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Effects of Dietary Weight Loss with and without Exercise on Interstitial Matrix Turnover and Tissue Inflammation Biomarkers in Adults with Knee Osteoarthritis: The Intensive Diet and Exercise for Arthritis Trial (IDEA)

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Summary

Objective—To examine the effects of dietary weight loss, with and without exercise, on selected soluble biomarkers in overweight and obese older adults with symptomatic knee OA.

Design—Blood samples were analyzed from 429 participants in the IDEA trial randomized to either an 18 month exericse control group (E), weight loss diet (D), or D+E. C1M, C2M, C3M and CRPM biomarkers and IL-6 were quantitated using ELISAs. Radiographic progression was defined as a decrease in joint space width of ≥ 0.7mm. Statistical modeling of group means and

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Author contributions

Study conception and design: all authors
Analysis and interpretation of the data: all authors
Drafting of the article: RL, DB, and AB-J who also take responsibility for the integrity of the work as a whole
Critical revision of the article for important intellectual content: all authors
Final approval of the article: all authors

Conflict of interests

Drs. Anne Bay-Jensen and Morton Karsdal are employees of and hold stock/stock options in Nordic Biosciences. Dr. Ali Guermazi holds stock/stock options in Boston Imaging Core Lab, LLC.

associations used mixed models adjusted for visit, baseline BMI, gender, and baseline values of the outcome.

Results—Compared to the E control group, C1M was significantly lower in the D and D+E groups at both 6 and 18 months while C3M was significantly lower in D and D+E at 6 months and in D+E at 18 months. C2M did not change in any group. Using data from all groups, change in C1M ($p<0.0001$), C3M ($p<0.0001$), as well as CRPM ($p=0.0004$) from baseline to 18 months was positively associated with change in weight. No marker was associated with change in WOMAC pain or radiographic progression. C3M ($p=0.008$) and CRPM ($p=0.028$) were positively associated with change in WOMAC function. Change in IL-6 was positively associated with change in C1M, C3M, and CRPM.

Conclusion—Overweight and obese adults with knee OA who lost weight from diet and diet plus exercise reduced serum markers of interstitial matrix turnover and inflammation but not type II collagen degradation.

Keywords

Osteoarthritis; biomarkers; collagen; weight loss; exercise

Introduction

Exercise and weight loss are effective in reducing pain and improving function in overweight and obese adults with osteoarthritis (OA) of the knee[1, 2]. Based on evidence from a number of successful randomized clinical trials, guidelines for the management of knee OA, including those from the Osteoarthritis Research Society International (OARSI)[3], the American College of Rheumatology[4], as well as several other groups (reviewed in[5]), include exercise and weight loss as key non-pharmacologic recommendations. Although there is substantial evidence in support of exercise and weight loss for symptomatic improvement, it is not clear if these interventions affect joint tissue metabolism or alter structural progression..

A seminal trial in support of the combined approach of exercise and weight loss was the Intensive Diet and Exercise for Arthritis (IDEA) trial[2]. The IDEA trial demonstrated that, compared to an exercise control group, an 18 month intervention that combined dietary-induced weight loss with exercise resulted in significant improvements in pain and function, measured using the WOMAC instrument, as well as a significant reduction in plasma IL-6 as a marker of inflammation. The diet only group also exhibited a significant decrease in knee compressive forces. Despite these improvements, there were no significant differences in changes in knee joint structural outcomes, including radiographic joint space narrowing and, in a subset of participants, MRI measures[6].

In addition to imaging, there is significant interest in developing biochemical markers that could be used to monitor the effects of an intervention on the joint tissues affected by OA, including the articular cartilage, bone, synovium, and other soft-tissue structures[7]. These include markers of type II collagen and aggrecan degradation and synthesis, as well as degradation of other extracellular matrix (ECM) proteins such as cartilage oligomeric

protein (COMP)[8] and type III collagen[9]. The degradation of ECM proteins in OA joints is primarily mediated by enzymes of the matrix metalloproteinase (MMP) family. MMP-mediated degradation occurs at specific sites within ECM proteins resulting in protein fragments that can be recognized by site-specific “neoepitope” antibodies[10]. To date, two of the most commonly studied ECM degradation markers have been type II collagen, which is predominately found in the articular cartilage, and type I collagen, found in bone and fibrous soft-tissues[7, 8].

Although a number of biochemical markers of joint tissue turnover have been developed and tested, most studies have been limited to cross-sectional studies of people with and without OA or observational studies of OA progression[11]. The objectives of our study were to examine the change in levels of biochemical markers of collagen degradation and tissue inflammation in blood samples that had been obtained from participants during the IDEA trial and to determine the association of selected clinical outcomes, including radiographic progression, with the change in biomarker levels over the course of the interventions. For this study, which represents a secondary analysis of the IDEA trial, markers of MMP-mediated degradation of type I (C1M), type II (C2M), and type III (C3M) collagen were measured, as well as a marker of C-reactive protein (CRP) degradation (CRPM). These markers have been suggested to measure inflammation-mediated tissue destruction including that caused by synovitis[12, 13].

Methods

Study Participants

Blood samples and radiographs used for our study were collected from participants in the IDEA trial (NCT00381290) which was an 18-month prospective, single-blind, randomized controlled trial that enrolled 454 overweight and obese ($27.0 \leq BMI \leq 40.5$ kg/m^2), older (age ≥ 55 yrs) adults with knee pain and radiographic evidence of tibiofemoral osteoarthritis (Kellgren Lawrence grade = 2 or 3) with or without mild or moderate patellofemoral OA. Details of the inclusion and exclusion criteria and study design, as well as the main outcomes, have been previously published[2, 14]. Participants were allowed to use non-steroidal anti-inflammatory drugs (NSAIDs) or discontinue use during the course of the study in consultation with the physician managing their OA. Data on NSAID use was only available at baseline.

Participants were randomized to one of three 18-month interventions: intensive dietary weight loss-only; intensive dietary weight loss-plus-exercise; or exercise-only control. Blood samples were collected at baseline, 6 and 18 months and knee radiographs at baseline and 18 months. Blood was collected in the early morning after a 10-hour fast and processed to produce serum (used for the C1M, C2M, C3M, and CRPM assays) and plasma (used for the IL-6 assays), which were stored as aliquots at −80°C until used for analysis. The 6- and 18-month samples were collected at least 24 hours after the last acute bout of exercise training and sampling was postponed (1–2 weeks after recovery from symptoms) in the event of an acute respiratory, urinary tract, or other infection. Bilateral, posteroanterior, weight-bearing, knee x-rays were obtained with the participants’ knees flexed at 15 degrees using a positioning device (Synaflexer) as described[6].

Analysis of biochemical markers

The four biochemical markers (CRPM, C1M, C2M and C3M) were assessed using solid phase competitive ELISAs as previously described[15–18]. In brief, a 96-well streptavidin plate was coated with the appropriate biotinylated synthetic peptide dissolved in assay buffer and incubated for 30 min at 20°C. Peptide calibrator or sample was added to appropriate wells, and then 100 uL of a conjugated monoclonal antibody against the target sequence was added to wells and incubated. The mix of primary antibody and samples was incubated for 2 hours at 20°C or 20 hours at 4°C. After thorough washing of the microtiter plate, 100µl tetramethylbenzinidine (TMB) (KemEn-Tec cat.438OH) was added and the plate was incubated for 15 minutes at 20°C in the dark. All the above incubation steps included shaking at 300 rpm. After each incubation step, the plate was washed five times in washing buffer (20 mM Tris, 50 mM NaCl, pH 7.2). The TMB reaction was stopped by adding 100ul of stopping solution (1% HCl) and measured at 450 nm with 650 nm as the reference. The samples were assessed in duplicates including five quality control samples on each microtiter plate. The measurement range of the assays were in the nanomole range for C1M, C3M and CRPM and in the picomole range for C2M, and the intra- and inter-assay CVs were below 15%.

Details of the analysis of plasma IL-6 and the results from the IDEA trial have been previously reported[2].

Radiographic measure of OA progression

The change in joint space width from baseline to 18 months was used as a radiographic measure of disease progression. The methods used to measure joint space width in the IDEA study have been published[6] as well as the criteria used to define progressors and non-progressors[19]. In brief, the minimum joint space width (mJSW) was measured in digitized radiographic images using an automated software application. A radiographic “progressor” was defined as exhibiting a decrease in JSW of ≥ 0.7mm in the medial tibiofemoral compartment from baseline to 18 months, which was based on the OARSI-OMERACT definition of relevant radiological progression[20]. A “non-progressor” was defined as a decrease in JSW of ≤0.35mm. From IDEA participants who had radiographs available at both baseline and 18 months, 76 progressors and 180 non-progressors were available for analysis.

Statistical Analyses

The present biomarker study represents a secondary analysis of data from the IDEA trial. Descriptive statistics were used for baseline characteristics of participants with biomarker data. Biomarker values were log-transformed for all analyses. Treatment group means and pairwise differences were assessed using mixed models adjusted for visit, treatment, the visit by treatment interaction, baseline BMI, gender, and baseline values of the outcome at 6 and 18 months, with visit-specific comparisons estimated using contrast statements. Cohen’s d effect sizes were estimated for diet and diet plus exercise groups compared to exercise alone. Associations between changes in biomarker values and clinical values including weight, pain, and function at 18 months were assessed using multivariable linear regression models adjusted for baseline BMI, gender, and baseline values of the biomarker. Finally, we

compared biomarker changes across OA progression status using ANCOVA at 18 months adjusted for baseline BMI, gender, treatment arm, and baseline value of the outcome. Statistical analyses were conducted using SAS 9.4 (SAS Institute Inc, Cary, NC), and all statistical comparisons were deemed significant when $p<0.05$ without adjustment for multiple comparisons.

Results

The demographic characteristics of the 429 IDEA participants from whom blood samples were available at baseline and 18 months (Table 1) were similar to the 454 individuals reported in the main outcomes paper[2]. On average, 58% of the participants were using NSAIDs at the baseline visit. Patellofemoral OA was present in at least one knee in 71% of the participants and 86% had bilateral tibiofemoral knee OA. There were no differences in these characteristics among the three intervention groups.

The C1M, C2M and C3M biomarkers recognize neoepitopes in types I, II, and III collagen, respectively, that are generated by MMP cleavage of collagen in the soft connective tissues (C1M and C3M) including synovium, tendons and ligaments but not in bone and the articular cartilage (C2M)[12, 13]. The CRPM biomarker recognizes a fragment of CRP and is thought to be a marker of chronic inflammation in OA[12]. The level of C1M declined in all three intervention groups over the course of the study with significantly lower levels at 6 and 18 months when the diet and the diet plus exercise groups were compared to the exercise only control group (Fig. 1A). Compared to exercise only, the effect sizes were −0.26 for diet only and −0.29 for diet plus exercise (Table 2). Likewise, C3M levels declined more in the diet and diet plus exercise groups compared to the exercise control group with significant differences noted at 6 months while at 18 months only diet plus exercise was significantly lower than the exercise controls with an effect size of −0.24 (Fig. 1B and Table 2). CRPM declined in all three groups over 18 months but there was no significant difference among the interventions (Fig. 2A) while C2M did not change in any of the three groups over the course of the study (Fig. 2B).

The decline in C1M and C3M in the diet and diet plus exercise groups compared to exercise alone suggested an association with weight loss since we had found that participants in the diet group lost on average 9.5% of their baseline body weight and the diet plus exercise group lost 11.4% while the exercise only group lost just 2.2% of their body weight[2]. Indeed, using the combined data from all three intervention groups, there was a highly significant positive association between change in weight from baseline to 18 months and change in C1M and C3M ($p<0.0001$) and CRPM ($p=0.0004$), however, change in weight was negatively associated with change in C2M ($p=0.0065$).(Table 3). We also explored the associations between change in the four biomarkers with change in WOMAC pain and function and found positive associations for change in C3M and CRPM with WOMAC function (Table 2).

In a previous study using data from the IDEA trial, we reported that changes in body weight and regional fat mass were positively associated with the change in IL-6[21] and so we determined whether the change in IL-6 was associated with change in the biomarkers. There

were significant positive associations between change in IL-6 and change in C1M, C3M, and CRPM but not C2M (Table 3) which trended toward a negative, rather than a positive association.

Finally, we looked for differences in the change in the biomarkers between radiographic progressors and non-progressors but did not find any significant association with the biomarkers or IL-6 (Table 4).

Discussion

There is significant interest in developing biochemical markers that can be used to measure the effects of interventions for knee OA on joint tissues[22]. In the present study, two potential markers of joint tissue inflammation (C1M and C3M) decreased over the course of an 18-month clinical trial in overweight and obese adults with knee OA assigned to dietary-induced weight loss or exercise plus weight loss interventions compared to an exercise without diet intervention that served as a control group. The decline in C1M and C3M appeared to be driven by the decrease in weight which, as previously reported[2] was significantly greater in the two groups that received the dietary intervention.

The C1M and C3M markers, which are elevated in the serum of patients with rheumatoid arthritis, were reported to decline in response to treatment with the anti-IL-6 antibody tocilizumab in combination with methotrexate[15] suggesting they could be markers of synovial inflammation. In support of this, both markers were increased in the conditioned media of OA synovial explants after treatment with the cytokines TNFα or IL-1β[13]. The finding that the change in IL-6 was associated with the change in both markers in the present study also suggests that these markers are responsive to a change in an inflammatory process. However, we were unable to determine if the change in C1M or C3M was due to a change in synovitis since MRI measures of synovitis were obtained from only 105 of the IDEA participants and synovitis was not found to differ among the three intervention groups at 18 months[6].

Adipose tissue in obese individuals is more inflamed than in non-obese individuals and is an important contributor to systemic inflammation, referred to as “metainflammation”[23]. We had previously shown a significant correlation between reduction in fat mass and decline in plasma IL-6 in the IDEA participants[21]. The present finding that declines in C1M, C3M, as well as CRPM were strongly associated with weight loss and with the decline in IL-6 suggests that metainflammation was reduced in the IDEA participants who lost weight over the 18 month intervention. The negative association between change in weight and change in C2M, albeit weak, is more difficult to explain and may represent a spurious result given that C2M levels did not change significantly in any of the intervention groups over the course of the study.

Finding biochemical markers that correlate with symptoms and disease progression in individuals with OA has been a challenge. However, recent work measuring 18 biomarkers in longitudinal samples from the observational Osteoarthritis Initiative (OAI) study revealed eight biomarkers that predicted OA cases defined as those with knee OA who exhibited

worsening of radiographic changes and pain between the 24 month and 48 month study visits[11]. In that study, the two strongest predictors of case status were urinary markers for type II collagen degradation, uC2C-HUSA and uCTX-II, while serum C2C to measure type II collagen degradation and serum C1,2C for types I and II collagen degradation were not predictive. In addition, serum CTX-I for type I collagen degradation, which reflects bone resorption, was modestly predictive (odds ratio 1.28). This shows that different neoepitopes of the same protein may provide independent information. However, no markers reflecting synovial or connective tissue turnover, other than bone and cartilage, were measured in the OAI cohort, thus it had not been shown whether markers of tissue inflammation would be associated with OA progression.

In the present study, we did not find any relationship between change in the serum markers and radiographic progression, measured as change in joint space width. Also, none of the markers measured were associated with the change in WOMAC pain. However, C3M and CRPM were significantly (albeit weakly) associated with change in WOMAC function. The lack of an association with radiographic progression could be due to the inclusion of only individuals with KL 2–3 OA and small numbers of progressors (n=76) who could be compared to the 180 non-progressors. In addition, the choice of a decrease in JSW of ≤0.35mm as the cut off for a non-progressor is less than the smallest detectable difference which could lead to misclassification and bias towards the null. However, the findings are consistent with our previous report that the interventions did not alter structural progression assessed by JSW on radiographs or cartilage loss by MRI in the subset of 105 participants[6].

There are limitations to this study. This was a secondary analysis using blood samples and data collected from a prior randomized controlled trial that was not designed or powered specifically for biomarker studies. Also the study could not fully evaluate the effects of exercise alone on the biomarkers because the control group in the IDEA trial received an exercise intervention. This was due to prior studies demonstrating the benefits of exercise and the thought that exercise should be part of the standard of care for knee OA. Although the IDEA trial showed marked improvement in pain and function in the diet and diet plus exercise groups, the change in biomarkers did not show strong correlations with the improvement in symptoms other than associations with change in C3M and CRPM with WOMAC function. One potential reason is that the biomarkers are measured in serum samples and so reflect systemic activity while the symptoms reported by the participants using the WOMAC instruments reflect local symptoms. Another is that many factors beyond what is happening in the joint influence how people perceive and report symptoms. This may be why symptoms and radiographic severity of OA do not show strong correlations in most studies.

In summary, using longitudinal data from an 18-month clinical trial of exercise and weight loss for knee OA, serum biomarkers of type I and type III collagen degradation were found to decrease in response to weight loss or exercise plus weight loss interventions when compared to an exercise only group. The decrease in these markers over the course of the study and two systemic markers of inflammation, CRPM and IL-6, were strongly associated with weight loss indicating that overweight and obese adults with knee OA who lose weight experience reduced inflammation at a systemic as well as tissue level.

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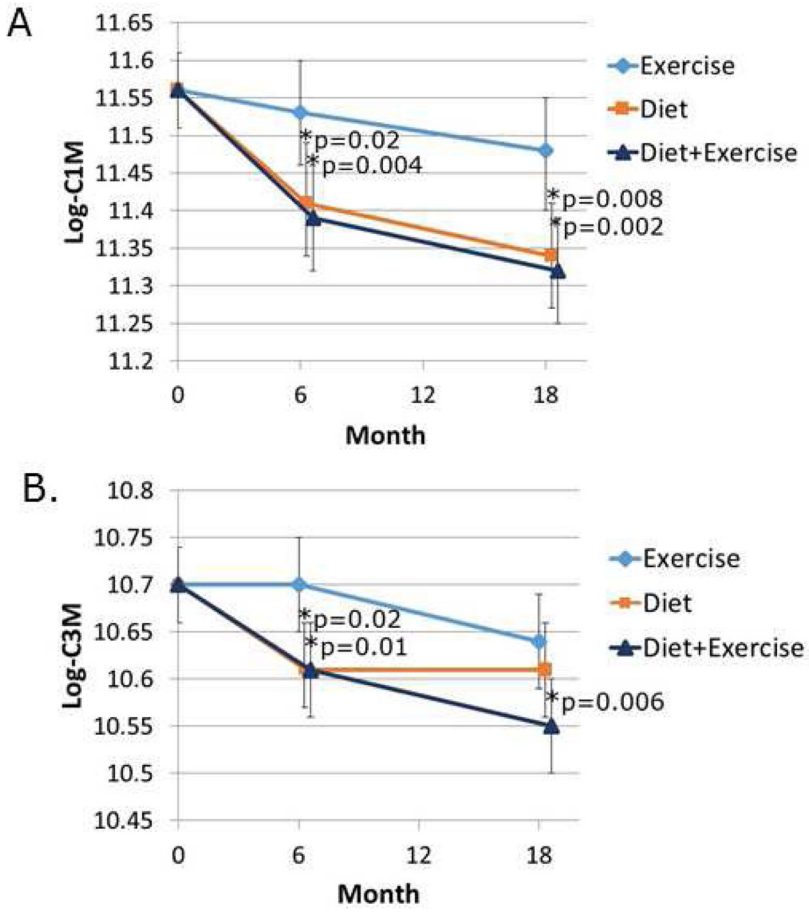

Fig. 1.

Effects of dietary weight loss and exercise interventions on biochemical markers of type I (C1M) and type III (C3M) collagen degradation. Serum samples from baseline, 6 month and 12 month blood collections were assayed for the indicated biochemical markers. The data (expressed as ng/ml) was log transformed and adjusted for baseline values and baseline BMI and gender. Mixed models were used to assess treatment group means and pairwise differences.

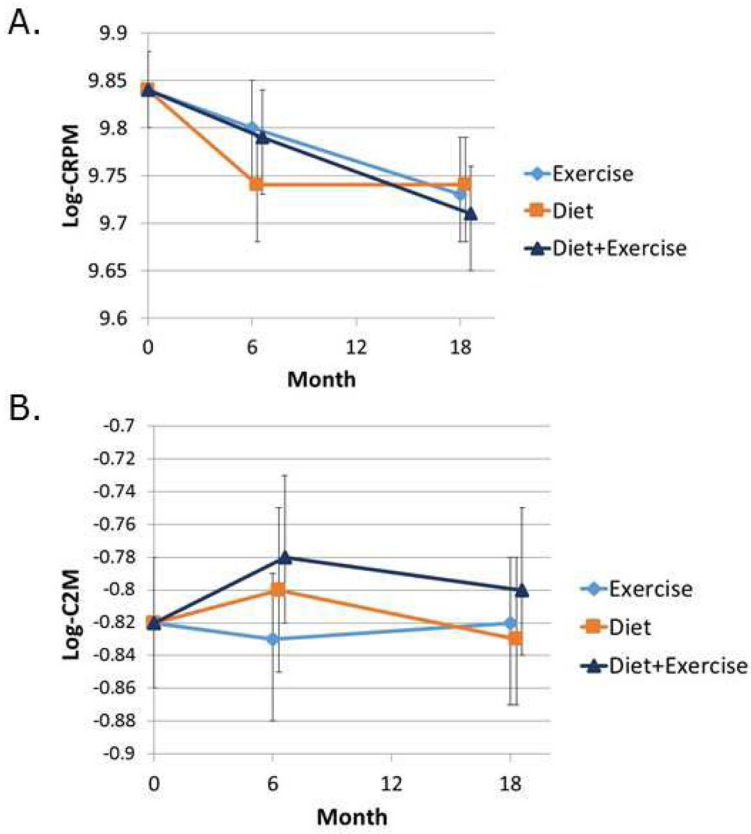

Fig. 2.

Effects of dietary weight loss and exercise interventions on biochemical markers of CRP (CRPM) and type II collagen (C2M) degradation. Serum samples from baseline, 6 month and 12 month blood collections were assayed for the indicated biochemical markers. The data (expressed as ng/ml) was log transformed and adjusted for baseline values and baseline BMI and gender. Mixed models were used to assess treatment group means and pairwise differences.

Table 1

Baseline characteristics of participants

	Exercise Only		Diet Only		Diet+Exercise		All	
Variable	**N**	**Mean ± SD or n (%)**	**N**	**Mean ± SD or n (%)**	**N**	**Mean ± SD or n (%)**	**N**	**Mean ± SD or n (%)**
Age (yrs)	145	65.62 ± 6.42	144	65.94 ± 6.24	140	65.72 ± 6.04	429	65.76 ± 6.22
Female	145	104 (71.7)	144	101 (70.1)	140	101 (72.1)	429	306 (71.3)
White Race	145	118 (81.4)	144	124 (86.1)	140	113 (80.7)	429	355 (82.8)
BMI (kg/m2)	145	33.49 ± 3.73	144	33.63 ± 3.79	140	33.49 ± 3.70	429	33.54 ± 3.73
Weight (kg)	145	92.30 ± 14.52	144	93.39 ± 15.48	140	92.68 ± 14.38	429	92.79 ± 14.77
Height (cm)	145	165.78 ± 8.96	144	166.31 ± 9.38	140	166.11 ± 9.02	429	166.07 ± 9.10
Gait Speed (m/s)	145	1.22 ± 0.18	144	1.18 ± 0.18	140	1.19 ± 0.19	429	1.20 ± 0.18
KL Grade 2	145	72 (49.7)	144	70 (48.6)	140	67 (47.9)	429	209 (48.7)
Bilateral OA	145	128 (88.3)	144	118 (81.9)	140	121 (86.4)	429	367 (85.5)
PF OA	145	104 (71.7)	144	104 (72.2)	140	96 (68.6)	429	304 (70.9)
NSAID use	145	86 (59.3)	144	83 (57.6)	140	82 (58.6)	429	251 (58.5)
SF-36 Physical	144	36.68 ± 9.07	141	35.81 ± 8.78	139	36.45 ± 9.48	424	36.31 ± 9.10
SF-36 Mental	144	56.40 ± 8.44	141	55.75 ± 8.44	139	57.57 ± 6.41	424	56.57 ± 7.85
WOMAC Pain (0–20)	144	6.15 ± 2.94	144	6.63 ± 2.99	140	6.65 ± 3.41	428	6.48 ± 3.12
WOMAC Function (0–68)	145	23.34 ± 10.21	144	25.03 ± 10.47	140	24.27 ± 11.71	429	24.21 ± 10.80
IL-6 (pg/ml)	145	2.96 ± 2.05	143	3.19 ± 2.35	140	3.29 ± 2.23	428	3.15 ± 2.21

BMI, body mass index; KL, Kellgren Lawrence; PF, patellofemoral; NSAID, non-steroidal anti-inflammatory drug; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; IL-6, interleukin-6

Table 2

Effects of exercise and diet interventions on biomarker levels.

		Exercise Only		Diet Only			Diet & Exercise			
	Baseline	18 months	Change	18 months	Change		18 months	Change		
Description	Mean, SE (95% CI)	Mean, SE (95% CI)	Mean, SE (%)	Mean, SE (95% CI)	Mean, SE (%)	Effect Size	Mean, SE (95% CI)	Mean, SE (%)	Effect Size	P-value (18 months)
Log C1M Mean Result	11.56, 0.03 (11.51, 11.61)	11.48, 0.04 (11.40, 11.55)	−0.08, 0.04 (−0.66)	11.34, 0.04 (11.27, 11.41)	−0.21, 0.04 (−1.82)	−0.26	11.32, 0.04 (11.25, 11.39)	−0.23, 0.04 (−2.00)	−0.29	0.0035
Log C2M Mean Result	−0.82, 0.02 (−0.86, −0.78)	−0.82, 0.02 (−0.87, −0.78)	0.01, 0.02 (−0.84)	−0.83, 0.02 (−0.87, −0.78)	0.00, 0.02 (−0.35)	−0.01	−0.80, 0.02 (−0.84, −0.75)	0.03, 0.02 (−4.20)	0.07	0.5565
Log C3M Mean Result	10.70, 0.02 (10.66, 10.74)	10.64, 0.02 (10.59, 10.69)	−0.05, 0.02 (−0.49)	10.61, 0.03 (10.56, 10.66)	−0.09, 0.03 (−0.82)	−0.09	10.55, 0.02 (10.50, 10.60)	−0.15, 0.02 (−1.37)	−0.24	0.0208
Log CRPM Mean Result	9.84, 0.02 (9.80, 9.88)	9.73, 0.03 (9.68, 9.79)	−0.08, 0.03 (−0.84)	9.74, 0.03 (9.68, 9.79)	−0.08, 0.03 (−0.83)	0.00	9.71, 0.03 (9.65, 9.76)	−0.11, 0.03 (−1.12)	−0.06	0.6922

All 18 month means adjusted for baseline values, baseline BMI and gender. Effect size is based on comparison to the exercise only group.

Table 3

Change in biomarkers over 18 months and associations with change in weight, WOMAC scores and IL-6*

Predictor (change per SD)	Outcome change	Slope (95% CI)	Partial correlation	P-value
Weight	Log-C1M	0.12 (0.08, 0.16)	0.30	<0.0001
Weight	Log-C2M	−0.04 (−0.07, −0.01)	−0.15	0.0065
Weight	Log-C3M	0.08 (0.05, 0.11)	0.28	<0.0001
Weight	Log-CRPM	0.06 (0.03, 0.09)	0.20	0.0004
Log-C1M	WOMAC Pain	0.13 (−0.20, 0.46)	0.04	0.43
Log-C2M	WOMAC Pain	0.09 (−0.24, 0.42)	0.03	0.59
Log-C3M	WOMAC Pain	0.20 (−0.13, 0.53)	0.07	0.24
Log-CRPM	WOMAC Pain	0.26 (−0.07, 0.58)	0.09	0.12
Log-C1M	WOMAC Function	0.65 (−0.38, 1.67)	0.07	0.22
Log-C2M	WOMAC Function	−0.36 (−1.39, 0.67)	−0.04	0.49
Log-C3M	WOMAC Function	1.16 (0.13, 2.19)	0.13	0.027
Log-CRPM	WOMAC Function	1.15 (0.14, 2.16)	0.13	0.026
Log-IL-6	Log-C1M	0.15 (0.11, 0.19)	0.37	<0.0001
Log-IL-6	Log-C2M	−0.03 (−0.06, −0.00)	−0.11	0.045
Log-IL-6	Log-C3M	0.08 (0.05, 0.11)	0.28	<0.0001
Log-IL-6	Log-CRPM	0.07 (0.04, 0.10)	0.23	<0.0001

Model-adjusted estimates of associations between 18-month change in weight (1SD = 8.05 kg) vs. 18-month change in biomarkers or between change in biomarkers and WOMAC pain and function subscales. Associations adjusted for baseline BMI, gender, and baseline value of biomarker.

Table 4

Change in biomarker levels at 18 months in radiographic progressors compared to non-progressors.*

Variable Mean change	Non-progressors N=180	Progressors N=76	P-value
Log C1M	−0.21 (−0.28, −0.15)	−0.21 (−0.30, −0.11)	0.91
Log C2M	0.03 (−0.01, 0.07)	0.03 (−0.02, 0.09)	0.82
Log C3M	−0.13 (−0.17, −0.09)	−0.09 (−0.15, −0.03)	0.29
Log CRPM	−0.12 (−0.17, −0.07)	−0.09 (−0.16, −0.02)	0.53
Log IL-6	−0.20 (−0.29, −0.12)	−0.15 (−0.28, −0.02)	0.44

*Tested using ANCOVA at 18 months, adjusted for baseline BMI, gender, randomization group, and baseline value of the outcome. Progressors defined as change in JSW < −0.7mm, while non-progressors had change in JSW > −0.35.