Dynamics of intrapericardial and extrapericardial fat tissues during long-term, dietary-induced, moderate weight loss

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ABSTRACT

Background: In view of evidence linking pericardial fat accumulation with increased cardiovascular disease risk, strategies to reduce its burden are needed. Data comparing the effects of specific long-term dietary interventions on pericardial fat tissue mobilization are sparse.

Objective: We sought to evaluate intrapericardial-fat (IPF) and extrapericardial-fat (EPF) changes during weight-loss interventions by different dietary regimens.

Design: During 18 mo of a randomized controlled trial, we compared a Mediterranean/low-carbohydrate (MED/LC) diet plus 28 g walnuts/d with a calorically equal low-fat (LF) diet among randomly assigned participants with moderate abdominal obesity. We performed whole-body MRI and volumetrically quantified IPF and EPF among 80 participants to follow the 18-mo changes.

Results: The participants [mean age: 48.6 y; mean body mass index (BMI; in kg/m^2); 31.7; 90% men] had baseline IPF and EPF (mean ± SD) volumes of 172.4 ± 53.3 mL and 194.9 ± 71.5 mL, respectively. The 18-mo moderate weight loss of 3.7 kg was similar in both groups, but the reduction in waist circumference was higher in the MED/LC group (−6.9 ± 6.6 cm) than in the LF diet group (−2.3 ± 6.5 cm; $P = 0.01$). After 18 mo, the IPF volume had reduced twice as much in the MED/LC group compared with the LF group [−37 ± 26.2 mL (−22% ± 15%) compared with −15.5 ± 26.2 mL (−8% ± 15%), respectively; $P < 0.05$, after adjustment for changes in weight or visceral adipose tissue]. The EPF volume had reduced similarly in both groups [−41.6 ± 30.2 mL (−23% ± 16%) in the MED/LC group compared with −37.9 ± 28.3 mL (−19% ± 14%) in the LF group; $P > 0.1$]. After controlling for weight loss, IPF and EPF volume reduction paralleled changes in lipid profile but not with improved glycemic profile variables: the IPF relative reduction was associated with a decrease in triglycerides (TGs) ($\beta = 0.090$; 95% CI: 0.026, 0.154; $P = 0.007$) and the ratio of TGs to high-density lipoprotein (HDL) cholesterol ($\beta = 2.689$; 95% CI: 0.373, 5.003; $P = 0.024$), and the EPF relative reduction was associated with an increase in HDL cholesterol ($\beta = -0.452$; 95% CI: −0.880, −0.023; $P = 0.039$) and a decrease in total cholesterol and HDL cholesterol ($\beta = 3.766$; 95% CI: 1.092, 6.440; $P = 0.007$).

Conclusions: Moderate but persistent dietary-induced weight loss substantially decreased both IPF and EPF volumes. Reduction of pericardial adipose tissues is independently associated with an improved lipid profile. The Mediterranean diet, rich in unsaturated fats and restricted carbohydrates, is superior to an LF diet in terms of the IPF burden reduction. This trial was registered at clinicaltrials.gov as NCT01530724. *Am J Clin Nutr* 2017;106:984–95.

Keywords: Mediterranean diet, cardiac magnetic resonance imaging, extrapericardial fat, intrapericardial fat, low-fat diet

INTRODUCTION

Pericardial fat, the ectopic fat surrounding the heart, consists of 2 different fat compartments separated by the pericardium: intrapericardial fat (IPF), i.e., epicardial fat, located between the myocardium and visceral serous pericardium; and extrapericardial

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Supplemental Tables 1 and 2 and Supplemental Material are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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Abbreviations used: ANP, atrial natriuretic peptide; EPF, extrapericardial fat; FFA, free fatty acid; IPF, intrapericardial fat; ITT, intention to treat; LF, low-fat; MED/LC, Mediterranean/low carbohydrate; PA, physical activity; SAT, subcutaneous adipose tissue; TC, total cholesterol; TG, triglyceride; VAT, visceral adipose tissue; WC, waist circumference.

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fat (EPF), which lies externally to the fibrous pericardium. These fat tissues differ in their embryonic origin and blood supply (1, 2). Whereas the accumulation of IPF is associated with an increased risk of cardiovascular diseases (3–6), cardiac dysfunction (7–9), and atrial fibrillation (10), EPF burden is associated with obesity-related diseases, such as metabolic syndrome, dyslipidemia, and type 2 diabetes mellitus (11, 12). Therefore, modulation of these adipose tissues after weight loss and their relation to cardiometabolic change and cardiovascular disease risk have gained scientific interest.

Whereas some studies have shown a reduction in EPF only after lifestyle-induced weight loss (13, 14) or insensitivity of IPF to weight changes (15), other studies have shown a substantial change in IPF or total pericardial fat burden after weight loss induced by diet (16–19), physical activity (PA) (20, 21), or bariatric surgery (22–24). Yet, the differential (25) or nondifferential (21) effect of different weight loss strategies on the reduction of either IPF or EPF, independent from amount of weight loss, is still unclear.

Currently, there is no widely accepted agreement on specific dietary strategies that may improve the dynamics of pericardial fat depots. Furthermore, it is unclear how changes in pericardial fat tissues relate to changes in hemodynamic and cardiometabolic profile during dietary weight-loss intervention. This is especially of interest in light of evidence of improved cardiac function and hemodynamics after dietary-induced weight loss (26), possibly suggesting that pericardial fat might serve as a mediator in this process.

Previously, we reported that Mediterranean/low-carbohydrate (MED/LC) diets could be as effective as low-fat (LF) diets in improving cardiometabolic risk (27) and in reversing atherosclerosis (28). Other trials have shown a Mediterranean diet to be superior to an LF diet in primary and secondary prevention of cardiovascular diseases (29, 30).

In this study, as part of a larger effort to determine the impact of different lifestyle strategies for weight-loss on the redistribution of fats in a variety of depots, we aimed to assess and compare the 18-mo effects of 2 isocaloric dietary regimens (a combined MED/LC diet compared with an LF diet) on the dynamics of IPF and EPF. We also sought to determine the changes in cardiometabolic risk variables that were associated with the dynamics of pericardial fat depots.

Therefore, we performed whole-body MRI and volumetrically quantified IPF and EPF among 80 participants to follow the 18-mo changes. Our a priori hypothesis was that IPF and EPF volumes would reduce significantly, but not necessarily differently, under MED/LC and LF diets and that EPF volume changes will be better associated with changes in cardiometabolic profile than IPF volume changes would be.

METHODS

Study population and design

The randomized controlled CENTRAL trial (clinicaltrials.gov Identifier: NCT01530724) was conducted between October 2012 and April 2014 in the Nuclear Research Center of the Negev, a workplace with an onsite medical clinic. Two hundred seventy-eight eligible participants were recruited based on the following criteria: abdominal obesity [waist circumference (WC) ≥102 cm for men and ≥88 cm for women] or a combination of high serum TGs (>150 mg/dL) and low HDL cholesterol (<40 mg/dL for men and <50 mg/dL for women). Exclusion criteria were an inability to start PA in the gym, current PA >3 times/wk, serum TGs >400 mg/dL, serum creatinine ≥2 mg/dL, clinical assessment of unlikeliness to complete the study, concomitant major illness that might require hospitalization (on physician's evaluation), pregnancy or lactation, disturbed liver function (≥2-fold level of alanine-aminotransferase and aspartate-aminotransferase enzymes), presence of active cancer or cancer within the last 3 y, or participation in another intervention trial. The participants provided written, informed consent, and this study was approved by the human subjects committee of Soroka Medical Center and Ben-Gurion University. Participants received no financial component or gift.

For this substudy, 80 of the 278 eligible subjects of the CENTRAL trial were double-blindly randomly selected to undergo cardiac MRI before and after the intervention. After completing baseline measurements, we equally randomly assigned the 80 participants into 1 of 2 diet groups: LF or MED/LC. Randomization for the entire study's population was performed by a computerized algorithm stratifying for inclusion in this substudy to result in equal-sized study groups. After 6 mo of dieting, participants of each dietary group were again randomly assigned into either diet with PA or a diet-only intervention. A detailed flowchart of the trial is illustrated in **Figure 1**.

Dietary intervention

Both diets aimed for an energy intake of 1500 kcal/d for women and 1800 kcal/d for men, with restricted intakes of *trans* fats and refined carbohydrates and an increased intake of vegetables. Lunch, which is typically the main meal in Israel, was provided exclusively by the workplace cafeteria during the work week.

A dietitian worked closely with the kitchen staff to adjust the dishes to each specific diet group. The 18-mo dietary intervention included a 90-min nutritional session in the workplace with clinical dietitians every week during the first month of the intervention and once every month thereafter. To maintain an equal intensity of treatment, the workshop format and the quality of the materials were similar across diet groups, except for the instructions and materials specific to each diet strategy. Text messages were sent to update participants and to motivate their adherence to the diets on specific occasions, such as upcoming celebratory events or holidays. Participants who did not attend nutritional sessions were subsequently contacted by phone.

LF diet

For the LF diet, based on the American Heart Association guidelines (31), the aim was to limit total fat intake to 30% of calories, ≤10% of saturated fat, and ≤300 mg cholesterol/d and to increase dietary fiber. Participants were counseled to consume whole grains, vegetables, fruits, and legumes and to limit their consumption of additional fats, sweets, and high-fat snacks.

MED/LC diet

The MED/LC diet combined the Mediterranean and low-carbohydrate diets described in the DIRECT trial (27); the diet restricted carbohydrate intake (<40 g/d in the first 2 mo, and

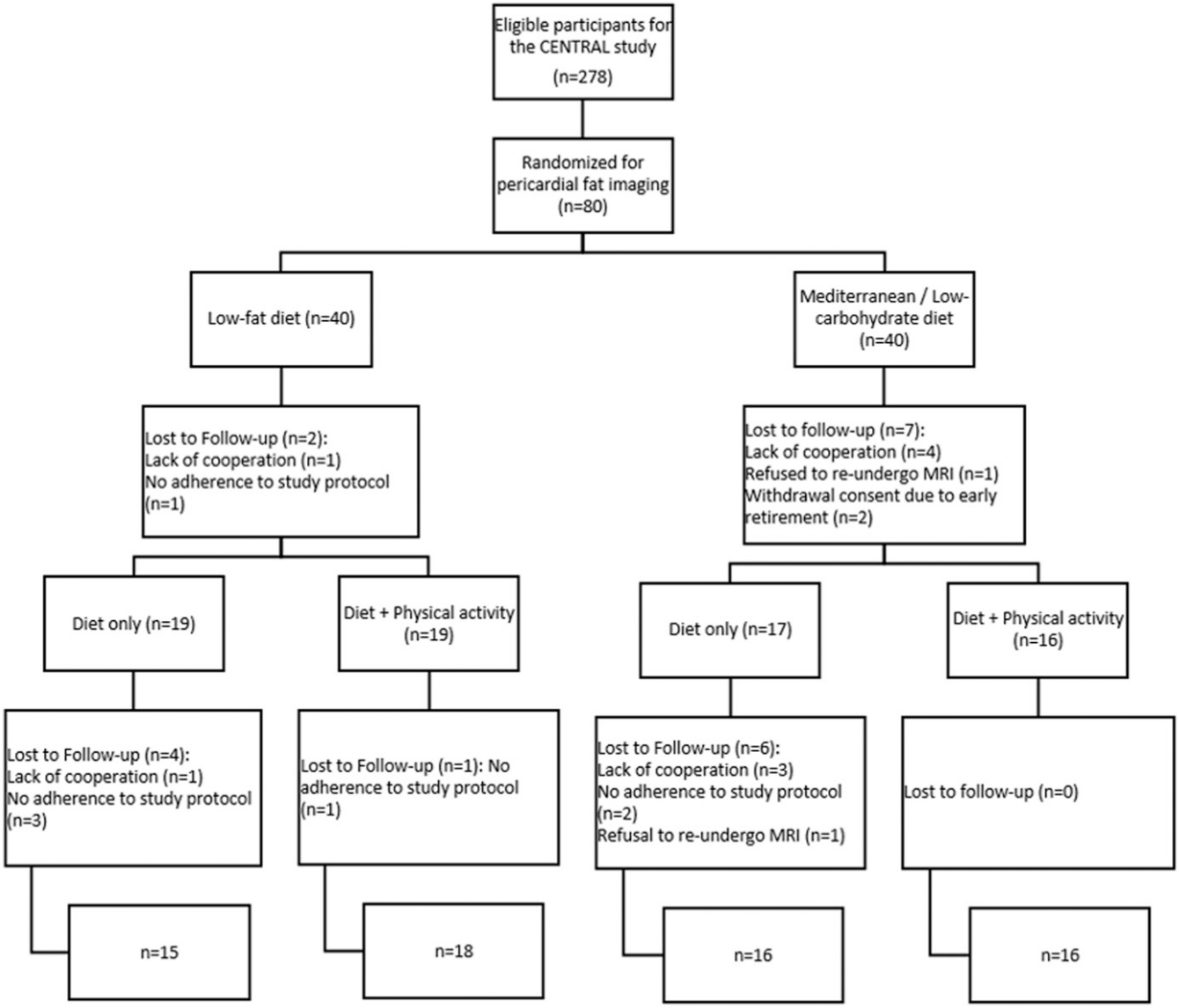

FIGURE 1 Study workflow.

thereafter a gradual increase to ≤70 g/d) and increased protein and fat intake, mostly from vegetarian sources, according to the Mediterranean diet (27, 32). The MED/LC diet was rich in vegetables and legumes and low in red meat, with poultry and fish replacing beef and lamb. This group was also provided with 28 g walnuts/d [160 kcal, 84% fat, mostly PUFA (omega-3 α-linolenic acid)].

Anthropometry and laboratory measurements

Blood and urine samples were taken after a 12-h fast. The blood samples were centrifuged and stored at −80°C. All lipid, glycemic, and inflammatory biomarkers (listed in **Table 1**) were evaluated simultaneously in the Leipzig University laboratory, Germany. Fasting plasma glucose was measured by using Roche GLUC 3 (hexokinase method). Plasma insulin was measured with an enzyme immunometric assay [Immulite automated analyzer; Diagnostic Products; CV: 2.5%]. Serum total cholesterol (TC; CV: 1.3%), HDL cholesterol, LDL cholesterol, and TGs (CV: 2.1%) were determined enzymatically with a Cobas 6000 automatic analyzer (Roche). Height was measured to the nearest millimeter with the use of a standard wall-mounted stadiometer. Body weight was measured without shoes to the nearest 0.1 kg. WC was measured half-way between the last rib and the iliac crest to the nearest millimeter by using a standard procedure with the use of a 150-cm anthropometric measuring tape. Blood pressure was determined by using an automated system (Datascope Acutor 4) after 5 min of rest.

Electronic questionnaires

Participants were interviewed with the use of a validated electronic questionnaire compiled of a validated food-frequency questionnaire (33), which includes 127 food items and 3 portion-size pictures for 17 selected food items, and a PA questionnaire that was converted into metabolic equivalents. The electronic interface of the questionnaires ensured that every question was fully answered.

TABLE 1
Baseline characteristics of the study population[1]

	Low-fat diet group (n = 40)	MED/LC diet group (n = 40)	Entire population (n = 80)
Age, y	48.8 ± 9.0	47.4 ± 8.3	48.1 ± 8.6
Men	39 (97.5)	33 (82.5)	72 (90)
BMI, kg/m^2	31.1 (29.8–33.7)	31.3 (28.9–34.4)	31.2 (29.1–33.9)
Waist circumference, cm	108.5 ± 8.2	109.4 ± 12.0	109 ± 10.2
Weight, kg	94.7 ± 12.8	94.7 ± 14.3	94.7 ± 13.5
Blood pressure			
Systolic, mm Hg	127.0 ± 15.4	123.5 ± 18.1	125.2 ± 16.8
Diastolic, mm Hg	81.6 ± 8.7	81.1 ± 12.1	81.3 ± 10.5
Metabolic syndrome criteria, n	2.4 ± 1.1	2.1 ± 1.3	2.2 ± 1.2
Serum biomarkers			
LDL cholesterol, mg/dL	119.7 ± 29.6	122.9 ± 37.4	120.6 ± 32.6
HDL cholesterol, mg/dL	42.1 ± 7.4	44.9 ± 11.2	43.5 ± 9.5
TGs, mg/dL	68.3 (52.9–102.3)	58.7 (42.8–84.8)	61.0 (46.7–99.6)
TC/HDL cholesterol ratio	4.9 ± 1.0	4.5 ± 1.1	4.7 ± 1.1
TG/HDL cholesterol ratio	2.5 ± 2.3	1.9 ± 1.8	2.2 ± 2.1
FPG, mg/dL	106.1 ± 15.5	107.7 ± 15.6	106.9 ± 15.5
Insulin, U	15.4 ± 6.1	16.9 ± 11	16.2 ± 8.9
HOMA-IR	4.1 ± 1.8	4.6 ± 3.4	4.3 ± 2.8
hsCRP, ng/L	3.5 ± 2.7	3.4 ± 3.3	3.4 ± 3.0
Medication treatment			
Antiplatelet	5 (12.5)	5 (12.5)	10 (12.5)
Antihypertensive	3 (7.5)	3 (7.5)	6 (7.5)
Lipid lowering	5 (12.5)	6 (15)	11 (13.75)
Antidiabetic	0 (0)	1 (2.5)	1 (1.25)
MRI-assessed adipose tissues			
Intrapericardial fat, mL	165.6 ± 56.0	179.3 ± 50.3	172.4 ± 53.3
Extrapericardial fat, mL	196.1 ± 69.2	193.7 ± 74.5	194.9 ± 71.5
Visceral adipose tissue, cm^2	189.9 ± 75.3	168.3 ± 64.6	179.1 ± 70.6
Deep subcutaneous fat, cm^2	231.9 ± 68.5	237.0 ± 92.5	234.4 ± 80.9
Superficial subcutaneous fat, cm^2	143.7 ± 55.1	154.9 ± 74.8	149.3 ± 65.5

[1] Data are presented as means ± SDs for continuous variables, medians (IQRs) for nonnormally distributed variables, and numbers (percentages) for numeric variables. FPG, fasting plasma glucose; hsCRP, high-sensitivity C-reactive protein; MED/LC, Mediterranean/low carbohydrate; TC, total cholesterol; TG, triglyceride.

MRI

Whole-body MRI was performed by using a 3T scanner (Ingenia; Philips Medical Systems). The thorax was imaged in a 2-block scan by using a 2-point modified-DIXON technique (34), a 3-dimensional T1-Fast-Field-Echo sequence with the use of multiple acquired echoes to generate water, in-phase, out-of-phase, and fat-only images automatically. Scans were performed in a single-shot, breath-hold sequence by using cardiac gating detected by the vector cardiac gating technique (Vector Cardiac gating; Philips Medical Systems). This imaging protocol for the quantification of pericardial fat was described and validated by another group (35) but does not include cine imaging for structural or functional assessment of the heart. Readers were blinded to the allocated intervention and acquisition time.

Quantification of IPF and EPF

Pericardial fat was analyzed from the of the pulmonary trunk to the level of the apex of the heart in cross-sectional axial view. Raw imaging data were reconstructed into slices (slice thickness, 5 mm; slice gap, 0 mm; slice overlap, 1 mm). By using a semi-automated MATLAB-based program, the first slice for each subject was used to determine the fat-recognition sensitivity threshold for the specific series analysis. This was done by using a region-of-interest method with a fixed-sized 2 × 2–pixel circle constantly placed in the aortic recess, just anterior to the conjunction between the ascending aorta and the pulmonary trunk emerging from the ventricles. Upper and lower threshold values were set as 2.5 SDs from the average region-of-interest set value. By using the threshold-index, fat was automatically detected on each slice. We distinguished IPF and EPF by identifying and drawing a polygon along the pericardium. Fat surrounding internal thoracic vessels, the aorta, the posterior part of esophagus, and the peridiaphragmatic area was excluded from the analysis. Pericardial adipose tissues were first measured in area (cm^2); fat volumes were calculated by multiplying the total measured fat area by slice thickness. All imaging acquisition and quantification for all time points were performed in the same manner by using the same anatomical reference points and landmarks as detailed above. The entire process of imaging analyses was performed by 2 specifically trained readers, trained and supervised by a cardiac imaging specialist doctor with 10 y of experience (AW), who also reviewed analyses and confirmed their appropriateness. Reliability of measurements between and within rates was measured by using Bland-Altman analysis, including 14 full analyses accounting for 280 image slices, with

an overall interclass correlation of 0.98 (0.95 for IPF, 0.99 for EPF; $P < 0.05$ for all) and intraclass correlation of 0.97 (0.94 for IPF, 0.97 for EPF; $P < 0.05$ for all).

Quantification of abdominal fat depots

The MRI scanner used a 3-dimesional modified DIXON imaging technique without gaps (2-mm thickness and 2-mm spacing), a fast-low-angle shot sequence with a multi-echo 2-excitation pulse sequence for phase-sensitive encoding of fat and water signals (repetition time 3.6 ms; echo time 1,1.19 ms; second echo time 2.3 ms; field of view 520 × 440 × 80 mm; 2 × 1.4 × 1 mm voxel size). Four images of the phantoms were generated, including in phase, out of phase, fat phase, and water phase. A breath-hold technique was used to prevent motion artifacts when the chest and abdomen were scanned. All MRI tests were performed after at least a 2-h fast. In all simultaneous quantifications and comparisons of fat depots, observers were blinded to time point and group treatment.

Abdominal fat was quantified by using MATLAB-based semiautomatic software that was written inhouse (36, 37). To obtain the distribution of abdominal subdepots, 3 slices were selected from the intravertebral space of L5–S1, L4–L5, and L2–L3 from both sagittal and axial images. A continuous line was drawn over the superficialis fascia to differentiate, by analyzing the 2-dimensional image, between the deep subcutaneous adipose tissue (SAT) and superficial SAT. Mean visceral adipose tissue (VAT), deep SAT, and superficial SAT were calculated from 3 axial slices. After quantification, fat tissues were divided into color-coded groups: superficial SAT fat was dark blue, deep-SAT fat was light blue, VAT was green, perimuscular fat (fat surrounding and within the latissimus dorsi and diaphragm) was purple, and nonclassified fat (fat surrounding the vertebrae and fat depots unrelated to any of the groups listed above) was red. Quantification of the fat mass regions included the area of each fat type and its proportion (percentage) of the total area of all fat types. To obtain absolute measurements in metric units, a scaling procedure was applied before the segmentation to determine the real pixel dimensions. A comparison of 2-dimensional analysis with 3-dimensional analysis for 30 scans showed the 2-dimensional analysis to be highly accurate ($r = 0.97$, $P = 0.001$).

Statistical analysis

Our specific aim in this CENTRAL substudy was to assess changes in IPF and EPF volumes between baseline and the end of the dietary intervention at 18 mo. Power calculations are detailed in **Supplemental Material**. Baseline data were examined across sex-specific tertiles of pericardial fat by comparing the highest tertile of EPF and IPF volumes with rest of study population and with the lowest tertile of EPF or IPF volumes. Furthermore, baseline associations between IPF and EPF volumes and other variables were examined by using Pearson's or Spearman's correlation coefficient according to each variable's distribution. The 18-mo changes in pericardial fat tissues were evaluated by using per-protocol and intention-to-treat (ITT) analyses (including all the study's population regardless of reason for withdrawal from the study), for within and between intervention groups. IPF and EPF changes across intervention groups were assessed by using a 2-on-2 factorial univariate-mean-of-differences model, including both dietary intervention groups (LF and MED/LC, i.e., the major intervention) and PA (i.e., the secondary intervention), and testing for interaction between the 2 interventions. We further examined IPF and EPF changes across study's subgroups in linear regression models including all subgroups as independent variables, with the LF diet-only group (LF^{PA-}) used as a reference. The 18-mo associations between the EPF and IPF relative changes with changes in other variables were analyzed by using multivariate linear regression models controlling for potential confounders. All P values were 2-sided, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed with the use of SPSS software Version 21 (SPSS). Values are expressed as means ± SDs.

RESULTS

Baseline characteristics of main outcome variables

Baseline characteristics of the study population across intervention groups are exhibited in Table 1. The age was 48.1 ± 8.6 y, and 72 of the 80 participants (90%) were men. Baseline weight was 94.7 ± 13.5 kg, with a median BMI of 31.2 (range: 29.1–33.9) and a WC of 109 ± 10.2 cm^2. The initial VAT proportion was 32.3% ± 10.4%, the IPF volume was 172.4 ± 53.3 mL, and the EPF volume was 194.9 ± 71.5 mL. Intervention groups did not differ significantly across a wide range of variables.

Baseline characteristics across sex-specific tertiles of pericardial fat tissues are shown in **Table 2**.

EPF and IPF volumes were highly correlated ($r = 0.74$, $P < 0.001$). Older age, greater VAT area, and higher concentrations of high-sensitivity C-reactive protein were related to higher volumes of both EPF and IPF. Obesity markers (WC, weight, and BMI) and deep subcutaneous adiposity were more strongly linked with elevated EPF volumes than IPF volumes.

Adherence to dietary intervention and weight loss

The retention rate was 82% at 6 mo and 77% at 18 mo and was similar across dietary intervention groups ($P = 0.12$). Participants who withdrew from the intervention did not differ in demographics or anthropometrics across dietary groups. At baseline, there were no significant differences in the consumption of energy or macronutrients between the LF and MED/LC diet groups. After the intervention, participants significantly decreased their energy intake after 6 and 18 mo ($P < 0.01$ compared with baseline); this was similar across diet groups. The intake of the total carbohydrates proportion significantly decreased, and the intake of total monounsaturated and polyunsaturated fat proportions significantly increased in the MED/LC diet group at 6 and 18 mo compared with the LF diet group ($P < 0.05$ for all), demonstrating adherence to the assigned diets. Energy and macronutrient consumptions at baseline and throughout intervention are detailed in **Supplemental Table 1**.

At the end of intervention, after 18 mo of dieting, participants lost 3.6 ± 6.9 kg (−2.4 ± 7.7 kg in LF group and −5.0 ± 5.7 kg in MED/LC group, $P = 0.2$ between groups) and had a decrease of 3.6% from baseline body weight. WC decreased by 4.4 ± 6.8 cm, with a significantly higher reduction in the MED/LC

TABLE 2
Baseline characteristics across sex-specific tertiles of pericardial fat tissues[1]

	Tertiles of IPF					Tertiles of EPF				
	Low	Middle	High	*P*, high vs. low	*P*, high vs. others	Low	Middle	High	*P*, high vs. low	*P*, high vs. others
Median, mL	117.3	173.2	234.8			138	194.7	266.6		
Age, y	44.7 ± 8.7	48.3 ± 7.8	51.3 ± 8.4	0.007	0.019	43 ± 8.1	48.5 ± 8.3	52 ± 7.6	<0.001	0.003
BMI, kg/m^2	31.6 ± 4.2	31.3 ± 3.1	32.2 ± 4.7	0.629	0.441	30.8 ± 3.5	30.7 ± 3	33.6 ± 4.9	0.022	0.012
Waist circumference, cm	108.3 ± 9.7	107.8 ± 10	110.7 ± 11.0	0.403	0.271	106.8 ± 8.7	105.2 ± 8	114.8 ± 11.2	0.007	<0.001
Weight, kg	92.7 ± 10.4	94.3 ± 13	97 ± 16.4	0.249	0.325	92.3 ± 11.4	91.4 ± 11.9	100.3 ± 15.3	0.037	0.016
Blood pressure, mm Hg										
Systolic	125.3 ± 14.1	121.4 ± 15.2	129 ± 20.2	0.436	0.150	124.2 ± 15.2	123.9 ± 16	127.6 ± 19.4	0.488	0.382
Diastolic	79.6 ± 9.3	79.7 ± 9.9	84.6 ± 11.7	0.100	0.050	79.6 ± 9.2	80.5 ± 9.8	83.9 ± 12.1	0.149	0.119
Blood biomarkers										
LDL-C, mg/dL	119.4 ± 34.5	128.1 ± 33.1	116.4 ± 33.5	0.749	0.348	116.2 ± 32.7	123.5 ± 32.1	124.3 ± 36.6	0.403	0.583
HDL-C, mg/dL	40.6 ± 10.3	46.4 ± 11.2	40.3 ± 9.6	0.914	0.188	42.4 ± 11.7	42.7 ± 11.1	42.1 ± 9.5	0.923	0.867
TGs, mg/dL	91.7 ± 54	70.1 ± 42.8	76.8 ± 50.2	0.307	0.752	89 ± 61.6	79.3 ± 46.5	69.7 ± 36.9	0.175	0.217
TG/HDL-C ratio	2.7 ± 2.5	1.74 ± 1.4	2.2 ± 2.2	0.434	0.116	2.6 ± 2.5	2.2 ± 2	1.9 ± 1.6	0.222	0.280
FPG, mg/dL	83 ± 18	80 ± 13	86 ± 18	0.163	0.116	82 ± 17	81 ± 12	86 ± 19	0.078	0.03
HOMA-IR	3.8 ± 1.7	4.2 ± 3.5	5.0 ± 2.7	0.074	0.087	3.8 ± 1.8	3.7 ± 1.6	5.5 ± 3.9	0.024	0.005
hsCRP, ng/L	2.6 ± 1.6	3.5 ± 3.7	4.2 ± 3.1	0.036	0.055	2.8 ± 3.7	3.3 ± 2.1	4.2 ± 2.8	0.012	0.042
MRI-assessed adipose tissues										
EPF, mL	146.2 ± 39.1	185.6 ± 56	251.1 ± 71.9	<0.001	<0.001	—	—	—	—	—
IPF, mL	—	—	—	—	—	134.8 ± 34.3	164.8 ± 41.1	216.4 ± 48.2	<0.001	<0.001
VAT, cm^2	151.7 ± 51.2	171.7 ± 2.2	212.9 ± 82.1	0.002	0.002	144.9 ± 50.4	167.1 ± 56.5	224.1 ± 77.9	<0.001	<0.001
Deep ASAT, cm^2	224.1 ± 81.3	233.7 ± 77.1	245.1 ± 85.8	0.366	0.403	224.6 ± 73.3	205.1 ± 61.6	273.2 ± 91.6	0.038	0.002
Superficial ASAT, cm^2	164.5 ± 85.3	139.7 ± 48.3	144.2 ± 58	0.318	624	156.3 ± 65.2	132.6 ± 49.7	159.3 ± 77.8	0.880	0.333

[1] Values are means ± SDs unless otherwise indicated. Comparisons were made by using independent *t* tests comparing tertiles of IPF or EPF. ASAT, abdominal subcutaneous adipose tissue; EPF, extrapericardial fat; FPG, fasting plasma glucose; HDL-C, HDL cholesterol; hsCRP, high-sensitivity C-reactive protein; IPF, intrapericardial fat; LDL-C, LDL cholesterol; TC, total cholesterol; TG, triglyceride; VAT, visceral adipose tissue.

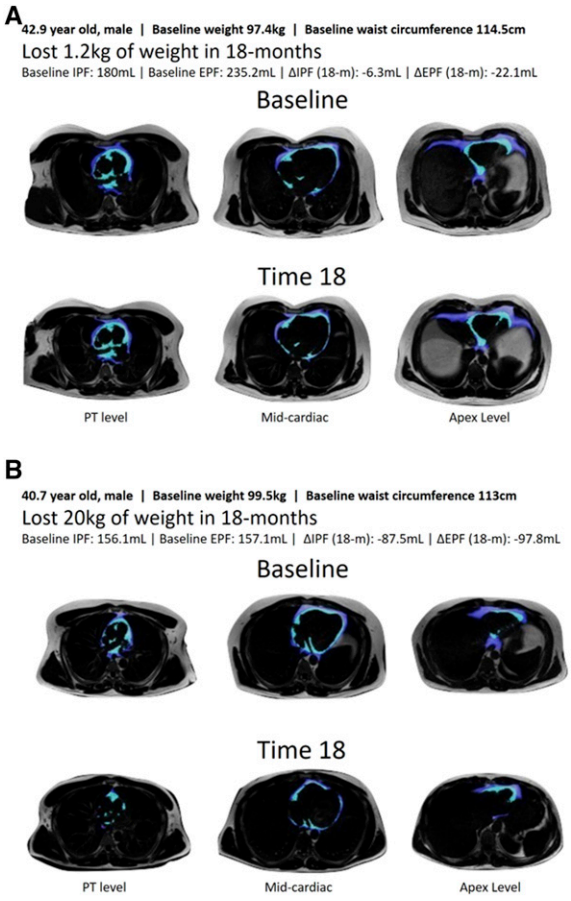

FIGURE 2 Pericardial fat trajectory in a low compared with a high weight reducer. (A) Three paired slices from 3 heights of the heart (at PAB, 5 cm below PAB, and at the apex of the heart) of a participant with 1.2 kg weight loss during 18 mo of intervention. This subject had a mild reduction in both IPF (light blue) and EPF (royal blue), and slice analyses reveal little, if any, pericardial adiposity change. (B) Three paired slices from the same heights as panel A of a subject with a 20-kg loss. This subject had a substantial reduction in both EPF (royal blue) and IPF (light blue). Both subjects were in their early 40s and had a similar baseline biophysical profile. EPF, extrapericardial fat; IPF, intrapericardial fat; PAB, pulmonary artery bifurcation; PT, pulmonary trunk; Δ, 18-mo change from baseline.

group (-6.9 ± 6.6 cm) than in the LF group (-2.3 ± 6.5 cm), $P = 0.01$. HDL cholesterol increased similarly in the 2 diet groups ($+3.1 \pm 8.4$ in the LF group compared with $+5.1 \pm 7.4$ in the MED/LC group, $P = 0.307$). Generally, at the end of the intervention, the MED/LC group had an improved lipid profile compared with the LF group for TC ($+15.3 \pm 37.6$ mg/dL in the LF group compared with -9.5 ± 48.1 mg/dL in the MED/LC group, $P = 0.023$), LDL cholesterol ($+11.7 \pm 25.2$ mg/dL in the LF group compared with -8.2 ± 41.2 mg/dL in the MED/LC group, $P = 0.022$), and serum TGs ($+2.6 \pm 65.2$ mg/dL in the LF group compared with -16.9 ± 37.3 mg/dL in the MED/LC group, $P = 0.028$). Further changes in anthropometry, hemodynamics, and serum biomarkers across dietary intervention groups are detailed in **Supplemental Table 2**.

Changes in pericardial fat during intervention

EPF volumes were reduced substantially during the intervention from 194.9 ± 71.5 mL at baseline to 165.2 ± 73.3 mL at 18 mo, a 15% decrease; IPF volume decreased by 11%, from 172.4 ± 53.3 mL to 153.6 ± 55.0 mL; $P < 0.001$ for both compared with baseline both in per-protocol and in ITT analyses. Sample images of pericardial fat changes in 2 men, one with a 1.2-kg weight loss and the other with 20-kg loss, are shown in **Figure 2**A, B.

Across the dietary intervention groups, the MED/LC diet had a favorable effect over the LF diet in reduction of IPF volume (-37 ± 26.2 mL compared with -15.5 ± 26.2 mL, $P = 0.002$, among completers or -25 ± 27.7 mL compared with -12.8 ± 24.5 mL among the ITT population, $P = 0.04$) which remained significant also after adjustment for age, inclusion in the PA intervention, changes in metabolic equivalents, and 18-mo weight change, BMI change, or VAT change separately (**Figure 3**). Conversely, the EPF volume had reduced similarly in both groups (-41.6 ± 30.2 mL in the MED/LC group compared with -37.9 ± 28.3 mL in the LF group; $P > 0.1$ both in per-protocol and ITT analyses). An example of the differential influence of dietary intervention in 2 individuals with similar weight loss in the 2 diets is illustrated in **Figure 4**.

There was no statistically significant interaction between dietary and PA interventions ($P = 0.172$). Across the 4 study subgroups (LF and MED/LC diets with or without PA), the LF diet-only (LF^{PA-}) group had the smallest reduction in IPF volume (-14.2 ± 32.3 mL) compared with the MED/LC group with PA (MED/LC^{PA+}), which had the greatest reduction in IPF (-39.5 ± 26.2 mL, $P = 0.01$). Differences between other groups were not significant: MED/LC diet-only (MED/LC^{PA-}): -33.3 ± 27.2 mL, $P = 0.075$ compared with LF^{PA-}); LF^{PA+}: -16.6 ± 20.7 mL, $P = 0.797$ compared with LF^{PA-}). EPF was reduced similarly in all study subgroups (LF^{PA-}: -36.0 ± 30.2 mL; LF^{PA+}: -39.5 ± 27.4 mL; MED/LC^{PA-}: -49.0 ± 23.3 mL; MED/LC^{PA+} group: -36.5 ± 33.9 mL; $P > 0.05$ for all comparisons).

Association between 18-mo changes in pericardial fat with changes in anthropometrics and cardiometabolic variables

Linear regression models for the association between 18-mo changes in IPF and EPF with changes in anthropometrics and cardiometabolic markers after 18 mo of intervention are detailed in **Table 3**. To assess whether the IPF or EPF changes merely reflected VAT redistribution or modification in body mass or had associations beyond such changes, we additionally adjusted each model to the 18-mo changes of VAT and BMI separately. After adjustment to the 18-mo change in BMI, the reduction in IPF remained significantly associated with a decrease in WC ($\beta = 0.364$, $P = 0.030$), serum TG dynamics ($\beta = 0.308$, $P = 0.007$), and serum ratio of TG to HDL cholesterol ($\beta = 0.257$, $P = 0.024$). Similarly, the EPF change remained significantly associated with increased serum HDL cholesterol ($\beta = -0.262$, $P = 0.039$) and an improved serum ratio of TC to HDL cholesterol ($\beta = 0.334$, $P = 0.007$). Models adjusting for the VAT change showed generally similar results (Table 3). In sensitivity analyses similar associations were observed in both dietary intervention groups and PA intervention groups.

DISCUSSION

In this 18-mo trial among participants with abdominal obesity, we found that moderate, but persistent, dietary-induced weight

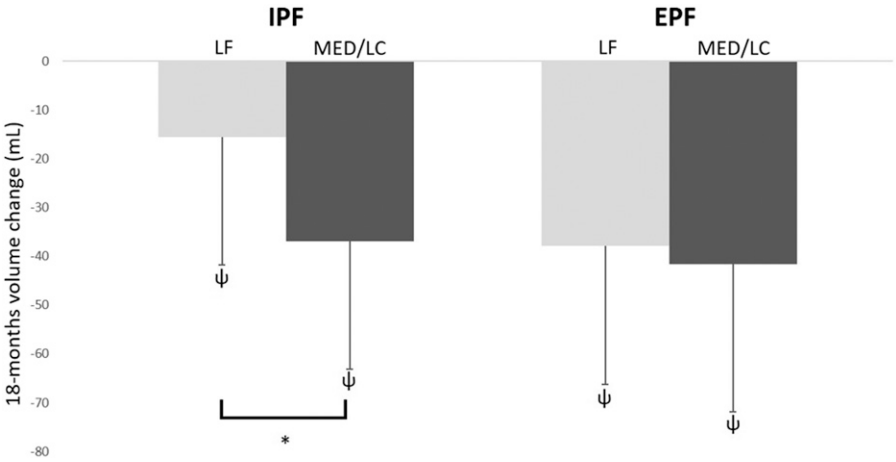

FIGURE 3 Dynamics of IPF and EPF volumes during 18 mo across diet groups. Data are presented as means ± SDs. $^{\psi}P < 0.01$, change from baseline. $^{*}P < 0.05$, between groups adjusted to include the physical-activity intervention and 18-mo BMI change, visceral adipose tissue change, or age separately. EPF, extrapericardial fat; IPF, intrapericardial fat; LF, low fat; MED/LC, Mediterranean/low carbohydrate.

loss substantially decreased both IPF and EPF volumes. Additionally, we observed a differential effect of dietary interventions on IPF volume changes: the MED/LC diet induced almost twice as much IPF volume reduction as the LF diet did. Importantly, these differences were discernable even after adjusting for the decline in VAT or BMI. The IPF and EPF volume reduction paralleled changes in lipid variables but not the glycemic profile. To our knowledge, this report is the first to show differential effects of diet on IPF beyond weight reduction.

Pericardial fat redistribution after weight reduction was previously addressed in trials among ≤40 participants with maximal intervention lengths of 6 mo (13–19, 21–23, 25). Most of these studies reported a statistically significant reduction in IPF, EPF, or both pericardial fat depots after weight reduction (13–24). These studies described a high correlation between pericardial adipose tissue reduction and mild-to-moderate weight loss (18, 25). Also, pericardial fat volume reduction achieved after a 16-wk, very-low-calorie diet remained stable after an additional 14 mo

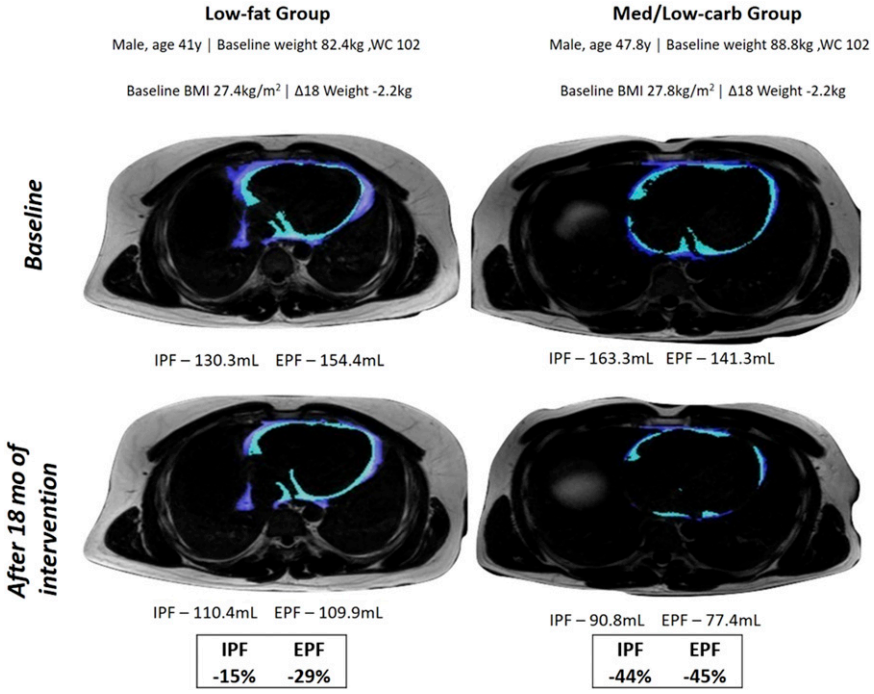

FIGURE 4 Example of 18-mo changes in pericardial fat in 2 participants, one from each dietary group. Pericardial-fat analysis in midcardiac height (7 cm below pulmonary artery bifurcation) of 2 subjects, one from each intervention group, at baseline (top) and after 18 mo of intervention (bottom). Both subjects were in their 40s with similar anthropometrics at baseline and similar reductions in weight (~2.5%) at the end of the intervention. The participant in the MED/Low-carb diet group had a 44% IPF (light blue) volume reduction, whereas the participant in the LF group had a 15% reduction. EPF (royal blue) volume reduction was also more substantial in the MED/Low-carb participant than in the LF participant, although it was less profound than the IPF volume reduction. EPF, extrapericardial fat; IPF, intrapericardial fat; LF, low fat; MED/Low-carb, Mediterranean/low carbohydrate; WC, waist circumference; Δ, 18-mo change from baseline.

TABLE 3
Associations of changes in IPF and EPF with changes in cardiometabolic profiles during 18 mo of intervention[1]

	ΔIPF,[2] %			ΔEPF,[2] %		
Variable change after 18 mo	Standardized β coefficient	Unstandardized β (95% CI)	*P*	Standardized β coefficient	Unstandardized β (95% CI)	*P*
Weight raw correlation, kg	0.582	1.360 (0.861, 1.859)	<0.001	0.502	1.075 (0.588, 1.562)	<0.001
BMI raw correlation, kg/m^2	0.584	4.258 (2.689, 5.828)	<0.001	0.533	3.523 (2.038, 5.009)	<0.001
Waist circumference, cm						
Unadjusted	0.598	1.421 (0.915, 1.926)	<0.001	0.469	1.012 (0.507, 1.517)	<0.001
Adjusted for ΔVAT proportion, %	0.575	1.425 (0.865, 1.985)	<0.001	0.394	0.849 (0.299, 1.399)	0.003
Adjusted for ΔBMI, kg/m^2	0.364	0.864 (0.088, 1.641)	0.030	0.145	0.312 (−0.450, 1.075)	0.415
Systolic BP, mm Hg						
Unadjusted	0.180	0.214 (−0.097, 0.525)	0.173	0.136	0.146 (−0.136, 0.427)	0.304
Adjusted for ΔVAT proportion, %	0.136	0.162 (−0.156, 0.480)	0.311	0.069	0.074 (−0.207, 0.355)	0.599
Adjusted for ΔBMI, kg/m^2	0.033	0.039 (−0.235, 0.313)	0.777	0.013	0.014 (−0.242, 0.269)	0.916
Diastolic BP, mm Hg						
Unadjusted	0.159	0.241 (−0.155, 0.636)	0.228	−0.002	−0.002 (−0.362, 0.357)	0.990
Adjusted for ΔVAT proportion, %	0.138	0.208 (−0.185, 0.601)	0.293	−0.034	−0.046 (−0.394, 0.302)	0.792
Adjusted for ΔBMI, kg/m^2	0.060	0.089 (−0.248, 0.427)	0.597	−0.096	−0.129 (−0.443, 0.185)	0.415
LDL cholesterol, mg/dL						
Unadjusted	0.077	0.036 (−0.089, 0.161)	0.568	0.168	0.070 (−0.040, 0.181)	0.206
Adjusted for ΔVAT proportion, %	0.050	0.024 (−0.101, 0.148)	0.705	0.134	0.056 (−0.052, 0.164)	0.303
Adjusted for ΔBMI, kg/m^2	0.026	0.012 (−0.094, 0.118)	0.821	0.141	0.059 (−0.038, 0.155)	0.230
HDL cholesterol, mg/dL						
Unadjusted	−0.228	−0.448 (−0.959, 0.064)	0.085	−0.430	−0.752 (−1.176, −0.329)	0.001
Adjusted for ΔVAT proportion, %	−0.210	−0.413 (−0.921, 0.095)	0.109	−0.407	−0.712 (−1.123, −0.301)	0.001
Adjusted for ΔBMI, kg/m^2	0.019	0.036 (−0.445, 0.518)	0.880	−0.262	−0.452 (−0.880, −0.023)	0.039
TGs, mg/dL						
Unadjusted	0.437	0.128 (0.057, 0.198)	0.001	0.336	0.087 (0.022, 0.153)	0.010
Adjusted for ΔVAT proportion, %	0.411	0.120 (0.048, 0.191)	0.001	0.289	0.075 (0.010, 0.141)	0.025
Adjusted for ΔBMI, kg/m^2	0.308	0.090 (0.026, 0.154)	0.007	0.230	0.059 (−0.002, 0.120)	0.058
TC/HDL cholesterol ratio						
Unadjusted	0.365	4.676 (1.479, 7.873)	0.005	0.461	5.274 (2.557, 7.991)	<0.001
Adjusted for ΔVAT proportion, %	0.332	4.263 (0.982, 7.544)	0.012	0.415	4.747 (1.997, 7.498)	0.001
Adjusted for ΔBMI, kg/m^2	0.179	2.288 (−0.745, 5.321)	0.136	0.334	3.766 (1.092, 6.440)	0.007
TG/HDL cholesterol ratio						
Unadjusted	0.385	4.038 (1.450, 6.627)	0.003	0.325	3.037 (0.671, 5.403)	0.013
Adjusted for ΔVAT proportion, %	0.358	3.751 (1.130, 6.373)	0.006	0.281	2.623 (0.276, 4.973)	0.029
Adjusted for ΔBMI, kg/m^2	0.257	2.688 (0.373, 5.003)	0.024	0.220	2.031 (−0.146, 4.207)	0.067
FPG, mg/dL						
Unadjusted	0.065	0.096 (−0.294, 0.487)	0.624	−0.146	−0.193 (−0.541, 0.154)	0.270
Adjusted for ΔVAT proportion, %	0.083	0.123 (−0.263, 0.508)	0.526	−0.123	−0.163 (−0.499, 0.174)	0.337
Adjusted for ΔBMI, kg/m^2	0.022	0.032 (−0.294, 0.358)	0.846	−0.193	−0.252 (−0.549, 0.045)	0.095
Insulin, U						
Unadjusted	0.268	0.522 (0.014, 1.031)	0.044	0.160	0.282 (−0.189, 0.758)	0.234
Adjusted for ΔVAT proportion, %	0.240	0.469 (−0.040, 0.977)	0.070	0.120	0.214 (−0.250, 0.678)	0.360
Adjusted for ΔBMI, kg/m^2	0.071	0.138 (−0.322, 0.599)	0.549	−0.024	−0.041 (−0.482, 0.399)	0.851
HOMA-IR						

(Continued)

TABLE 3 (*Continued*)

	ΔIPF,[2] %			ΔEPF,[2] %		
Variable change after 18 mo	Standardized β coefficient	Unstandardized β (95% CI)	*P*	Standardized β coefficient	Unstandardized β (95% CI)	*P*
Unadjusted	0.239	1.528 (−0.152, 3.027)	0.074	0.099	0.579 (−0.987, 2.144)	0.462
Adjusted for ΔVAT proportion, %	0.224	1.432 (−0.229, 3.092)	0.090	0.079	0.458 (−1.059, 1.974)	0.548
Adjusted for ΔBMI, kg/m^2	0.054	0.342 (−1.156, 1.841)	0.649	−0.077	−0.443 (−1.870, 0.985)	0.537
hsCRP, mg/L						
Unadjusted	−0.048	−0.203 (−1.347, 0.940)	0.723	0.000	0.002 (−1.019, 1.023)	0.997
Adjusted for ΔVAT proportion, %	−0.098	−0.417 (−1.566, 0.732)	0.470	−0.065	−0.247 (−1.252, 0.758)	0.624
Adjusted for ΔBMI, kg/m^2	−0.168	−0.718 (−1.669, 0.233)	0.136	−0.112	−0.422 (−1.313, 0.469)	0.346

[1] BP, blood pressure; EPF, extrapericardial fat; FPG, fasting plasma glucose; hsCRP, high-sensitivity C-reactive protein; IPF, intrapericardial fat; TC, total cholesterol; TG, triglyceride; VAT, visceral adipose tissue; Δ, 18-mo change from baseline.

[2] Linear regression analyses (dependent variable ΔIPF or ΔEPF, accordingly).

of follow-up (16). In our trial, moderate weight loss that was sustained for 18 mo substantially reduced pericardial fat burden.

We further aimed to examine whether pericardial fat could be differentially influenced by diet by comparing a MED/LC diet with an LF diet (31). A prior study among women that examined the effects of 20 wk of similarly hypocaloric lifestyle interventions on pericardial fat showed a significant, but similar, reduction in pericardial fat volume in all intervention groups (21). Therefore, our a priori assumption was that both IPF and EPF volumes would decline significantly but similarly in both dietary intervention groups, in correspondence with overall weight loss. Contrary to expectation, we found that after 18 mo, the IPF volume reduction was highly sensitive to the dietary intervention, beyond the influence of weight loss, whereas the EPF volume reduction was similar across dietary interventions, influenced by weight loss alone.

Because of its intimate relation to the myocardium and coronary arteries, IPF, originating from the same embryonic origin as abdominal VAT (1, 2), has long been studied for its role in coronary atherosclerosis and cardiac hemodynamics and structure. IPF's high free fatty acid (FFA) uptake and turnover serves as an important energy source for the myocardium and paracrinely affects coronary vessels and the myocardium contractility (2, 6). Our findings of associations between higher weight, abdominal visceral adiposity, and increased volumes of IPF at baseline match observations from past cross-sectional studies (3, 4, 7). Previous reports also linked increased IPF burden with coronary artery obstructive disease and decreased left ventricular function (7, 9). Hence, there is growing interest in defining feasible weight-loss strategies to effectively reduce IPF burden.

So far, reported pericardial volumes were highly variable and represented mixed-sex populations mostly in the normal range of BMI. In our study, baseline IPF volumes were higher than those reported in studies among mixed populations (3, 35) yet are well in line with reported IPF volumes in obese and metabolically impaired populations (38). These differences in baseline IPF volumes may also derive from the high percentage of men in our study.

The marked reduction in IPF with the MED/LC diet might be explained by several mechanistic hypotheses. Recent evidence suggests bidirectional, paracrine-type cross-talk between the myocardium and IPF, supported by the finding that IPF can infiltrate, and become tightly interconnected with, certain regions of the myocardium: myocardial lipid oxidation products modulate IPF adiponectin secretion via peroxisome proliferator–activated receptor γ, and in turn, IPF-produced adiponectin decreases myocardial oxidative stress, constituting a bidirectional regulatory feedback loop (39). As well, atrial natriuretic peptide (ANP), secreted from atrial cardiomyocytes, was shown to exhibit a lipolytic effect on epicardial adipocytes (40) and decrease oxidative stress (41). Because polymorphism in ANP was associated with cardiometabolic protection in both North American (42) and Mediterranean populations (43), we suggest future studies to investigate a putative mediatory role of ANP in the link between lifestyle intervention, IPF trajectory, and improved cardiometabolic health. From another perspective, IPF and the myocardium share the same blood supply via coronary circulation (6). Because the myocardium was shown to exhibit high FFA

uptake activity (44), it is plausible that FFA released from IPF can contribute to myocardial FFA uptake (6). Nevertheless, to date, whether delivery of FFA from IPF to the myocardium occurs via the coronary circulation or via direct diffusion has not been established. Thus, future studies should explore whether the preferential decrease in IPF in response to the MED/LC diet is mediated by greater induction of IPF lipolysis, and if so, what might be the role of enhanced secretion of myocardium-derived prolipolytic factors, such as ANP, and/or whether an MED/LC diet can enhance myocardial capacity to use IPF-released FFA.

A reduction in the ratio of TG to HDL cholesterol, a biomarker for the identification of insulin resistance associated with elevated cardiometabolic risk (45), was associated with a reduction in IPF. This finding, along with the reported association between increased IPF burden and increased cardiovascular disease risk (3–6), might reflect a potential link between the ratio of TG to HDL cholesterol, IPF burden, and cardiometabolic risk.

In contrast to IPF, EPF has mainly been related to increased metabolic risk and decline in insulin sensitivity and only weakly linked with coronary artery obstructive disease and cardiac dysfunction (5, 11, 12). EPF was not independently associated with increased cardiovascular disease risk but rather through its association with other cardiometabolic risk factors (1, 6). In this trial, EPF reduction was associated with improved HDL cholesterol and ratio of TC to HDL cholesterol but not with glycemic profile changes, after adjusting for changes in BMI or VAT. These findings suggest that EPF might play a role in dyslipidemia (5, 6, 11, 12).

Limitations of our study should be considered. Most participants were men, so we cannot draw specific conclusions regarding women. Also, we had no direct assessment of coronary obstructive disease, vascular atherosclerosis, or cardiac function. Our volumetric method to assess pericardial fat volumes was not directly validated by our group but was independently validated by another group (35). Nevertheless, we achieved high reproducibility with high interclass and intraclass correlation coefficients; furthermore, all imaging analyses were performed in the same manner, which mitigates potential minor inaccuracies in assessing changes in pericardial fat volumes. Although our study was the largest of its kind, the sample size was limited.

In conclusion, our study demonstrated a favorable reduction in IPF volume with the MED/LC diet compared with the LF diet, even after adjustment for changes in VAT or BMI. The reduction in EPF correlated with a better cholesterol balance, whereas decreases in IPF were associated with reductions in serum TGs and ratio of TG to HDL cholesterol. Because IPF has been related to the risk of coronary artery atherosclerosis and cardiovascular disease, our findings might imply that IPF changes play a role in mediating the benefits of the MED/LC diets compared with an LF diet. Our findings, along with other reports, might suggest that IPF serves as a surrogate, linking between body mass, visceral adiposity, metabolic state, and cardiovascular disease risk.

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The authors' responsibilities were as follows—I Shai, AR, MJS, YH, D Schwarzfuchs, AW, and I Shelef: designed the research; GT, HA-H, YG, NC, NB, MR, D Serfaty, SK, LT, HZ, AY-M, OK, and AB: conducted the research; YC: provided the software engineering services; UC, MS, MB, and JT: analyzed the blood and urine samples; DD: provided the scientific consultation; GT, YG, and AW: analyzed the imaging; GT: analyzed the data; GT, AW, and I Shai: wrote the paper; I Shai: had primary responsibility for the final content; and all authors: had full access to all the data in the study and had responsibility for the integrity of the data and the accuracy of the data analysis. None of the authors reported a conflict of interest related to the study.

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