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Osteoarthritis Cartilage. Author manuscript; available in PMC 2017 September 01.

Published in final edited form as:

Osteoarthritis Cartilage. 2016 September ; 24(9): 1528–1534. doi:10.1016/j.joca.2016.04.002.

Exploratory Secondary Analyses of a Cognitive-Behavioral Intervention for Knee Osteoarthritis Demonstrate Reduction in Biomarkers of Adipocyte Inflammation

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Abstract

Objective—To investigate the effects of pain coping skills training (PCST) and a lifestyle behavioral weight management (BWM) program on inflammatory markers and biomarker associations with pain and function in the OA LIFE study.

Method—Serum samples were available from a subset (N=169) of the overweight or obese knee OA participants in the OA LIFE study that evaluated: PCST, BWM, combined PCST+BWM, or standard care. Inflammatory markers (hsCRP, IL-1ra, IL-1β, IL-6, IL-8, TNF-α, TNFRI, TNFRII, and hyaluronic acid (HA)), and adipokines (leptin and adiponectin) were measured before and after the 24-week treatment period. Biomarkers were assessed for effects of treatment and for associations with change in weight, pain and disability (unadjusted and adjusted for age, race, sex, baseline BMI, and baseline biomarker concentration).

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Contributions

Conception and Design, Acquisition of Data, analyses and interpretation of data: Huebner, Landerman, Somers, Keefe, Guilak, Blumenthal, Caldwell, Kraus

Drafting of the article, Critical revision for intellectual content: Huebner, Landerman, Somers, Keefe, Guilak, Blumenthal, Caldwell, Kraus

Final approval of the version to be submitted: Huebner, Landerman, Somers, Keefe, Guilak, Blumenthal, Caldwell, Kraus

Competing interest statement:

No authors have any financial or personal relationships with people or organizations that could potentially influence their work and conclusions. Examples (employment, consultations, stock ownership, honoraria, paid expert testimony, patent applications, research grants or other funding.

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Results—PCST+BWM was associated with significant reductions in hsCRP (p=0.0014), IL-6 (p=0.0075), and leptin (p=0.0001). After adjustment, there was a significant effect of PCST +BWM on changes in leptin (b=−0.19, p=0.01) and IL-6 (b=−0.25, p=0.02) relative to standard care. Reductions in leptin and IL-6 were significantly correlated with reductions in weight, BMI and WOMAC pain; reductions in IL-6 were correlated with improvements in WOMAC and AIMS physical function. By mediation analyses, weight loss was responsible for 54% of the change in IL-6 and all of the change in leptin.

Conclusions—OA-related inflammatory markers were reduced by a 24-week combined PCST +BWM intervention. This suggests that the inflammatory state can be successfully modified in the context of a readily instituted clinical intervention with a positive clinical outcome.

Keywords

Osteoarthritis; Obesity; Biomarkers; Intervention

Introduction

Obesity is a growing problem throughout the developing world; the most recent data reports the prevalence of obesity among U.S. adults to be 35.6% [1]. Excess weight and obesity increase the risk of incident osteoarthritis (OA) of the knee [2], pain [3], and disability [4]. Obesity is a risk factor whose modification is recommended in all treatment guidelines for OA [5–7]. Despite these recommendations, the presence of generalized pain interferes with positive weight loss behaviors [8]. To address this issue, the OA LIFE study was designed to examine the long-term efficacy of a combined treatment of pain coping skills training and weight management in overweight and obese patients with knee OA.

Obesity often plays a prominent role in knee OA [9] and is a primary and modifiable risk factor for knee OA [10]; however, the mechanisms by which increased body weight and adiposity increase the risk for joint disease are not fully understood and likely involve a combination of biomechanical, metabolic, and behavioral factors [11–13]. Although several past studies have been successful in combining diet and exercise to enable obese individuals with knee pain and/or OA to achieve significant weight loss and reductions in pain and disability [14–17], the OA LIFE study was unique because it demonstrated that a behavioral intervention that addressed both pain and weight simultaneously was more effective in improving pain and reducing weight than interventions that addressed pain and weight alone [18]. Moreover, in response to the combined treatment, the reductions in weight and pain in the primary OA LIFE study were maintained over a one-year period [18]. Specifically, OA LIFE examined the long-term efficacy, over an 18-month period, of a combined intervention (PCST and BWM) on weight, pain, physical and psychological disability (assessed by the WOMAC and AIMS scales), compared to either protocol alone or standard care in overweight and obese individuals with knee OA. The combined treatment of PCST and BWM resulted in more weight loss, decreased physical disability, decreased pain and stiffness, and increased self-efficacy, suggesting that pain coping skills combined with weight management may be a critical component of weight management in overweight and obese OA patients [18].

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Overweight or obese individuals are more likely to have increased levels of inflammatory markers including hsCRP, IL-1ra, IL-1b, IL-6, IL-8, TNF-α, TNFRI and TNFRII [19–22]. Study of these inflammatory molecules secreted from adipose tissue can provide insights into the link between obesity and OA [23]. Weight loss in this population has been shown to be effective at reducing markers of inflammation [24, 25], including both cytokines and adipokines, in response to diet [21, 25, 26], exercise [27], or both [17, 28].

The secondary aim of the study, which is the focus of this report, was to perform an exploratory analysis to determine the effect of the combined intervention of the OA LIFE study on inflammatory markers and adipokines immediately after 24-weeks of treatment, and to analyze the correlations of biomarkers with pain and function outcomes over this time interval. We hypothesized that biomarkers would be more likely to reflect changes indicative of treatment effects, with greater reductions in pro-inflammatory cytokines and adipokines over this time interval, comparing baseline to immediate post-treatment (after the 24-week therapy).

Methods

Participants and Procedures—All study procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. The study design and population have been described previously in detail [18] and the trial has been registered at clinicaltrials.gov (NCT00305890). Briefly, participants were recruited on the basis of being overweight or obese (body mass index [BMI] between 25–42 kg/m^2), meeting ACR criteria for knee OA [29], and having radiographic evidence of knee OA in at least one knee based on the Kellgren-Lawrence grading system [30]; thus it is possible for participants to have a K-L grade of 0 in the unaffected knee. Participants were excluded if they: 1) had a significant medical condition that would increase the risk of an adverse health event during physical activity, 2) had rheumatoid arthritis, 3) used oral corticosteroids regularly, or 4) were already participating in a regular exercise or weight loss program.

After completing a baseline series of questionnaires to assess pain, physical, and psychological disability, participants underwent radiography of the knees and collection of blood and urine for biomarker assessments. Participants were randomized to one of the four treatment groups as described previously [18]: 1) Pain Coping Skills Training alone (PSCT-only), which involved an educational rationale regarding the role of pain coping in the pain experience and systematic training in the use of cognitive and behavioral techniques such as relaxation, meditation, and activity pacing, to enhance pain coping; 2) Behavioral Weight Management alone (BWM-only) which addressed behavioral and psychosocial factors that influence weight management using the LEARN (**L**ifestyle, **E**xercise, **A**ttitudes, **R**elationships, and **N**utrition) to Eat program which emphasizes diet, physical activity and behavioral factors [31]; 3) Combined therapy of PCST and BWM; and 4) a Standard Care control in which participants continued to receive routine care. Participants were assessed immediately following the 24 week treatment period, and at 6 and 12 months post treatment. Biomarker analyses were conducted on the baseline and immediate post treatment (24 week)

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samples from 169 participants, which was the maximum number of participants from which serum samples were available.

Assessments of Pain and Disability—To provide context for the biomarker results, we evaluated whether the clinical outcomes (changes in weight, pain and function from baseline to immediately after the 24-week treatment period) in the subsample available for these secondary analyses (N=169) were representative of the primary study (N=232). Effects of the various treatments on pain, physical, and psychological disability were assessed using the Western Ontario and McMaster Universities Arthritis Index (WOMAC) [32] and Arthritis Impact Measurement Scales (AIMS) [33] questionnaires. The WOMAC was designed to assess pain, stiffness, and physical function in patients with hip and/or knee OA and consists of 24 items divided into 3 subscales: pain during walking, using stairs, in bed, sitting or lying, and standing; stiffness after waking and later in the day; and physical function including assessment of daily activities, which can be reported separately or as an overall score where higher scores reflect a worse condition. The AIMS questionnaire assesses disease-specific measures of physical, social, and emotional well-being as an outcome measure of arthritis. Summary scales range from 0 to 10, with higher scores indicating greater pain and disability.

Assessment of Serum Biomarker Concentrations Pre- and Post-Treatment—Blood samples were collected from each of the participants at baseline and immediately after the 24-week treatment period. Samples were spun at 3500 rpm for 15 minutes and serum aliquots were prepared and stored at −80°C until analyses were performed. Serum concentrations of 11 biomarkers were measured by enzyme linked immunosorbent assay (ELISA): adiponectin (#44-ADPH-0512, ALPCO, Salem, NH;), hsCRP (#AD-401, United Biotech, Mountain View, CA;), hyaluronic acid (HA) (#029-001, Corgenix, Westminster, CO;), Leptin (#EZHL-80SK, Linco, St Charles, MO;), six cytokines (IL-1β, IL-1ra, IL-8, TNF-α, TNFRI, and TNFRII) via a multiplex ELISA with detection by Luminex (#LCP007, Invitrogen, Carlsbad, CA;), and IL-6 using a single-plex high sensitivity and high dynamic range ELISA (#K151AKC-1, MesoScale Discovery, Gaithersburg, MD;). Intra- and inter-assay coefficients of variation for each assay were as follows: adiponectin: 3.1%, 16.3%; hsCRP: 6.5%, 9.1%; HA: 2.5%, 5.5%; leptin: 5.2%, 8.1%; IL-1β: 7.8%, 10.2%; IL-1ra: 5.9%, 20.9%, IL-8: 7.2%, 27.2%, TNF-α: 7.6%, N/A; TNFRI: 6.0%, 11.9%, TNFRII: 6.0%, 33.3%, and IL-6: 4.8%, 14.3%, respectively. All samples yielded measurable concentrations for all biomarkers with the exception of TNF-α, for which only 31% yielded measurable concentrations. For this reason, TNF-α results were excluded from the analyses. All biomarker measurements were conducted in duplicate as per the manufacturer's instructions and blinded to treatment status. Biomarker concentrations and change (from baseline to 24 weeks) were reported as means and uncertainty reported with 95% confidence intervals (lower limit, upper limit). Values for measured biomarkers were log transformed to achieve normality.

Statistical analyses

Assessment of treatment groups at baseline—The subsample used for these analyses (n=169 of the n=232 of OA LIFE study) had baseline and post-treatment samples

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available for analyses. As this subsample differed from the original randomized study sample due to missing biospecimens for some study participants, we used the non-parametric Kruskal-Wallis test to assess for baseline differences in the treatment groups in this subsample with respect to age, sex, race, weight, BMI, OA severity, and measures of pain and disability as assessed by WOMAC or AIMS.

Assessment of effects of the interventions on clinical outcomes—To contextualize the biomarker results from this subsample, the Wilcoxin Signed Rank test was used to evaluate the effects of the change over 24 weeks in clinical outcomes in each treatment group of the subsample, to determine if they were representative of results reported in the primary study.

Assessment of treatment on biomarkers—Change over time in biomarkers by treatment group was assessed with Wilcoxon signed rank test. Although the groups in the subsample were balanced with respect to covariates (described below and in Table 1), linear models were also performed, without and with adjustment, to address potential residual confounding of biomarker concentrations by the covariates and to improve the precision of the estimates. Linear models were used to test for any significant difference in biomarkers by treatment group with all four treatments groups taken together. When significant, results of each treatment group were evaluated for significance with a post-hoc comparison of each treatment group relative to the standard care control. Sensitivity analyses revealed similar results without and with adjustment.

Correlation and mediation analyses—Pearson correlations were used for bivariate analyses to assess the relationship of the changes in biomarker concentrations to changes in weight, BMI, pain, and physical function independent of treatment group. To obtain precise estimates and confidence intervals for indirect effects of the combined intervention via weight change on the biomarker, we used the “INDIRECT” macro described in Hayes [34], controlling for age, race, sex, baseline BMI, and baseline biomarker. All analyses were performed using either SAS or Prism Graph Pad 6.0 and a p value of <0.05 was considered statistically significant.

Results

Two hundred and thirty two participants met study criteria and were randomized into the primary study. Samples and data obtained at baseline and immediately after 24 weeks of treatment were included in these exploratory secondary analyses and were derived from a subset of 169 participants for whom serum samples and complete data for these two time points were available. These participants were on average 59 years of age, having a mean BMI of 34 kg/m^2, 83% female, and 60% white (Table 1). The treatment groups of this subsample did not differ significantly at baseline with respect to age, sex, race, weight, BMI, OA severity, and measures of pain and disability as assessed by WOMAC or AIMS (Table 1). KL grades for each knee ranged from 0–4 with KL3 being the most frequent level of severity.

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Clinical outcomes in this subsample were confirmed to be representative of results reported in the primary study. Namely, the PCST+BWM group experienced the most significant weight loss amounting to 6% over the 24-week treatment period ($p<0.0001$). In this subsample, only the combined treatment group achieved highly significant reductions in all 6 of the WOMAC and AIMS outcomes ($p=0.01$ to <0.0001). Less dramatic weight changes were observed for the PCST (1% gain), BWM (2% loss) and standard care (0% loss) comparators. PCST, BWM and standard care achieved significant reductions in 2 ($p=0.02$ to 0.006), 4 ($p=0.01$ to 0.003) and 2 ($p=0.02$ to 0.003) of the WOMAC or AIMS subscales, respectively.

Mean concentrations of 10 analytes at baseline and after 24 weeks for each treatment group are shown in Table 2. Relative to standard care, there were significant reductions in hsCRP, IL-6, and leptin during the treatment period for only the PCST+BMW combined treatment group and these changes remained significant after adjusting for multiple comparisons. There were no statistically significant differences with treatment among the other 7 analytes measured. By linear models, adjusted for age, race, sex, baseline BMI, and baseline biomarker, there was a group effect of treatment on the change in serum biomarker concentrations of IL-6 ($p=0.03$) and Leptin ($p=0.02$), but not hsCRP ($p=0.18$). There were significant reductions in IL-6 ($b=-0.25$, $p=0.02$) and Leptin ($b=-0.19$, $p=0.01$) in response to only the combined intervention relative to standard care.

Bivariate analyses were used to assess the relationship of the biomarker changes to changes in weight, BMI, pain, and physical function independent of treatment group. A reduction in leptin was significantly associated with a reduction in weight ($r=0.663$, $p<0.0001$), BMI ($r=0.614$, $p<0.0001$), as well as reductions in the WOMAC ($r=0.233$, $p=0.003$) and AIMS ($r=0.165$, $p=0.040$) pain subscales. A reduction in IL-6 was significantly associated with a reduction in weight ($r=0.224$, $p=0.003$), BMI ($r=0.198$, $p=0.01$), and reductions in the WOMAC pain and physical function subscales ($r=0.15$, $p=0.05$ and $r=0.199$, $p=0.01$, respectively), as well as the AIMS physical disability subscale ($r=0.192$, $p=0.018$).

Given the significant relationship between change in biomarker concentrations (IL-6 and leptin) with change in weight, mediation analyses [34] were performed using ‘change in weight’ to determine how much of the group effect of treatment on the change in biomarker concentrations was due to change in weight alone. In mediation analyses, 54% of the differential decline in IL-6 was mediated by weight change (CI 12%, 108%); 100% of the differential decline in leptin was mediated by weight change (CI 58%, 189%). Both mediation effects were estimated controlling for age, race, sex, baseline BMI, and baseline biomarker and were statistically significant.

Discussion

To our knowledge, this is the first study to investigate the impact of a combined pain coping skills training and behavioral weight management intervention for knee OA on biomarkers associated with obesity and inflammation. Over the 24-week treatment period, the combined PCST + BWM intervention group experienced significant reduction in weight, OA

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symptoms and inflammatory markers known to be associated with OA severity such as circulating levels of leptin and IL-6 [35, 36].

The increase in adiposity associated with obesity impacts the production of proinflammatory adipokines, such as leptin [37]. Leptin is produced by adipocytes and has been shown to mediate both metabolic and inflammatory processes [38]. Leptin expression is increased in OA chondrocytes and concentrations in synovial fluid of patients with OA correlate with BMI [39]. A report on the distribution of leptin between serum and synovial fluid of OA patients revealed higher concentrations of leptin in the joint as well as in women who have an increased risk of OA suggesting a possible role for leptin in the development of the disease [40]. In obese mice, leptin levels are highly correlated to OA severity [41], and leptin-deficient mice show morbid obesity but no OA [42]. The results of this study were consistent with these findings, demonstrating that the circulating concentrations of leptin were directly proportional to BMI. Our analyses revealed that over the 24-week treatment period, all of the change in leptin was mediated by the change in weight. Several other studies have reported reductions in leptin with weight loss in knee OA [28, 43]. Although there are well documented benefits of weight loss in persons with knee OA, including reduction in knee joint compressive loads [44], improvement of knee OA symptoms [17, 25, 26], the extent to which reductions in circulating leptin contribute to beneficial clinical outcomes remains uncertain. The fact that leptin, in conjunction with IL-1β, can induce nitric oxide synthase activity [45] and alone, has the ability to stimulate proinflammatory cytokines from adipose tissue including IL-1β, PGE_2, TNF-α, and IL-6 [46] may provide a means by which leptin exerts its effect in mediating the inflammation associated with OA.

Circulating IL-6 concentrations were also significantly reduced by the combined intervention. Half of the change in circulating IL-6 appeared to originate directly from body fat; the other half may originate from the joint itself. The source of excess IL-6 produced both by adipose tissue and the osteoarthritic joint is most likely the macrophage. Macrophages comprise up to 50% of the cell population in obese adipose tissue, but only 5–10% of cells in lean adipose [47]. Macrophages play a direct role in OA as well [48–50]. Patients with OA have varying degrees of synovitis which has been shown to drive symptoms and OA progression and to produce proinflammatory cytokines originating in large part from activated macrophages [50, 51]. Studies in culture in which macrophages were depleted demonstrated the downregulation of macrophage-derived cytokines, IL-1β and TNF-α, as well as inhibition of proinflammatory cytokines produced by synovial fibroblasts (IL-6 and IL-8) and matrix metalloproteinases, providing evidence that these degradative pathways are macrophage-driven [48]. This same study reported that treatment of OA synovial cell cultures with etanercept (a human recombinant TNFα receptor) and neutralizing IL-1β antibody inhibited the production of IL-6 and IL-8 by 60%. More recent studies have been able to demonstrate direct *in vivo* evidence of activated macrophages in the joint and their association with OA pain and symptoms [50] suggesting that drugs targeting macrophages or macrophage-associated inflammatory pathways may decrease OA symptoms. Therefore, a non-pharmacologic treatment including PCST + BWM that reduces IL-6 and promotes weight loss (responsible for half the decline in IL-6 from the combined intervention), may be a more attractive treatment for patients in early stages of disease. Furthermore, other cytokines and adipokines may have catabolic effects on joint tissues [52],

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and additional studies of the metabolic and inflammatory influences of obesity are needed to determine the mechanisms linking obesity and OA.

A total of 10 inflammatory biomarkers were assessed in this subset of subjects, but only IL-6 and leptin demonstrated significant reductions with the combined intervention. HA is presumed to reflect synovial inflammation of OA, however, no significant reductions in HA were observed in subjects who received the combined intervention. This may be explained by the fact that, in contrast to IL-6 and leptin that are both produced by adipocytes, HA is produced by synoviocytes and chondrocytes. The dichotomy between IL-6 and leptin compared with HA suggests that the immediate effect of PCST+BWM over 24 weeks is primarily on adipose derived inflammation as opposed to a change in synovial inflammation. Given that the reductions in IL-6 and leptin were largely or completely mediated by weight loss, it is not surprising that the PCST and BWM alone groups did not demonstrate significant reductions in these biomarkers relative to standard care, as the amount of weight loss in these two groups in this subset of patients was more modest (6% loss, 1% gain, and 2% loss for the combined treatment, PCST alone, and BWM alone groups, respectively).

A limitation of this study was that we were not able to demonstrate a difference between the three active treatment groups, but rather the effects of each treatment group relative to standard care. A larger study would be warranted to evaluate relative differences between active treatments. A second limitation of this study was the higher than desirable inter-assay (plate-to-plate) coefficients of variation for analytes measured via a multiplex (Luminex) ELISA. This might in part explain why significant differences were not observed for the inflammatory cytokines measured by this technology. Another limitation of this study was that we confined the analysis to the immediate post-treatment timepoint biomarker outcomes. However, we chose this strategy because this time point had the greatest number of available specimens for analysis and we hypothesized that the greatest chance of observing changes in biomarkers would be at the time point immediately following the intervention. Given the promising results identified in this study for the immediate post-intervention time point, it would be of interest in future to evaluate the sustainability of these biomarker changes. In summary, this study demonstrated that both the clinical symptomatology and systemic inflammatory state can be successfully modified with a unique combined non-pharmacological clinical intervention. Neither the pain coping skills nor weight loss alone treatment was sufficient to bring about significant change in clinical outcomes or inflammatory markers at 24-weeks, suggesting that pain coping skills may be a critical component of a successful intervention in overweight and obese OA patients. Since it is typically delivered by psychologists who are not typically available in primary practices, providing PCST as an intervention for patients with OA can be challenging. However, recently, this combined intervention of PCST and exercise was successfully delivered by a trained physiotherapist to patients with knee OA experiencing pain [53], illustrating that it may be possible for well-trained non-psychologists to safely and effectively provide a combined intervention that will greatly benefit the growing OA population.

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Acknowledgments

Supported in part by NIH Grants P01 AR 050245, P30 AG028716, R01 AG15768, R01 AG46927, and the Arthritis Foundation.

We would like to acknowledge and thank the following individuals for their contributions to this program of research: Michael A. Babyak, PhD, Linda W. Craighead, PhD, John Rice MD, Daphne C. McKee, PhD, Laura J. Lacaille, PhD, Rebecca A. Shelby, PhD, Lisa Campbell, PhD, Jennifer J. Pells, PhD, Ersela L. Sims, PhD, Robin Queen, PhD, James W. Carson, PhD, Mark Connelly, PhD, Kimberly E. Dixon, PhD, William J. Rejeski, PhD, Daniel Schmitt, PhD.

Role of the funding source:

This study was supported in part by NIH Grants P01 AR 050245, P30 AG028716, R01 AG15768, R01 AG46927, and the Arthritis Foundation. The study sponsors had no role in the study design, collection, analysis and interpretation of the data, in the writing of the manuscript or in the decision to submit the manuscript for publication.

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Table 1

Baseline characteristics of the OA LIFE subset of subjects utilized for the biomarker study.

		Total N=169	PCST only N=42	BWM only N=42	PCST+BWM N=49	SC N=36	P value*
Sex, N (% female)		140 (83%)	30 (72%)	37 (88%)	44 (90%)	29 (81%)	0.0927
Non-white, N (%)		68 (40%)	17 (40%)	16 (38%)	20 (41%)	15 (42%)	0.9896
Age, mean (CI) in years		58.7 (57.2, 60.2)	59.1 (55.5, 62.8)	58.9 (56.0, 61.7)	58.3 (55.5, 61.1)	58.5 (55.1, 61.9)	0.9780
[Range]		[37–83]	[37–82]	[41–76]	[39–83]	[44–79]	
Weight, mean (CI) in lbs		205.7 (200.8, 210.7)	213.0 (201.9, 224.0)	202.0 (191.9, 212.2)	203.5 (193.9, 213.0)	204.7 (195, 214.4)	0.5633
[Range]		[134–297]	[153–297]	[137–280]	[134–278]	[138–260]	
BMI, mean (CI) in kg/m^2		34.1 (33.4, 34.8)	35.0 (33.7, 36.3)	33.5 (32.1, 34.8)	34.0 (32.7, 35.4)	33.9 (32.4, 35.4)	0.4199
[Range]		[25–43]	[27–42]	[25–42]	[25–42]	[27–43]	
Kellgren-Lawrence grade, % grade		7/15/18/	6/8/18	6/20/12	6/18/17	11/13/26	0.4813
0/1/2/3/4/TKR		38/18/3	46/18/4	43/17/2	35/20/3	28/18/4	
WOMAC	Pain	43.5 (40.4, 46.6)	44.2 (36.7, 47.7)	42.1 (36.7, 47.7)	44.3 (38.3, 50.4)	42.9 (35.1, 50.7)	0.9326
	Stiffness	54.8 (51.0, 58.5)	53.5 (45.9, 61.2)	49.9 (42.7, 57.2)	60.1 (53.5, 66.6)	54.6 (45.2, 64.0)	0.2281
	Physical Function	45.7 (42.6, 48.9)	46.5 (40.3, 52.8)	42.7 (37.6, 47.8)	46.8 (40.5, 53.2)	46.9 (38.3, 55.5)	0.7785
AIMS	Pain	5.4 (5.1, 5.7)	5.5 (5.0, 6.0)	5.1 (4.6, 5.6)	5.5 (5.0, 6.1)	5.6 (4.8, 6.3)	0.6258
	Psychological Disability	2.9 (2.7, 3.1)	2.9 (2.4, 3.3)	3.1 (2.5, 3.7)	2.7 (2.2, 3.1)	3.0 (2.5, 3.5)	0.7320
	Physical Disability	1.6 (1.4, 1.7)	1.7 (1.3, 2.0)	1.3 (0.9, 1.6)	1.6 (1.3, 2.0)	1.7 (1.3, 2.1)	0.1665

PCST = pain coping skills training; BWM= behavioral weight management; SC = Standard Care

Data shown as Mean with 95% Confidence Intervals

*P-values determined by non-parametric 1-way ANOVA (Kruskal-Wallis test)

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Table 2

Serum biomarker concentrations (mean (95% CI)) at baseline and 24 weeks for each treatment group.

Biomarker	PCST-only		BWM-only		PCST+BWM		Standard Care	
	Baseline	**Post Tx**	**Baseline**	**Post Tx**	**Baseline**	**Post Tx**	**Baseline**	**Post Tx**
Adiponectin (ng/ml)	11470 (7529,15411)	9080 (8156, 10004)	10683 (8731,12635)	10443 (8647, 12249)	9337 (8194,10480)	9641 (8436, 10846)	9468 (8014,10922)	9211 (7598, 10825)
hsCRP (ng/ml)	6483 (4386, 8579)	6586 (3419, 9753)	5280 (3561, 6999)	5880 (3667, 8092)	**7098 (5110, 9087)**	**5422$^{\#}$ (3241, 7602)**	6727 (3695, 9758)	8204 (3649, 12759)
Hyaluronan (ng/ml)	80 (57, 103)	89 (64, 114)	74 (54, 94)	95 (66, 124)	74 (52, 95)	81 (60, 103)	76 (56, 96)	87 (65, 110)
IL-1β (pg/ml)	238 (136, 340)	278 (150, 407)	441 (259, 623)	388 (225, 551)	988 (−325, 2300)	1003 (−358, 2364)	397 (146, 648)	452 (173, 731)
IL-1Ra (pg/ml)	4031 (2308, 5753)	5231 (2931, 7530)	8485 (4568, 12401)	7111 (4101, 10122)	8614 (2664,14565)	8407 (2084, 14730)	16365 (−145, 32875)	14154 (4045, 24264)
IL-6 (pg/ml)	1.26 (1.03,1.50)	1.32 (0.91, 1.70)	1.08 (0.91, 1.25)	1.26 (1.05, 1.48)	**1.65 (1.13, 2.18)**	**1.19$^{\pm}$ (0.93, 1.45)**	1.69 (1.08, 2.31)	1.67 (1.02, 2.32)
IL-8 (pg/ml)	92 (70,114)	97 (71, 123)	129 (74,185)	131 (61, 202)	95 (78, 113)	95 (77, 113)	99 (72, 127)	94 (74, 113)
Leptin (ng/ml)	45 (36, 53)	45 (37, 53)	49 (41, 58)	43 (35, 52)	**52 (46, 59)**	**43* (37, 50)**	50 (41, 60)	49 (38, 60)
TNFRI (pg/ml)	4196 (3618, 4774)	3996 (3496, 4497)	4579 (4060, 5098)	4553 (4166, 4940)	4947 (3910, 5984)	4794 (3732, 5857)	6822 (3647, 9996)	6529 (4581, 8477)
TNFRII (pg/ml)	2907 (2475, 3339)	2878 (2441, 3315)	3234 (2658, 3811)	3330 (2712, 3949)	3639 (3049, 4229)	3711 (3096, 4326)	3371 (2739, 4003)	3467 (2664, 4270)

PCST = pain coping skills training; BWM = behavioral weight management; SC = Standard Care; Tx=treatment.

Values in bold represent a significant change over time for hsCRP, IL-6, and Leptin in the PCST+BMW combined treatment group as determined by the non-parametric, Wilcoxon signed rank test.

$^{\#}$p=0.0014;

$^{\pm}$p=0.008

*p=<0.0001.