

3.2. Myocardial triglyceride content and FMD

Differences in MTGC between baseline and 6 months and between baseline and 12 months of the control and FMD group are shown in Fig. 2 and Supplemental Table 2. For baseline vs. 6 months, MTGC differences were not significantly different. However, between baseline and 12 months, MTGC did significantly decrease in the FMD group by a median of −0.26 % MTGC (−0.37 %–0.05 % MTGC, p = 0.027), while no significant change was found in the control group (median = 0.12 % MTGC, −0.17 %–0.28 % MTGC, p = 0.236). Individual twelve months differences of both groups are illustrated in Fig. 3.

We investigated the MTGC differences between the three measurements using linear regression and found a significant relationship (p = 0.018) between following an FMD program and twelve months difference in MTGC (Table 3). The linear regression model was progressively corrected for confounders, specifically sex, age, weight at baseline and weight change (over the specific period). The previous relationship stayed significant with each correction for confounding factors (p = 0.025). No significant relationship between FMD and 6-months differences in MTGC could be found. A significant relationship between weight at baseline and 6-months difference in MTGC was shown (p = 0.035), but the coefficient was small (β = 0.01 % MTGC) and the overall linear regression model was not statistically significant.

Table 2
Baseline characteristics of the participants with MRS at baseline as well as at 12 months follow-up.

	FMD group	Control group	p
N	13	13	
Male	5 (38 %)	7 (54 %)	0.45
Age in years, median (IQR)	66 (57–69)	64 (56–69)	0.46
Height in cm, mean (SD)	169 (10)	172 (8)	0.39
Weight, mean kg (SD)	93 (16)	95 (7)	0.59
BMI, median kg/m^2(IQR)	31 (29–36)	32 (30–34)	0.61
Time since diagnosis T2D, median years (IQR)	10 (4–11)	4 (3–6)	0.06
HbA1c, mean mmol/mol (SD)	54.1 (7.6)	66.1 (16.6)	0.84
HbA1c, mean % (SD)	7.1 (0.7)	7.2 (1.5)	0.84
Cholesterol, mmol/L (SD)	4.81 (1.28)	4.58 (0.83)	0.59
HDL	1.21 (0.28)	1.27 (0.37)	0.62
LDL	2.79 (1.12)	2.49 (0.73)	0.45
Chol./HDL	4.14 (1.32)	3.72 (0.93)	0.36
MTGC, % (IQR)	1.27 (1.10–1.44)	0.99 (0.69–1.28)	0.59

The individual measurements for the control and FMD group at baseline and 12-months follow-up are illustrated in Fig. 3. Both groups had a combination of increased and decreased MTGC and some individuals had relatively large MTGC changes compared to others. However, 62 % of the FMD group had a decreased MTGC, while the increases of MTGC in the FMD group were minimal (0.01–0.23 % MTGC). In the control group, 54 % had an increase of MTGC which was more substantial (0.12–1.28 % MTGC).

In the subgroup from the FIT trial analyzed in this study, HbA1c decreased significantly in the FMD group from 52 to 47 mmol/mol (p = 0.009) in the first six months, but this effect was not significant between baseline and 12 months (49 mmol/mol). In the control group, HbA1c stayed at 54 mmol/mol. Weight did not change between baseline and 6 or 12 months follow up for either group and there was no significant change in weight between groups.

4. Discussion

4.1. FMD and MTGC

The study results demonstrated that patients with type 2 diabetes who received an FMD program alongside usual care, experienced a significant reduction in MTGC over the course of twelve months, while the control group which received usual care only, saw no significant change in MTGC. This change was significant after correction for several confounders. This finding suggests that FMDs may hold promise in ameliorating myocardial steatosis in patients with type 2 diabetes. The observed reduction in MTGC in the FMD group is noteworthy, as it aligns with the hypothesis that dietary modifications, particularly those emphasizing reduced caloric intake and changes in macronutrient composition, can positively influence cardiac metabolism.

It is worth noting that this change was not significant over the course of the first six months. This aligns with the thought that cardiac changes, such as cardiometabolic changes or cardiac function, take more time than initial metabolic effects such as weight change. It was previously shown that MTGC also does not significantly decrease in the first six months after bariatric surgery in morbidly obese patients [33]. A separate investigation concerning the impacts of a very low calorie diet (800 kcal per day continuously) revealed an initial relative elevation of around 50 % in MTGC after one week, followed by a significant relative reduction of about 25 % compared to baseline after eight weeks of dietary restriction [34]. Although our study did not demonstrate an initial elevation in MTGC, the observed decline in MTGC over an extended duration mirrors the findings from this more stringent dietary regimen. Consequently, an FMD may induce a comparable effect on MTGC as a less attainable very low calorie diet, albeit requiring a longer time period.

HbA1c decreased in the first six months in the FMD group, but the change in HbA1c between baseline and twelve months was not statistically significant. However, it is worth noting that these were two different subgroups, because only participants with successful MRS measurement at baseline and respectively six months or twelve months were included. As shown in other literature on all 100 participants of the same study group, HbA1c did decrease significantly in the FMD group by on average 3.2 mmol/mol compared to control group at twelve months

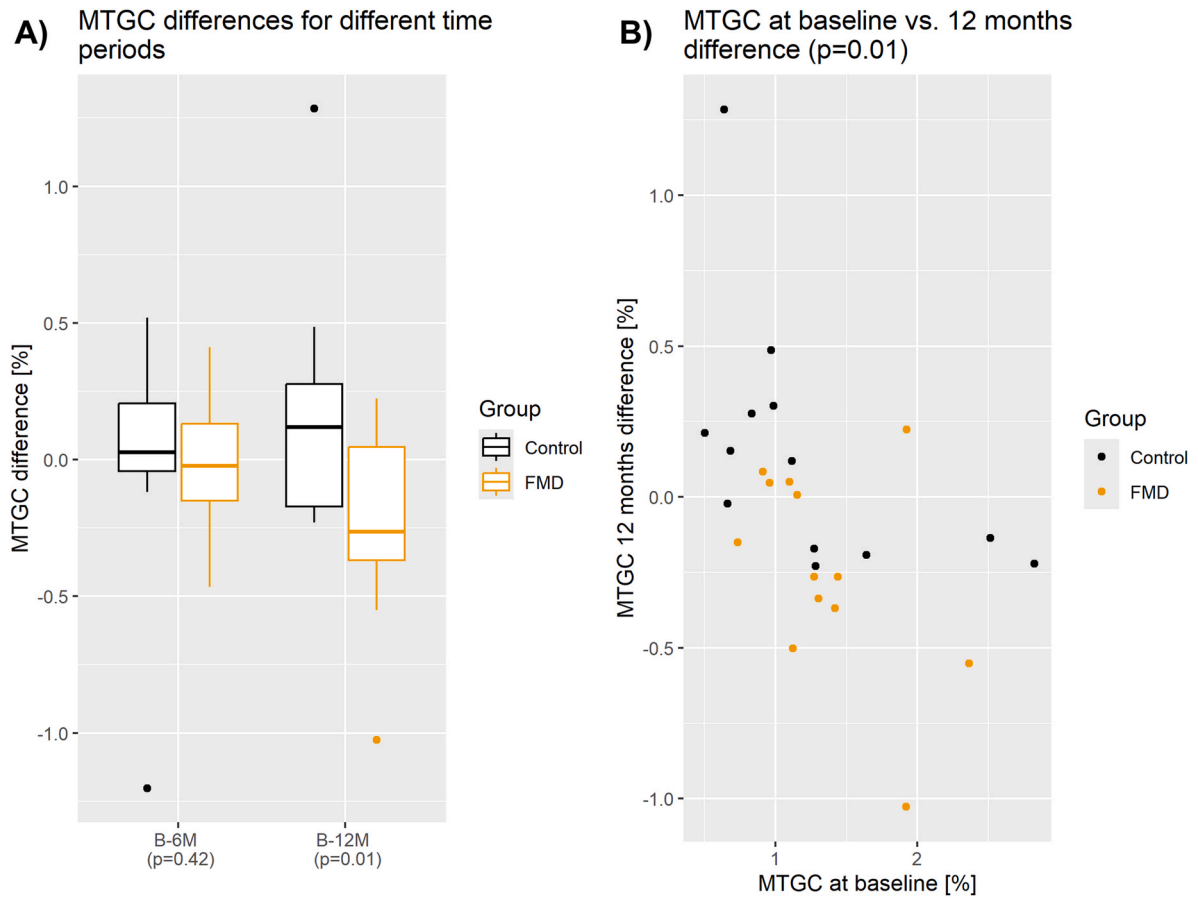

Fig. 2. Differences in Myocardial Triglyceride Content (MTGC) in control and FMD group. A) MTGC difference between baseline and 6 months (Control N = 16; FMD N = 15), and baseline and 12 months (Control N = 13; FMD N = 13). B) Individual MTGC differences between baseline-12 months plotted by MTGC at baseline. B=Baseline; 6 M = 6 months; 12 M = 12 months.

(p = 0.04) [22]. There was no effect on systolic or diastolic blood pressure in these 100 participants, but weight decreased significantly in the FMD group by around 3.8 Kg and 3.6 Kg after six and twelve months respectively [22].

4.2. Baseline MTGC and type 2 diabetes

Our study revealed that most patients with type 2 diabetes had higher MTGC at baseline than reference values in slightly younger nondiabetic people (<0.7 % MTGC), with an average of 1.29 % (SD = 0.54 %) as measured in the interventricular septum [30]. This finding is consistent with previous research showing a high prevalence of myocardial steatosis in patients with type 2 diabetes characterized by a MTGC of 1.06 % (SD = 0.62 %), as compared to a MTGC of 0.46 % (SD = 0.30 %) in lean people [13,30]. The elevated MTGC in type 2 diabetes is believed to result from the metabolic dysregulation associated with the disease, which leads to an increased uptake and storage of triglycerides within cardiac myocytes [16]. An increased MTGC is associated with increased CVD risk and myocardial dysfunction, and therefore underscores the clinical relevance of myocardial steatosis as a feature of type 2 diabetes, emphasizing the need for interventions to mitigate this condition [14,30,35].

4.3. Clinical implications

The significant relationship observed between FMD and MTGC reduction underscores the potential clinical relevance of dietary interventions in managing myocardial steatosis in patients with type 2 diabetes. Given the strong connection between myocardial steatosis and adverse cardiovascular outcomes, including heart failure and cardiac remodeling through lipotoxicity, strategies aimed at reducing MTGC hold promise for improving cardiac health in this high-risk population [30,36].

Given the observed reduction in MTGC in patients with type 2 diabetes who used metformin or diet only, as well as the well-established cardiovascular risks associated with myocardial steatosis, the adoption of FMDs holds promise as a potentially vital clinical tool in mitigating CVD risk within the type 2 diabetes population, particularly when conventional dietary programs prove less effective or more difficult to adhere to.

Besides the change in MTGC, the integration of a monthly FMD program has been shown to reduce the need for glucose-lowering medication in this patient group, as described in other literature [22]. HbA1c also improved and there was a reduction in body weight, BMI, waist circumference and body fat percentage compared with regular care only [22]. Furthermore, participants following the FMD program improved diet quality and increased physical activity, which was self-initiated [37]. These studies showed that full compliance to the FMD program was achieved in 61 % of participants assigned to the FMD group, while 27 % discontinued the FMD [22]. No diet change or physical activity change was reported in the control group [37].

4.4. Limitations

This study holds several limitations that are imperative to recognize. MRS acquisition was not feasible in all participants, which may introduce selection bias. Several reasons for the limited MRS data were problems during MRI acquisition (errors in signal acquisition, time

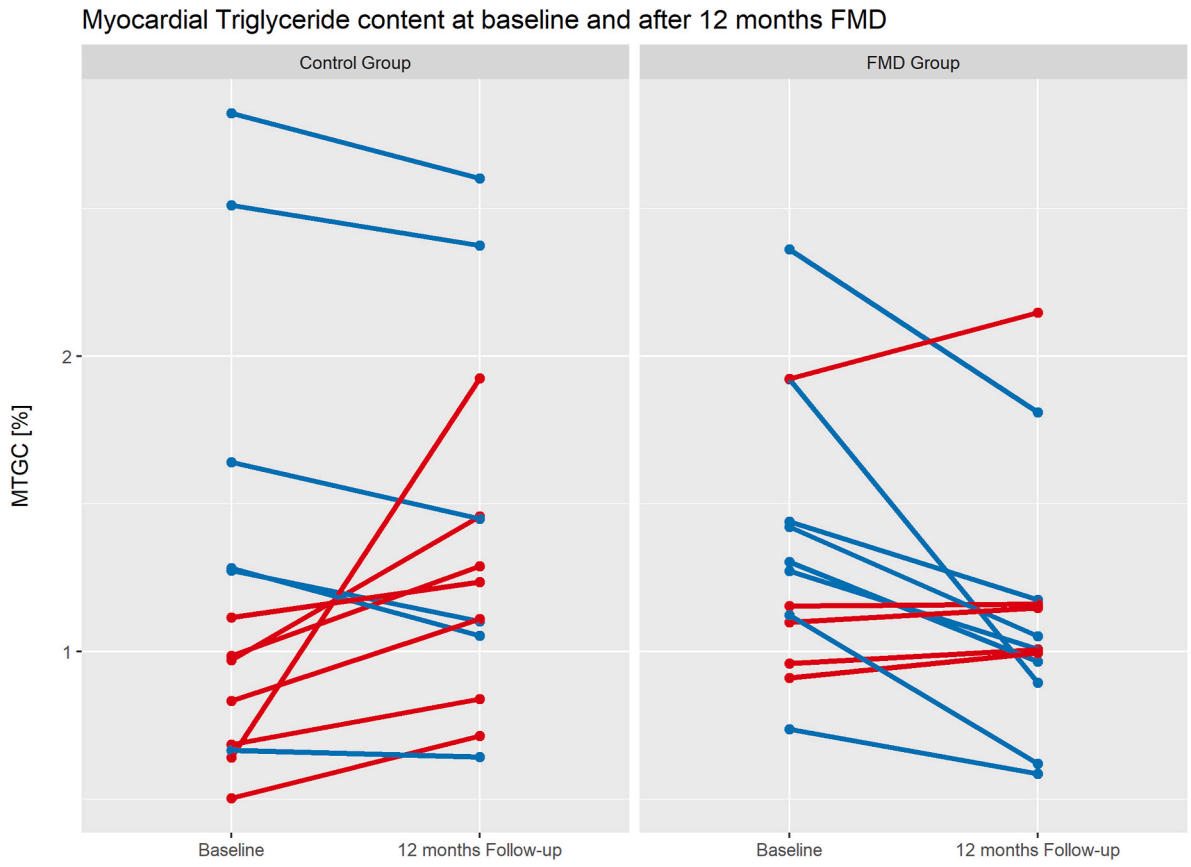

Fig. 3. Myocardial Triglyceride Content (MTGC) at baseline and 12 months follow-up in control and FMD group. In the FMD group, most participants had a decrease of MTGC (n = 8), whereas in the control group, most participants had an increase of MTGC (n = 7). Line color indicates a decrease (blue) or increase (red) of MTGC. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 3
Regression analysis of MTGC difference and FMD with correction for confounders.

	Baseline - 6 months (N = 31)				Baseline - 12 months (N = 26)			
	B†	Error	t	p	B†	Error	t	p
Without confounders								
FMD	−0.05	0.12	−0.45	0.656	−0.38	0.15	−2.55	0.018[a]
With Sex								
FMD	−0.07	0.12	−0.53	0.601	−0.41	0.15	−2.82	0.010[a]
Sex (male)	−0.05	0.13	−0.41	0.687	−0.22	0.15	−1.51	0.144
With Sex + Age								
FMD	−0.04	0.13	−0.28	0.780	−0.41	0.16	−2.62	0.016[a]
Sex (male)	−0.04	0.13	−0.35	0.731	−0.21	0.16	−1.29	0.210
Age	−0.01	0.01	−0.77	0.446	0.00	0.01	−0.16	0.875
With Sex + Age + Weight at baseline								
FMD	−0.01	0.13	−0.06	0.956	−0.40	0.16	−2.52	0.020[a]
Sex (male)	−0.15	0.13	−1.16	0.258	−0.22	0.17	−1.27	0.217
Age	0.00	0.01	−0.72	0.480	0.00	0.01	−0.19	0.854
Weight at baseline	0.01	0.00	2.22	0.035[a]	0.00	0.01	0.21	0.835
With Sex + Age + Weight at baseline + Weight change								
FMD	0.07	0.18	0.39	0.702	−0.47	0.19	−2.42	0.025[a]
Sex (male)	−0.14	0.13	−1.09	0.285	−0.25	0.18	−1.39	0.181
Age	0.00	0.01	−0.41	0.683	0.00	0.01	−0.37	0.719
Weight at baseline	0.01	0.00	2.23	0.035[a]	0.00	0.01	0.16	0.877
Weight change	0.02	0.03	0.57	0.571	−0.01	0.02	−0.64	0.532

[a] Significant ($p < 0.05$), †Coefficients in MTGC%.

constraints) and problems in MRS quality (low signal-to-noise ratio, artefacts). Some participants also discontinued the FMD program. Additionally, the follow-up duration was limited to 12 months. Longer-term investigations with larger cohorts are necessary to confirm the sustainability and generalizability of the observed effects. No restrictions on the use of medication other than type 2 diabetes were instructed. Medication such as lipid lowering medications (statins) were allowed.

Furthermore, the study did not investigate the direct impact of MTGC reduction on clinical outcomes or cardiac function, nor long term effects of FMDs on these outcomes. Future studies should explore these aspects to provide a more comprehensive understanding of the clinical significance of MTGC reduction by FMDs in patients with type 2 diabetes, and the specific mechanisms underlying the effects shown in this study.

5. Conclusion

An FMD program in patients with type 2 diabetes who use metformin only or no glucose-lowering medication significantly reduces MTGC. The observed reduction in MTGC suggests that dietary modifications, particularly those aimed at mimicking the metabolic effects of fasting, may hold promise in managing myocardial steatosis in patients with type 2 diabetes. Further research is warranted to elucidate the long-term effects and clinical implications of MTGC reduction in patients with type 2 diabetes.

Personal thanks

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Conflict of Interest

Health~Holland, Top Sector Life Sciences & Health, the Dutch Diabetes Foundation and L-Nutra, as the funders, have had no role in the design or conduct of the study nor in the preparation, review or approval of the manuscripts. 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.

Author contributions and Guarantor Statement

E.L.vdB., M.P.S., P.G.vP., M.E.N., H.P. and H.J.L. have contributed to the study protocol of the FIT trial. E.L.vdB. and M.P.S. have performed MRI acquisition. P.R.R. has performed MRS analysis, statistical analysis and wrote the first draft of the manuscript. J.J.M.W. and E.L.vdB. edited the manuscript. All authors reviewed the manuscript. P.R.R. is the primary author. All authors approved the final version of the manuscript.

Prior presentation

Parts of this study were presented in rapid fire form at the annual meeting CMR24 on January 25, 2024 and as electronic poster at the annual meeting ECR24 on 28 February – March 3, 2024.

Sources of funding

The project was co-funded by Health~Holland, Top Sector Life Sciences & Health, and the Dutch Diabetes Foundation. 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).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2025.103860.

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