Published in final edited form as:

Cells Tissues Organs. 2017 ; 203(4): 258–266. doi:10.1159/000449407.

IMPACT OF DIET AND/OR EXERCISE INTERVENTION ON INFRAPATELLAR FAT PAD MORPHOLOGY - SECONDARY ANALYSIS FROM THE INTENSIVE DIET AND EXERCISE FOR ARTHRITIS (IDEA) TRIAL

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Abstract

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AUTHOR CONTRIBUTIONS

- Substantial contribution to study conception and design: All authors
- Substantial contribution acquisition of data (IPFP): Pogacnik Murillo, Eckstein, Wirth
- Statistical analysis: Beavers
- Analysis & interpretation of data: All authors
- Writing of first manuscript draft: Pogacnik Murillo and Eckstein
- Critical manuscript revision and approval of final manuscript: All authors

ROLE OF THE STUDY SPONSOR

The statistical analysis and writing of this article was independent from and not contingent upon approval from the study sponsors.

Competing Interest

- Felix Eckstein is CEO of Chondrometrics GmbH, a company providing MR image analysis services to academic researchers and to industry. He has provided consulting services to MerckSerono, Abbvie and Servier, has prepared educational sessions for Medtronic, and has received research support from Pfizer, Eli Lilly, MerckSerono, Glaxo Smith Kline, Centocor R&D, Wyeth, Novartis, Stryker, Abbvie, Kolon, Synarc, Ampio, Orthotrophix, and Samumed.
- Wolfgang Wirth has a part time employment with Chondrometrics GmbH and is a co-owner of Chondrometrics GmbH.
- The other authors declare no competing interest

Objectives—The infrapatellar fat pad (IPFP) represents intra-articular adipose tissue that may contribute to intra-articular inflammation and pain by secretion of pro-inflammatory cytokines. Here we examined the impact of weight loss by diet and/or exercise interventions on IPFP volume.

Methods—Intensive Diet and Exercise for Arthritis (IDEA) was a single-blinded, single-center, 18-month, prospective, randomized controlled trial that enrolled 454 overweight and obese older adults with knee pain and radiographic osteoarthritis. Participants were randomized to 1 of 3 groups: exercise only control (E), diet-induced weight loss (D), and diet-induced weight loss + exercise (D+E). In a subsample (n=106; E: n=36; D: n=35; D+E: n=35), magnetic resonance images were acquired at baseline and 18-month follow-up, from which we analyzed IPFP volume, surface areas and thickness in this secondary analysis.

Results—Average weight loss in each group amounted to 1.0% in E, 10.5% in D, and 13.0% in D+E. A significant ($p< 0.01$) reduction in IPFP volume was observed in E (2.1%), D (4.0%) and D +E (5.2%). The IPFP volume loss in D+E was significantly greater than that in E ($p<0.05$) when not adjusting for parallel comparisons. Across intervention groups, there were significant correlations between IPFP volume change, individual weight loss (r=0.40), and change in total body fat mass (DXA; r=0.44; n=88) and in subcutaneous thigh fat area (CT; r=0.32; n=82).

Conclusions—As a potential link between obesity and knee OA, the IPFP was sensitive to intervention by diet and/or exercise, and its reduction was correlated with change in weight and body fat.

Keywords

infrapatellar fat pad; quantitative imaging; weight loss; knee osteoarthritis

INTRODUCTION

Knee osteoarthritis (OA) represents one of the leading causes for chronic disability among the elderly population [Guccione et al., 1994] and is known to be associated with structural alteration in most articular and para-articular tissues [Poole, 2012]. Obesity is one of the most important risk factors of knee OA and reduced quality of life [Losina et al., 2011], despite being mostly preventable. It has been recently suggested that obesity-related risk of knee OA incidence and progression may not only be conveyed by biomechanical factors, but also by endocrine and inflammatory mechanisms [Issa and Griffin, 2012; Berenbaum et al., 2013; Pogacnik Murillo, 2015]. Adipokines, a group of adipocyte-derived cytokines, are thought to mediate intra-articular inflammation and up-regulation of cartilage matrix degradation [Issa and Griffin, 2012; Richter et al., 2015].

The infrapatellar fat pad (IPFP) represents intra-articular (i.e. intra-capsular, extra-synovial) adipose tissue [Hoffa, 1904; Haug, 2014], with its macroscopic anatomy having been previously examined in relation to knee function, pathology and surgical approaches by Gallagher and coworkers [Gallagher et al., 2005]. These authors [Gallagher et al., 2005] found the IPFP to be constant in shape, consisting of a central body with medial and lateral extensions. More recently, the IPFP also has been identified as a source of leptin and other pro-inflammatory cytokines [Hui et al., 2012; Distel et al., 2009; Klein-Wieringa et al., 2011; Gandhi et al., 2011; Gegout et al., 2008]. In knee OA, the IPFP was found to yield

high expression levels of enzymes that are involved in fat metabolism [Gandhi et al., 2011], suggesting that it represents a link between obesity and knee OA. The Intensive Diet and Exercise for Arthritis (IDEA) trial [Messier et al., 2009] showed that 18-month diet-induced weight loss plus exercise resulted in a significant reduction in knee symptoms, an improvement in knee function, and better physical health-related quality of life scores compared with exercise alone [Messier et al., 2013]. This improvement was associated with a significant reduction in the mechanistic primary outcomes, i.e. knee compressive forces and systemic inflammatory marker levels, specifically interleukin (IL) 6 [Messier et al., 2013].

Few studies thus far have quantitatively analyzed IPFP morphology. In a recent paper, Diepold et al. reported that men displayed a significantly greater ratio of IPFP volume/body weight than women, similar amounts of inter-muscular fat, and strikingly less subcutaneous fat than women [Diepold et al., 2015]. Studies that have examined the relationship between IPFP volume and knee pain or radiographic OA status have provided partially contradictory results [Cowan et al., 2015; Pan et al., 2015; Chuckpaiwong et al., 2010; Han et al., 2014; Cai et al., 2015; Teichtahl et al., 2015; Steidle-Kloc et al., 2015; Eckstein et al., 2015]. Although the IPFP has been reported to be preserved under starvation conditions [Ioan-Facsinay and Kloppenburg, 2013], there appears to be some dynamic window, as a longitudinal increase in IPFP volume was reported in mice with high-fat feeding and weight gain [Chang et al., 2011]. However, to date no study has examined the relationship between IPFP volume and weight change in humans, and no interventional trial has studied the sensitivity of IPFP morphology to exercise and/or weight loss. Therefore, in this secondary analysis of the IDEA trial [Messier et al., 2013], we examined whether 18-month diet-induced weight loss (with and without exercise) was associated with change in IPFP morphology in patients with knee pain and mild to moderate OA. Further, we determined whether change in IPFP morphology differed between groups with exercise intervention only (E), diet-induced weight loss intervention only (D), and combined diet-induced weight loss + exercise (D+E) intervention. Finally, we examined whether change in IPFP volume correlated with change in body weight and fat, independent of intervention.

MATERIALS AND METHODS

Study population

IDEA was a single blind, single-center, 18-month randomized controlled trial [Messier et al., 2013; Messier et al., 2009], which was conducted from July 2006 to June 2011 at Wake Forest University and the Wake Forest School of Medicine, Winston-Salem, North Carolina, USA. The study was approved by the human subjects institutional review board of Wake Forest Health Sciences. Informed consent was obtained in writing from all participants (trial registration: NCT00381290) [Messier et al., 2013; Messier et al., 2009].

The IDEA trial included 454 ambulatory, community-dwelling persons aged ≥ 55 years with:

1. Kellgren-Lawrence grade (KLG) [Kellgren, and Lawrence, 1957] 2–3 (mild to moderate) radiographic tibiofemoral OA or tibiofemoral plus patellofemoral OA of one or both knees.
2. Pain on most days, due to knee OA.
3. A body mass index (BMI) ranging from 27 to 41 kg/m^2.
4. A sedentary lifestyle, i.e. < 30 min/week of formal exercise in the past 6 months.

Participants were recruited from the community over a 37-month period (November 2006 to December 2009) [Messier et al., 2013; Messier et al., 2009]. A stratified-block randomization method assigned all eligible persons to 1 of 3 intervention arms, stratified by BMI and gender: exercise-only control (E); diet-induced weight loss only (D); diet-induced weight loss plus exercise (D+E) [Messier et al., 2013; Messier et al., 2009]. The E intervention group was designated as the comparison (control) group because previous work indicated that aerobic walking or resistance training should be part of the standard of care for knee OA patients [Ettinger et al., 1997], and because the original study [Messier et al., 2013] was designed [Messier et al., 2009] to test whether diet alone, or diet in combination with exercise, leads to greater improvements than the “standard of care” (exercise) alone. Detailed description of the diet-induced weight loss and exercise interventions, trial design and rationale, and the primary outcomes have been reported elsewhere [Messier et al., 2013; Messier et al., 2009]. In brief, the diet intervention was initially based on partial meal replacements, and one daily meal of 500–750 kcals. Exercise intervention consisted of aerobic walking (15 min), strength training (20 min), another aerobic phase (15 min), and cool-down (10 min), and was conducted 3 times weekly, for 1h, over the entire 18-month observation period [Messier et al., 2013; Messier et al., 2009].

Due to budget restrictions, magnetic resonance (MR) images were obtained on a randomly selected subsample of 106 participants at baseline and 18-month follow-up [Hunter et al., 2015]. The sample size per group was: E: n=36, D: n=35, D+E: n=35.

Image acquisition and analysis of the IPFP

A 1.5 Tesla (SIGNA HDx, General Electric Medical Systems, Milwaukee, Wisconsin) scanner and an extremity coil was used to obtain MR images of the most affected knee [Hunter et al., 2015; Messier et al., 2013]. The segmentation of the IPFP was performed using a sagittal non-fat-suppressed T1-weighted spin echo sequence (time of repetition = 600 ms, time of echo = 11 ms, contiguous slices with a thickness = 4.5mm, in-plane resolution 0.625mm × 0.625mm, field of view = 16cm, image matrix = 256 × 256 pixels). All segmentations in this study were performed by the first author of this study (A.P), who was trained using standardized test data sets [Steidle-Kloc et al., 2016]. Baseline and follow-up images were read as pairs, but the reader (A.P.) was blinded to the time of image acquisition and type of intervention during segmentation. Brightness, intensity, contrast, and grey value limits were adjusted manually in each image to warrant optimal contrast between the IPFP and surrounding tissue, with the reader processing all slices (from medial to lateral) that clearly depicted the IPFP. By applying different labels, the reader manually traced the anterior border of the IPFP (the one facing the patellar ligament) and the posterior border

(the one facing the knee joint) [Fig. 1a)]. Clefts (supra- and infra-hoffatic recesses [Roemer et al., 2016]) located in the periphery of the IPFP, and the anterior intermeniscal ligament were excluded from the segmentation. However, small alterations completely surrounded by adipose tissue were included in the volume segmentations. Based on these segmentations, the IPFP volume, the size of the anterior and posterior surface area, and the mean and maximal depth from the anterior to posterior surface were computed using custom image analysis software [Fig. 1b)] [Diepold et al., 2015; Steidle-Kloc et al., 2016], with the intra- and inter-observer reliability having been reported [Steidle-Kloc et al., 2016]. For further methodological details please see [Pogacnik Murillo, 2015].

Analysis of body and thigh composition

The body mass index (BMI) of all participants was calculated as mass (measured in kilograms on a standard calibrated scale) divided by body height squared (measured in meters). The whole body fat mass was measured at baseline and 18-month follow-up using dual energy x-ray absorptiometry (DXA) in a subsample of the participants (n=88). DXA scans were obtained with a fan-beam scanner, Delphi A™, Hologi (Waltham, MA) using the manufacturer's recommendations for patient positioning, scan protocols, and scan analysis, with the reliability (coefficients of variation (%CV) of repeated measurements) being reported as 1.2% for whole body fat mass [Messier et al., 2009]. Further, baseline and 18-month follow-up computed tomography (CT) scans of the thigh were obtained in a subsample (n=82), and measurements of subcutaneous thigh fat, intra-muscular thigh fat and total thigh fat were obtained [Messier et al., 2009].

Statistical analysis

Baseline anthropometric measures and quantitative measures of the IPFP are reported as means and standard deviations (SD). Within- and between-group comparisons of longitudinal changes in IPFP morphology were evaluated using ANCOVA, adjusting for baseline values of the outcome, baseline BMI, and sex, but not adjusting for multiple between-group comparisons in this post hoc exploratory analysis. IPFP volume was considered the primary analytic focus of the current analysis, and IPFP anterior surface area, posterior surface area, mean and maximal depth as exploratory measures. Correlations between IPFP change vs. BMI change, fat mass change (DXA) or thigh composition change (CT) were studied across the entire sample, independent of the randomized controlled trial design and specific type of intervention, using Spearman correlations. The level of significance for all comparisons was set at 0.05. All analyses were performed using SAS v9.4 (SAS Institute, Cary, NC).

RESULTS

There were no significant differences in age, sex, BMI and IPFP morphology measures between the three intervention groups at baseline [Table 1]. There was a significant ($p<0.01$) reduction in IPFP volume in each of the three intervention groups over the 18-month observation period [Table 2 and Fig. 2]: −2.1% (95% CI −0.8%, −4.8%) in E, −4.0% (−1.9%, −5.7%) in D and −5.2% (−3.5%, −7.5%) in D+E. As a reference, the mean percent (%) body weight loss from baseline amounted to −1.0% in E, −10.5% in D and −13.0% in D

+E. Changes in kg and their 95% CIs are shown in Table 2. There was a significant ($p<0.01$) within-group decrease in IPFP posterior surface area for each intervention group, and a significant ($p<0.001$) within-group decrease in IPFP anterior surface area in the D+E group; change in IPFP volume therefore appeared to be driven more by a change in surface areas than by change in IPFP depth [Table 2]. Between group comparisons revealed a significantly greater reduction in IPFP volume and IPFP posterior surface area in the D+E group than in the E (control) group ($p<0.05$); other between-group differences in the longitudinal changes in IPFP morphology did not reach statistical significance [Table 2 & Table 3].

Across the three intervention groups, there was a significant ($p<0.01$) correlation between IPFP volume change and weight loss ($r=0.40$), BMI change ($r=0.39$), total body fat mass change ($r=0.44$; $n=88$; DXA), subcutaneous thigh fat change ($r=0.32$; $n=82$; CT), and inter-muscular thigh fat change ($r=0.29$; $n=82$; CT) [Table 4]. Across all intervention types, each percent of weight loss was related to a 0.27% reduction in IPFP volume.

DISCUSSION

In this first study investigating the effect of diet-induced weight loss, with and without exercise, on IPFP morphology, we observed a significant reduction of IPFP size in all intervention groups. Further, the findings suggest that the combination of D+E was more effective in reducing IPFP volume than E alone, and that, independent of the type of intervention, the reduction in IPFP volume was significantly correlated with loss in body weight and fat mass.

A limitation of the current analysis is that only a subsample of the IDEA cohort was examined [Hunter et al., 2015]; yet the subsample was reasonably representative of the larger sample and sufficient to demonstrate responsiveness of the IPFP to diet and exercise intervention. A strength of the current study is its randomized controlled design, which allowed for the analysis of the effects of diet-induced weight loss, with and without exercise, on the IPFP volume. Further, randomization of the subsample to the different intervention groups appeared to be without bias, as anthropometric and IPFP morphometric baseline values were similar between the intervention groups. Another limitation of the current study was that a standard no-treatment reference group (with neither exercise nor diet intervention) was not available because the intent of the original study was to test whether diet, whether in combination with exercise or not, was more effective in reducing clinical symptoms than exercise, which is part of the standard of care for people with knee OA, and that no additional reference group with or without known OA status in other joints, e.g. of the upper limb was available.

Interestingly, exercise intervention alone resulted in a small, but statistically significant within-group reduction in IPFP volume, despite a minimal and statistically non-significant reduction in body weight. Diet in combination with exercise was more effective in reducing IPFP volume, despite reductions in body weight being similar in the D and D+E groups. Although the mechanism behind exercise-related effects on the IPFP is unclear, this could potentially be due to modifying inflammation and edema within the IPFP. These findings indicate that exercise may be effective in modifying IPFP morphology, at least partly

independent of weight loss. Further interventional studies should examine whether specific types of exercises are more effective than others in reducing IPFP volume, whether reduction in IPFP volume is associated with less inflammatory activity and release of adipokines, and whether modification of the IPFP (including surgical reduction) is related to joint health.

Previous studies that examined the relationship between IPFP size and knee OA have revealed partly contradictory results: Chuckpaiwong et al. found no differences in IPFP volume between patients with knee OA and healthy controls in a small (and likely underpowered) sample [Chuckpaiwong et al., 2010]. A smaller IPFP size was found to be associated to cartilage defects compared to the control group, but only in women [Duran et al., 2015]. Furthermore, differences in IPFP volume between patients with cartilage defects and healthy controls disappeared after adjustment for age and BMI [Duran et al., 2015]. The IPFP volume in joints with patellofemoral OA was reported to be greater than in those without patellofemoral OA [Cowan et al., 2015]. Greater IPFP maximal sagittal cross-sectional area, however, appeared to be beneficial in terms of structural changes and knee pain, but these observations were limited to a single slice [Pan et al., 2015; Han et al., 2014; Teichtahl et al., 2015]. In this context, a strength of the present study was that the complete IPFP volume was studied, and not only a single slice, two-dimensional representation of its tissue [Pan et al., 2015; Han et al., 2014]. This type of volumetric analysis is reproducible within and between observers [Steidle-Kloc et al., 2016]. Also, volumetric analysis permitted us to examine the responsiveness of different measures of IPFP morphology, indicating that reduction in (posterior) surface area may be more sensitive to exercise and diet-induced weight loss than IPFP depth.

The IPFP is a local source of pro-inflammatory mediators, including a variety of cytokines and adipokines, such as leptin and adiponectin [Hui et al., 2012; Distel et al., 2009; Klein-Wieringa et al., 2011; Gandhi et al., 2011; Gegout et al., 2008]. Inflammatory activity of the IPFP affects synovial inflammation [Eymard et al., 2014], while high levels of inflammatory mediators are associated with cartilage degradation [Ding et al., 2008; Bao et al., 2010; Kang et al., 2010; Stannus et al., 2015]. The close spatial relation of the IPFP to the synovium-lined knee joint cavity suggests that it may more directly influence inflammatory mediator levels involved in the pathogenesis of knee OA than systemic factors [Clockaerts et al., 2010]. Findings that the IPFP of patients with knee OA display high expression levels of enzymes involved in fat metabolism led to the conclusion that the IPFP may be responsive to the overall nutritional state; reduction in IPFP volume may thus be associated with a reduction in IPFP inflammatory activity and the secretion of inflammatory mediators into synovial fluid, and potentially a reduction in cytokines involved in cartilage degradation, inflammation, and joint pain. The role of the IPFP in inflammatory processes of the knee, however, is still controversial [Berenbaum et al., 2013]. Yet, conditioned adipose tissue medium of the IPFP from OA patients was found to block catabolic processes induced by IL-1β in articular cartilage [Bastiaansen-Jenniskens et al., 2012]. Further, local production of inflammatory mediators in the knee was not only attributed to the IPFP, but also to osteophytes and the synovium [Gegout et al., 2008; Presle et al., 2006]. No intra-articular inflammatory or other cytokine markers were examined in our current study; hence, follow-up studies, preferably with intra-synovial aspiration, will need to address whether there

exists a direct relationship between diet- and exercise-induced reduction in IPFP volume and inflammation. Messier et al. reported, among overweight and obese adults with knee OA, knee compressive forces to be lower after 18 months of D intervention compared with E, concentrations of IL-6 to be lower with D+E intervention compared with E, and knee pain levels to be lower (and knee function better) with D+E intervention compared with both D and E interventions [Messier et al., 2013]. The D+E intervention group also had better physical health-related quality of life scores than the E intervention group. In extension to the original study [Messier et al., 2013], it was further shown that a) weight loss led to a reduction in bone mineral density at the femoral neck and hip, irrespective of whether diet was combined with exercise intervention or not [Beavers et al., 2014], b) high subcutaneous fat had similar significant associations with knee joint forces as abdominal fat despite its much smaller volume and thus could be an important therapeutic target for patients with knee OA [Messier et al., 2014], c) intentional total body fat mass and abdominal fat volume reductions were independently associated with significant reductions in inflammatory serum markers [Beavers et al., 2015], and d) despite the potent effects of weight loss on symptoms and mechanistic outcomes there was no statistically significant difference between the three active interventions on radiographic joint space width change, quantitative cartilage thickness loss, or semi-quantitative measures of Hoffa-synovitis and joint effusion [Hunter et al., 2015]. However, whether symptomatic improvement and increased physical health-related quality of life scores observed with the diet and exercise intervention [Messier et al., 2013] is mediated by longitudinal change in the IPFP volume, or whether the latter should rather be considered as an “innocent bystander” in this process is beyond the focus and design of this report, and may be elucidated in further studies.

In summary, the IPFP, a potential link between obesity and knee OA, was sensitive to intervention by diet-induced weight loss and/or exercise in overweight or obese patients with symptomatic knee OA. The reduction in IPFP volume correlated with individual level of weight and body fat change. Diet in combination with exercise appeared to be more effective in reducing IPFP volume than exercise alone.

Acknowledgments

Financial support: Support for the study was provided by grants from the National Institutes of Health: R01397 AR052528-01, P30 AG21332, M01-RR00211, and General Nutrition Centers, Inc.. Support for the image analysis of the IPFP was received from the Paracelsus Medical University Forschungsförderungsfond (PMU FFF) R-14/0/061/WIT. The funding sources were not involved in the study design and in the statistical analysis of the data. These data have been submitted as diploma thesis titled: “Impact of Diet and/or Exercise Intervention on Infrapatellar Fat Pad Morphology - A Secondary Analysis from a Randomized Controlled Trial” by Aarón Leonardo Pogacnik Murillo in April 2015 for obtaining the academic degree of Medical Doctor (Dr. med. univ.) at Paracelsus Medical University, Salzburg, Austria. This diploma thesis is publically available at http://www.rheumatologie.at/pdf/Pogacnik_Aaron_Diplomarbeit.pdf. We would like to thank Anja Ruhdorfer, MD, PhD, Eva Steidle, PhD and Torben Dannhauer, PhD at the Institute of Anatomy at Paracelsus Medical University for their support and critical discussion of IPFP segmentation in this study.

List of abbreviations

3D	three-dimesional
BMI	body mass index

CI	confidence interval
CT	computed tomography scans
CV	coefficients of variation
D	diet intervention group
D + E	diet plus exercise intervention group
DXA	dual energy x-ray absorptiometry
E	exercise intervention group
Fig	figure
FR	frequency
IDEA	Intensive Diet and Exercise for Arthritis trial
IL	interleukin
IPFP	infrapatellar fat pad
KLG	Kellgren-Lawrence grade
MC	mean change
MR	magnetic resonance
n	sample size
OA	osteoarthritis
SD	standard deviation
vs	versus

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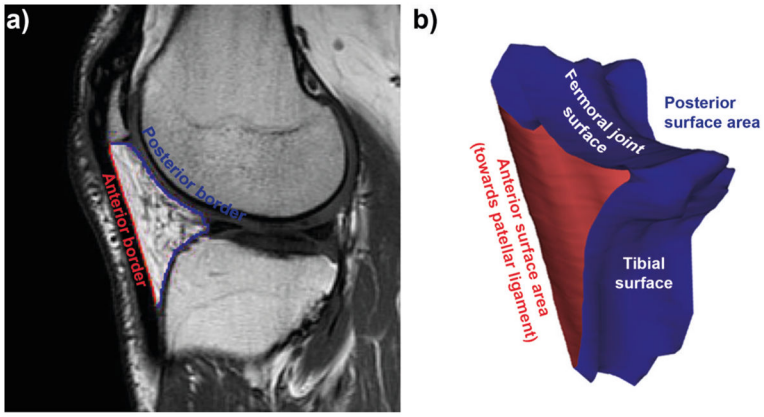

Figure 1.

a) Sagittal MR image showing the segmentation of the infrapatellar fat pad (IPFP) anterior surface (red, facing the patellar ligament) and posterior surface (blue, facing the inferior patellar pole, the distal femur and proximal tibia).

b) 3D reconstruction of the IPFP; posterior view. The anterior surface area is colored in red and the posterior (femoral and tibial) surface area in blue.

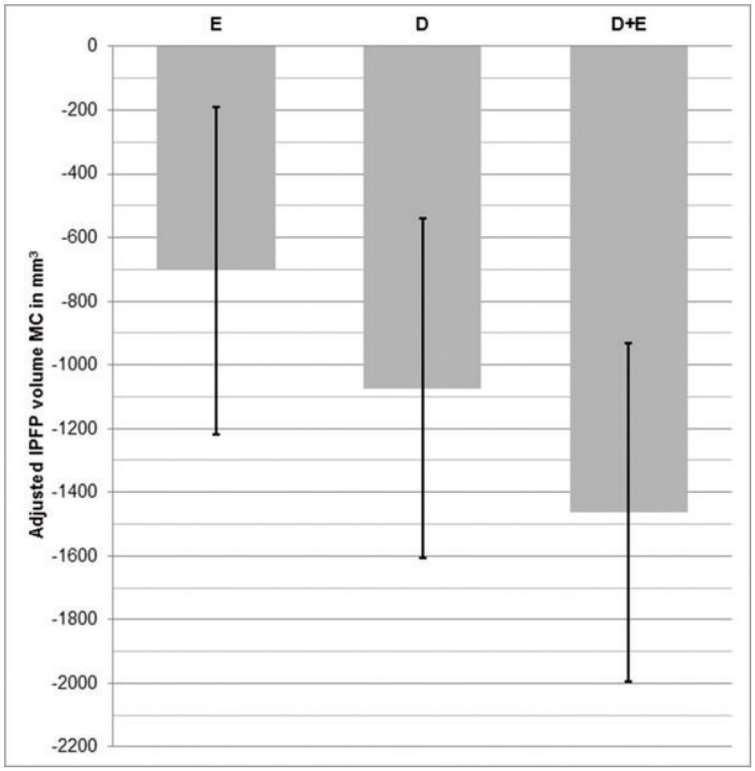

Figure 2.

Mean changes (MC) between baseline and 18-month follow-up in infrapatellar fat pad (IPFP) volume in the exercise (E), diet (D) and diet + exercise (D+E) intervention groups, adjusted for baseline values of the outcome, baseline BMI, and sex. Error bars represent 95% confidence interval.

Table 1

Baseline characteristics in the exercise (E), diet (D) and diet + exercise (D+E) intervention groups.

Intervention group	**All**		**E**		**D**		**D+E**	
n=	**106**		**36**		**35**		**35**	
	Mean or FR	**SD or %**	**Mean or FR**	**SD or %**	**Mean or FR**	**SD or %**	**Mean or FR**	**SD or %**
Demographics								
BMI [kg/m^2]	33.9	±3.8	33.7	±3.7	34.3	±4.1	33.7	±3.7
Body weight [kg]	93.5	±14.0	91.6	±13.0	96.9	±15.7	91.9	±13.0
Sex [female]	77	72.6	27	75.0	24	68.6	26	74.3
[male]	29	27.4	9	25.0	11	31.4	9	25.7
IPFP parameter								
Volume [cm^3]	26.7	±7.0	25.3	±6.3	28.0	±7.6	26.6	±6.9
Anterior surface area [cm^2]	24.6	±5.6	24.1	±5.5	25.3	±6.2	24.4	±5.3
Posterior surface area [cm^2]	37.3	±7.8	35.9	±7.4	38.7	±8.9	37.4	±6.9
Mean thickness [mm]	6.5	±0.6	6.4	±0.5	6.6	±0.7	6.5	±0.7
Maximal thickness [mm]	15.0	±1.6	14.9	±1.5	15.3	±1.6	14.9	±1.6

n = sample size, IPFP = infrapatellar fat pad, FR = frequency, SD = standard deviation

Table 2

Mean changes within exercise (E), diet (D) and diet + exercise (D+E) intervention groups between baseline and 18-month follow-up in BMI, body weight and infrapatellar fat pad (IPFP) morphology; results for IPFP morphology were adjusted for baseline values of the outcome, baseline BMI, and sex.

Intervention group	**E (95% CI)**	**D (95% CI)**	**D+E (95% CI)**
n=	**36**	**35**	**35**
Anthropometrics			
BMI [kg/m^2]	−0.26 (−0.74, 0.22)	−3.45 (−4.46, −2.43)	−4.31 (−5.43, −3.20)
Body weight [kg]	−0.89 (−2.16, 0.39)	−10.18 (−13.16, −7.21)	−11.93 (−14.86, −9.01)
IPFP parameter			
Volume [mm^3]	−704^a (−1217, −190)	−1074^b (−1607, −540)	−1462^b (−1994, −930)
Anterior surface area [mm^2]	−20.7 (−73.5, 32.1)	−25.4 (−78.5, 27.6)	−71.4^a (−120.0, −17.8)
Posterior surface area [mm^2]	−90.3^a (−156.7, −24.0)	−141.9^b (−210.2, −73.6)	−182.0^b (−250.5, −113.5)
Mean thickness [mm]	0.00 (−0.09, 0.10)	0.00 (−0.09, 0.10)	−0.01 (−0.10, 0.09)
Maximal thickness [mm]	0.00 (−0.25, 0.25)	−0.16 (−0.42, 0.09)	−0.06 (−0.32, 0.19)

CI = confidence interval,

^{a} p<0.01,

^{b} p<0.001

Table 3

Pairwise comparisons between intervention groups for mean changes (MC) in infrapatellar fat pad (IPFP) morphology between baseline and 18-month follow-up, adjusted for baseline values of the outcome, baseline BMI, and sex.

Intervention group	E vs. D (95% CI)	E vs. D+E (95% CI)	D vs. D+E (95% CI)
IPFP parameter			
Volume [mm^3]	370 (−328, 1068)	759[a] (68, 1450)	389 (−307, 1085)
Anterior surface area [mm^2]	4.7 (−65.9, 75.4)	50.7 (−19.7, 121.0)	45.9 (−25.1, 117.0)
Posterior surface area [mm^2]	51.6 (−38.6, 141.7)	91.7[a] (2.3, 181.0)	40.1 (−49.8, 130.1)
Mean thickness [mm]	0.00 (−0.13, 0.13)	0.01 (−0.11, 0.14)	0.01 (−0.11, 0.14)
Maximal thickness [mm]	0.17 (−0.18, 0.51)	0.07 (−0.27, 0.40)	−0.10 (−0.44, 0.24)

CI = confidence interval,

[a] $p<0.05$, E = exercise, D = diet, D+E = diet + exercise, vs. = versus

Table 4

Spearman correlations between infrapatellar fat pad (IPFP) volume changes and changes in body composition predictors. Sample sizes (n) vary based on predictor.

	n	Correlation	P-value
Body or thigh composition predictor			
Weight change [kg]	106	0.40	<0.0001
BMI change [kg/m^2]	106	0.39	<0.0001
DXA total fat mass change [kg]	88	0.44	<0.0001
CT subcutaneous thigh fat change [cm^3]	82	0.32	0.0030
CT inter-muscular thigh fat change [cm^3]	82	0.29	0.0074

BMI = body mass index; DXA = dual x-ray absorptiometry, CT = computed tomography