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Biomarker clusters differentiate phenotypes of lumbar spine degeneration and low back pain: The Johnston County Osteoarthritis Project

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Abstract

Objective: Describe the association between biomarkers and lumbar spine degeneration (vertebral osteophytes [OST], facet joint osteoarthritis [FOA], and disc space narrowing [DSN]),

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Author contributions

All authors of this work have made substantial contributions to the conception and design, acquisition of data, analysis, interpretation, drafting of manuscript and final approval of submission.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ocarto.2022.100270.

Declaration of competing interest

All authors disclose they have no financial or personal relationships with other people or organizations that could potentially and inappropriately bias their work and conclusions.

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for persons with and without low back pain (LBP) and determine whether clusters based on biomarkers differentiate lumbar spine structure with and without LBP.

Methods: Using data from the Johnston County Osteoarthritis Project (2006–2010), we measured serum N-cadherin, Keratin-19, Lumican, CXCL6, RANTES, HA, IL-6, BDNF, OPG, and NPY, and urinary CTX-II. Biomarkers were used to group participants using k-means cluster analysis. Logistic regression models were used to compare biomarker clusters.

Results: The sample consisted of 731 participants with biospecimens and lumbar spine radiographic data. Three biomarker subgroups were identified: one characterized by structural degenerative changes; another characterized by structural degenerative changes and inflammation, with pain; and a referent cluster with lower levels of biomarkers, pain, and structural degenerative changes. Compared to the referent subgroup, the structural change subgroup was associated with DSN (OR = 1.94, 95% CI 1.30–2.90) and FOA (OR = 1.72, 95% CI 1.12–2.62), and the subgroup with structural degenerative change, inflammation, and pain was associated with OST with LBP (OR = 1.60, 95% CI 1.04–2.46), FOA with LBP (OR = 1.59, 95% CI 1.04–2.45), and LBP (OR = 1.63, 95% CI 1.11–2.41). The subgroup with structural degenerative changes was more likely to have OST (OR = 1.82, 95% CI 1.06–3.13) and less likely to have FOA with LBP (OR = 0.62, 95% CI 0.40–0.96) compared to the group with inflammation and pain.

Conclusion: Clustering by biomarkers may assist in differentiating patients for specific clinical interventions aimed at decreasing LBP.

Keywords

Low back pain; Biomarkers; Phenotype; Spine osteoarthritis; Lumbar osteoarthritis

1. Introduction

Chronic low back pain (LBP) impacts over 31 million Americans [1] and has increased threefold in prevalence over a 10-year period [2], resulting in $100-$200 billion per year in total U.S healthcare expenditures [3]. Chronic LBP is associated with a number of etiologies, including degeneration of the intervertebral disc (IVD), vertebral osteophytes (OST), and facet joint osteoarthritis (FOA) [4–8]. However, determining which, if any, of these structures contributes to the development of LBP is a major clinical challenge. Therefore, improving the classification of individuals who may have specific structural degeneration linked with chronic LBP may lead to advances in tailored clinical intervention delivery.

Positive associations have been found between biochemical biomarkers and lumbar spine disc space narrowing (DSN), OST, and FOA [9–13]. For example, urinary type II collagen (CTX-II) and serum hyaluronic acid (HA) reflect differences in the etiological process of degeneration between DSN, OST, and FOA [9,10]. Our recent pilot study identified several significant associations between DSN and individual biomarkers related to inflammation; osteoprotegerin (OPG) [14], interleukin-6 (IL-6) [15], and pain neuropeptide-Y (NPY) [11]. In addition, we identified clusters of biomarkers, significantly associated with DSN, representing different combinations of biomarkers associated with structure (Lumican [16], Keratin-19 [17,18]), inflammation (OPG [14], RANTES [19]), and pain (NPY [11]). The

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findings from this small cluster analysis suggested that subgroups of participants may be distinguished by biochemical biomarkers reflecting different phenotypes of DSN. Previous studies have not examined these biochemical biomarkers in groups of participants with and without lumbar spine structural changes to determine whether these markers differentiate LBP from lumbar spine degeneration.

Phenotype development has the potential to impact clinical outcomes by differentiating individuals who may be at high risk for a potential outcome or are more likely to respond to a particular intervention [20]. This may be especially important when a substantial amount of heterogeneity exists within a clinical condition, such as LBP. As such, this study has two main objectives: 1) to describe the association between individual biomarkers and lumbar spine degeneration for persons with or without LBP, and 2) to determine whether clusters based on systemic biomarker profiles differentiate lumbar spine structure with versus without LBP. We hypothesized that biochemical biomarkers known to be related to changes in spine structure, inflammation, and pain would help identify underlying structural or symptomatic changes; these findings may help to differentiate DSN, OST, or FOA with versus without LBP.

2. Methods

2.1. Participants

Details of the sampling strategy and recruitment methods, the Johnston County Osteoarthritis Project (JoCoOA), are described in detail elsewhere [21,22]. The primary purpose of the JoCoOA was to determine the incidence, prevalence, and progression of knee, hip, hand and spine osteoarthritis (OA). This ongoing longitudinal study includes Black (nearly 1/3 of the cohort) and White participants living in North Carolina. Civilian, non-institutionalized residents aged 45+ years from six townships in Johnston County were enrolled between 1991 and 1998 (n = 3187, Original Cohort), and additional residents were enrolled from 2003 to 2004 (n = 1015, Enrichment Cohort). Participants in JoCoOA completed follow-up clinic and interview data collection approximately every 5 years. Lumbar spine radiographs were added to JoCoOA in 2003. The current analyses used data from 731 participants who completed a study visit during 2006–2010and had available biospecimens (serum and urine) and complete lumbar spine radiographic data. We followed the Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) statement [23], a 22-item checklist for reporting of observational studies. All participants in JoCoOA have provided informed consent for participation, and JoCoOA has been continuously approved by the institutional review boards of the University of North Carolina and the Centers for Disease Control and Prevention.

2.2. Demographic and clinical characteristic data

Demographic (age, race, and sex) and clinical data as well as body mass index (BMI) (calculated from height measured without shoes and weight measured with a balance beam scale) were collected by interview and clinical examination. Presence of LBP was defined as an affirmative response to the question: “On most days do you have symptoms of pain,

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aching or stiffness in your lower back?” Those participants who reported “yes” were also asked to quantify the severity of their symptoms as “mild,” “moderate,” or “severe.”

Participants completed weight bearing postero-anterior knee radiography of both knees with a Synaflexer™ (CCBR-Synarc, San Francisco, CA) positioning device. The primary reason for a participant not having knee radiographs was presence of knee arthroplasty. All knee radiographs were read for Kellgren-Lawrence grade [24] by a single bone and joint radiologist. Inter-rater and intra-rater reliability have been reported previously with a weighted Kappa of 0.86 and 0.89 for the knee [25]. Knee OA for these analyses was defined as a Kellgren-Lawrence grade of 2–4 in at least one knee.

2.3. Pressure-pain threshold and depressive symptoms

Pressure-pain threshold (PPT) measurements, using a standard mechanical pressure-based dolorimeter, were used to assess each participant’s threshold (measured in kilograms) for pressure-pain at the upper trapezius. Similar to our other studies, a distal PPT measurement may indicate central pain sensitization [11,26,27]. A single trained research assistant conducted all PPT clinical measurements, which began with a “practice trial” of the device. Measurements were then collected from both the left and right upper trapezius muscle. Beginning with the left side, pressure was applied to the trapezius at a rate of 1 kg per second until self-reported pain. Per the institutional ethical review board protocol, if a participant did not report pain at 4 kg, the value was recorded as “>4.0 kg” Trials were continued until two consecutive readings were within ±0.4 kg for a maximum of four trials. The same procedure was repeated for the right side. Values from the left and right trapezius were averaged to provide a single PPT score. Depressive symptoms were measured with the Centers for Epidemiological Studies Depression Scale (CES-D). We measured both PPT and depressive symptoms because several studies and our prior work have found that depressive symptoms confound the relationship between PPT and radiographic findings [11, 26].

2.4. Biomarkers

We categorized biomarkers based on their affinity with lumbar spine structural changes, inflammation, or pain. Biomarkers that were related to structural changes included N-cadherin and Keratin-19, biomarkers of IVD structure that have been identified as the top biomarker candidates for testing in clinical populations [28] and as potential key markers for regenerative medicine efforts [17,18]. Lumican, a proteoglycan that regulates collagen formation, may represent unique degradation properties of the IVD [16]. Type-II collagen (CTX-II) has been found to be associated with DSN from our prior work [9,10]. Another category of biomarkers for these analyses were those related to inflammation—these included HA [9,10], OPG [14], interleukin-17A (IL-17A) [29], RANTES [19], and C-X-C Motif Chemokine Ligand 6 (CXCL6) [30], all of which have been found to be significantly associated with lumbar spine degeneration. A final category were those biomarkers related to pain, which included IL-6, a cytokine, and NPY, a neuropeptide involved in pain regulation and perception, both of which have also been associated with chronic LBP [19]. Brain-derived neurotrophic factor (BDNF), commonly studied as a pain biomarker [31], was also included since it has also been found to be derived from IVD cells and may represent degradation [32].

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Details of the collection of biospecimens have been described elsewhere [9]. Briefly, all participants had blood and urine collected at the clinic visit on the same day that radiographs were taken. Therefore, all samples were collected after completion of morning activity at a time (>1 h after arising) when these serum markers have attained equilibrium [33]. Analytes measured from human serum included N-cadherin, Keratin-19, Lumican, CXCL6, RANTES, IL-17A, IL-6, HA, BDNF, OPG and NPY. In addition, we measured CTX-II, adjusted for urine creatinine levels, a biomarker reflecting degradation of type II collagen of hyaline cartilage. Our previous work has demonstrated that measurement of these biomarkers has excellent reliability and validity [11]. The only exception was IL-17A, for which the majority of the samples had concentrations below the lower limit of detection, and which was therefore excluded from analyses. Additional details of the distributions, manufacturer, intra- and inter-assay variability, lower limit of detection, and required dilution are provided in Supplementary Table 1. Intra- (within assay) and inter-assay (between assay) coefficients of variation were below 15% representing good reliability.

2.5. Radiographic spine evaluation

Lateral lumbar spine films were taken with participants lying on their left side with the central beam centered at the lumbar spine as this is a commonly used position for clinical imaging. All lateral lumbar spine radiographs were graded at each lumbar level for features of DSN, OST, and FOA using the Burnett Atlas [34]. DSN and OST were graded as none, mild, moderate, or severe, while FOA was graded as absent or present at each lumbar level. The grading for OST was done for each superior and inferior aspect of the anterior face of each lumbar vertebra. Both DSN and OST were dichotomized as absent (none) or present (mild, moderate, or severe). Our prior analyses have examined different cut-offs for defining DSN and OST without any significant change in the findings [5,6,9–11]. The intra-rater reliability of this radiologist for the spine features has been reported previously with weighted kappa scores of 0.89 for DSN, 0.90 for OST, and 0.73 for FOA [10]. Lumbar spine radiographs were read paired for this study (i.e., both T2 and T3 radiographs were read together) by a single bone and joint radiologist.

2.6. Statistical analysis

Concentrations of biomarkers less than the lower limit of detection (LLOD) were imputed at ½ × the LLOD [35]. Testing for differences across the absence or presence of each radiographic feature was conducted using t-tests and chi-square tests, as appropriate. Some biomarkers having skewed distributions so each biomarker was transformed via its natural logarithm prior. Binary logistic regression was used to model the bivariate and multivariable relationship between each radiographic feature with each individual biomarker. For the individual biomarker analyses, we analyzed each log-transformed biomarker with each lumbar spine radiographic feature ignoring self-reported symptoms, and then separately among those self-reporting LBP. All multivariable models included age and BMI as continuous variables and race, sex, PPT, and depressive symptoms as dichotomous variables [36]. We included knee OA in multivariable models because we found in our prior work that knee OA is an important confounder of the relationship between lumbar spine radiographic features and biomarkers. We have also identified that adjusting for hip and hand OA had a

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minimal effect on spine-related associations when knee OA was included the model [9]. To determine independence of the relationship, we adjusted for the presence of the other two radiographic features (i.e., spine OA for FOA as the outcome, and FOA with spine OA as the outcome).

We then conducted k-means cluster analysis to group participants with similar biomarker profiles. All biomarkers were linearly transformed to a 0–1 scale to meet cluster analysis assumptions and to allow interpretability across biomarkers with different scales of measurement [37]. Participant information about demographics, clinical characteristics, or outcomes (i.e., LBP, DSN, OST, or FOA) were not included in forming the clusters. Therefore, the biomarker clusters that were formed were derived independently from the k-means model. K-means cluster analysis was chosen as an unsupervised learning approach [38], and the number of clusters selected for final comparisons was based upon principal component analysis eigenvalues and the variance explained. This approach has been used in other biochemical biomarker studies [11,37]. A 3-cluster solution was chosen to allow for variation across the domains of biomarkers being analyzed (i.e., structural, inflammatory and pain). The number of clusters was motivated by 1) our sample size, 2) principal component analysis with these data in which the scree plots supported 3 distinct components and 3) cubic clustering criterion of greater than 3 to indicate good clustering [39].

Analysis of variance (ANOVA) and chi-square tests were used to determine whether differences among phenotypic clusters. Significant effects found in ANOVA were followed by testing of post-hoc pairwise mean differences via the Tukey method to correct for multiple comparisons. Separate binary logistic regression models were then conducted for the clusters entered as an explanatory variable; all pairwise comparisons were considered. Statistical significance was set at $p < 0.05$ for all analyses. Odds ratios were the measure of association, and 95% confidence intervals were calculated as a measure of precision. All analyses were conducted in SAS 9.4.

3. Results

Fig. 1 illustrates the selection of participants available for this study. At the second follow-up of JoCoOA, there were 1697 participants. Participants were selected if they had complete lumbar spine radiographs (n = 819). Of those participants with complete paired lumbar spine readings, some participants (n = 74) had participated in a pilot study to understand the validity and reliability of the proposed biomarkers [6] and were therefore excluded. There were also some participants having missing covariate information (i.e., dolorimeter and pain measures, n = 14), leaving 731 participants available for this study.

Table 1 describes the distribution of means and standard deviations or frequencies and percentages for each outcome. As expected in this cohort, a large percentage of participants had OST, FOA, or DSN present at any level of the lumbar spine (70.7%, 84.4%, or 78.4%, respectively). Participants with DSN or FOA were older compared to those without these features. Women had a significantly higher percentage of OST (64.8%) compared to men, while White participants had a significantly higher percentage (70.6%) of DSN compared to Black participants. A high percentage of knee OA was present with each of the lumbar

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spine radiographic features. Mean levels of OPG were higher in those with DSN than those without, but the same was not true for those with OST or FOA. Mean levels of HA were higher in the group with FOA than those without, but the same was not true for the groups with DSN or OST. Mean levels of BDNF were lower in groups with any of the lumbar spine structural changes. There were no significant differences in mean levels of PPT, N-cadherin, CTX-II, Lumican, CXCL6, IL-6, NPY, or RANTES in groups with versus without any of the lumbar spine structural changes.

Table 2 describes the multivariable-adjusted associations between the individual log-transformed biomarkers and lumbar spine structural changes alone and with LBP. RANTES was associated with OST (OR = 1.83, 95% CI 1.15–2.90), CTX-II was associated with DSN (OR = 1.39, 95% CI 1.07–1.80), and HA with FOA (OR = 1.54, 95% CI 1.14–2.08). Elevated levels of OPG were associated with OST (OR = 1.98, 95% 1.17–3.35) and DSN (OR = 1.80, 95% CI 1.16–2.78). However, in contrast to the association with OST and DSN, the relationship between OPG and FOA was inverse, with higher levels of OPG associated with participants without FOA (OR = 0.62, 95% CI 0.38–0.99). BDNF was inversely associated with FOA (OR = 0.49, 95% CI 0.26–0.95). CXCL6 was associated with FOA with LBP (OR = 2.07, 95% CI 1.30–3.28) and LBP alone (OR = 1.61, 95% CI 1.08–2.39). OPG and PPT levels ≤4 kg (low threshold for pain) were associated with each of the lumbar spine radiographic features and in the group reporting the presence of LBP. There were no significant associations with structural changes alone or with LBP for N-cadherin, Lumican, IL-6, or NPY.

Table 3 describes the distributions of outcomes and covariates across the three identified clusters, and Fig. 2 provides an overview of key cluster characteristics. A three-cluster solution was selected based on the number of eigenvalues from principal components analyses (n = 3), the variance explained by the principal components (48%) and a cubic clustering criterion of 7.76. This cluster solution is depicted graphically in Supplementary Figure 1. Biomarker cluster 1 consisted of 243 (33%) participants with higher DSN, older mean age, higher percentages of men and Whites, and higher mean levels of N-cadherin and HA, but lower mean levels of BDNF, compared to cluster 2 or 3. Biomarker cluster 1 was characterized by a higher percentage of lumbar spine structural changes; as such, we describe this cluster as a structural change subgroup. Biomarker cluster 2 consisted of 306 (42%) participants, with significantly lower percentages of DSN and FOA, and lower mean levels of Lumican, CTX-II, OPG, IL-6, and HA compared to cluster 1 or 3. In addition, biomarker cluster 2 had a lower percentage of knee OA, and the least proportion of participants with a lower threshold for pain (PPT ≤4 kg; i.e., high pain sensitivity). Based on these characteristics, we chose this cluster to be a reference subgroup for comparisons. Biomarker cluster 3 consisted of 182 (25%) participants and had a higher percentage of FOA with LBP, higher percentages of female and Black participants, higher mean BMI, and a higher percentage of knee OA and participants with PPT ≤4 kg compared to biomarker cluster 1 or 2. Additionally, higher levels of Lumican, CTX-II, RANTES, and CXCL6 were found in this cluster. As such, we describe biomarker cluster 3 as a pain and inflammation subgroup.

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Table 4 describes the relationship between subgroups for LBP and lumbar spine structural change outcomes. Compared to the reference subgroup, the structural change subgroup was associated with DSN (OR = 1.94, 95% CI 1.30–2.90) and FOA (OR = 1.72, 95% CI 1.12–2.62). Compared to the reference subgroup, the subgroup with pain and inflammation was associated with OST with LBP (OR = 1.60, 95% CI 1.04–2.46), FOA with LBP (OR = 1.59, 95% 1.04–2.45), and LBP (OR = 1.63, 95% CI 1.11–2.41).

4. Discussion

We identified two unique subgroups of participants with structural degeneration with or without markers of inflammation and pain. These cluster solutions could aid in development of broader definitions of clinical phenotypes. For example, the structural change subgroup, characterized by a combination of elevated mean N-cadherin and HA and lower BDNF, was significantly older and more likely to be men compared to the other subgroups. We also identified an inflammation with pain subgroup characterized by elevated CTX-II, CXCL6, RANTES, and BDNF that was more likely to include women, Black participants, those with knee OA, and those with a lower pain threshold (i.e., lower PPT measures). Compared with these subgroups, the structural change subgroup tended to have lumbar spine structural features of DSN and FOA, whereas the inflammation with pain subgroup tended to have LBP and FOA. These findings may have utility for differentiating particular subgroups of patients who may have a nociception generating structure (i.e., FOA) resulting in pain that may help to add targeting specificity when considering interventions such as lumbar spine facet joint injections.

We identified several significant relationships between OPG and DSN, and OST and FOA. Levels of OPG and FOA may yield insights into LBP etiologies. For instance, participants with FOA tended to have significantly lower levels of OPG compared to participants without FOA. However, participants with FOA and LBP had significantly higher OPG levels compared to FOA without LBP. This suggests that high levels of OPG may be present among those who have LBP. Thus, biomarkers, such as OPG, may be able to help differentiate nociception generating structures resulting in LBP. We also identified CXCL6 as a promising pain biomarker. This is in contrast to one other study that reported significantly elevated mean levels of systemic CXCL6 in human participants with signs of IVD degeneration compared to participants without such degeneration [30]. However, in contrast to our study that controlled for the presence of FOA, to our knowledge this other study did not account for the presence of FOA, which may have influenced their results. Given the consistent relationship between CXCL6 and FOA with LBP and LBP alone, this biochemical marker should be considered further as a predictor for FOA with LBP.

We found a statistically significant relationship between BDNF and FOA without LBP. BDNF is typically studied as a pain biomarker. However, BDNF has been found to be expressed by IVD cells [11,32] and skeletal muscle cells [40]; this may indicate utility of this biomarker for reflecting structural changes of the spine. Our finding of a group with lower BDNF and FOA may be reflective of a structural relationship rather than a pain-related subgroup. A commonly utilized objective pain measure is PPT, which has been associated with structure and self-reported pain. We found that for each of our outcomes

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that involved LBP, pressure pain greater than 4 kg was significantly associated with less structural changes with LBP or LBP alone. This is a similar finding to the relationship we found between knee and hip OA with symptoms [26]. These findings continue to support a role for central pain sensitization that is independent of structural changes found on radiographs. Future studies should evaluate whether PPT may be a useful pain measure to differentiate individuals who might have structural findings that may lead to LBP.

Biomarkers of inflammation are elevated during acute phases of LBP, suggesting possible clinical utility for intervention decision-making [41]. A common clinical challenge is differentiating whether structural changes found on imaging are related to the current reports of LBP. In fact, most patients seeking care for LBP will have one or more of the radiographic degenerative features included in this study during an initial visit [42]. Differentiating what lumbar structure, if any, is a primary source of nociception leading to LBP has led to many different clinical approaches for treatment. One important aspect of this study was to determine if biomarkers, together with demographics and clinical characteristics, could further differentiate individuals with or without LBP. Of the two subgroups we identified, the group that was significantly older and more likely to be men, and with DSN, did not tend to have LBP. This subgroup may have this radiographic feature as a result of increasing age rather than a pathology that results in LBP. However, participants in our second identified subgroup were significantly more likely to be women and Black, and have knee OA and a lower threshold for pain (higher pain sensitivity). Compared to other subgroups, participants in this subgroup had LBP and FOA or OST with LBP. Our previous studies identified a strong association between knee OA and FOA, suggesting a more systemic nature or genetic nature to the OA process in the facet joint rather than potential age related degeneration found with the IVD. Further studies should determine whether these subgroups predict the worsening of these features.

There are several strengths to our study including a well-defined community-based sample, large biomarker sample size, and protocol-driven approach to data collection with both lumbar spine radiographs and ascertainment of LBP. Also, our study is not without limitations. The primary limitation of this study is its cross-sectional design; thus, we could not address the temporal relationship between the onset of biomarker abnormalities and onset of spine degeneration. The parent study (JoCoOA) only included radiographic images of the lumbar spine. Other types of spinal imaging (MRI or CT scans) may provide a greater level of detail of the intervertebral disc and associated structure. As such, our findings may underestimate the true effect between lumbar spine structure and biomarkers (i.e., non-differential misclassification). Lateral lumbar spine radiographs may not be the optimal image or view for FOA, which could lead to non-differential misclassification of FOA status since lateral views may underestimate the occurrence of FOA. However, prevalence estimates of FOA based on lateral spine radiography [21] are similar to those previously reported based on computed tomography scans [43]. In addition, radiographic images were only available for the lumbar spine; however, thoracic and cervical spine levels, in addition to other peripheral joint sites, may influence systemic biomarker concentrations. We adjusted for peripheral joint OA to take into account its potential to contribute to systemic biomarker concentrations and thereby reveal potential independent associations of spine features and biomarkers. Some of our biomarkers are specific to turnover of

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cartilage structure (i.e., CTX-II) while other measures may reflect a systemic biological process not specific to a structure in the lumbar spine. Although we controlled for common comorbidities that may be involved with biological processes that could affect biomarkers, we could not control for every possible factor (such as some medication use, liver function, and kidney function, diet/activity, or ethnicity) that could affect levels of biomarkers. The JoCoOA protocol excluded women of childbearing age from having lumbar spine radiographs to prevent unnecessary radiation exposure; therefore, the results may not be generalizable to this subgroup. Lastly, we measured the presence of LBP but did not include any measures of how LBP interfered with daily activity. In addition, our question for LBP also includes pain, aching, and stiffness, which may overestimate LBP since stiffness may be present without pain.

5. Conclusion

We identified two “at-risk” subgroups, one that appeared to be related to spine structural changes and one that appeared to be related to spine structural changes and LBP. Demographic and clinical characteristics were necessary for understanding the relationships between subgroups. These findings support the need for additional work to determine how clinical phenotypes may be informed by biomarkers, key radiographic findings, and specific demographic characteristics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Role of the funding source

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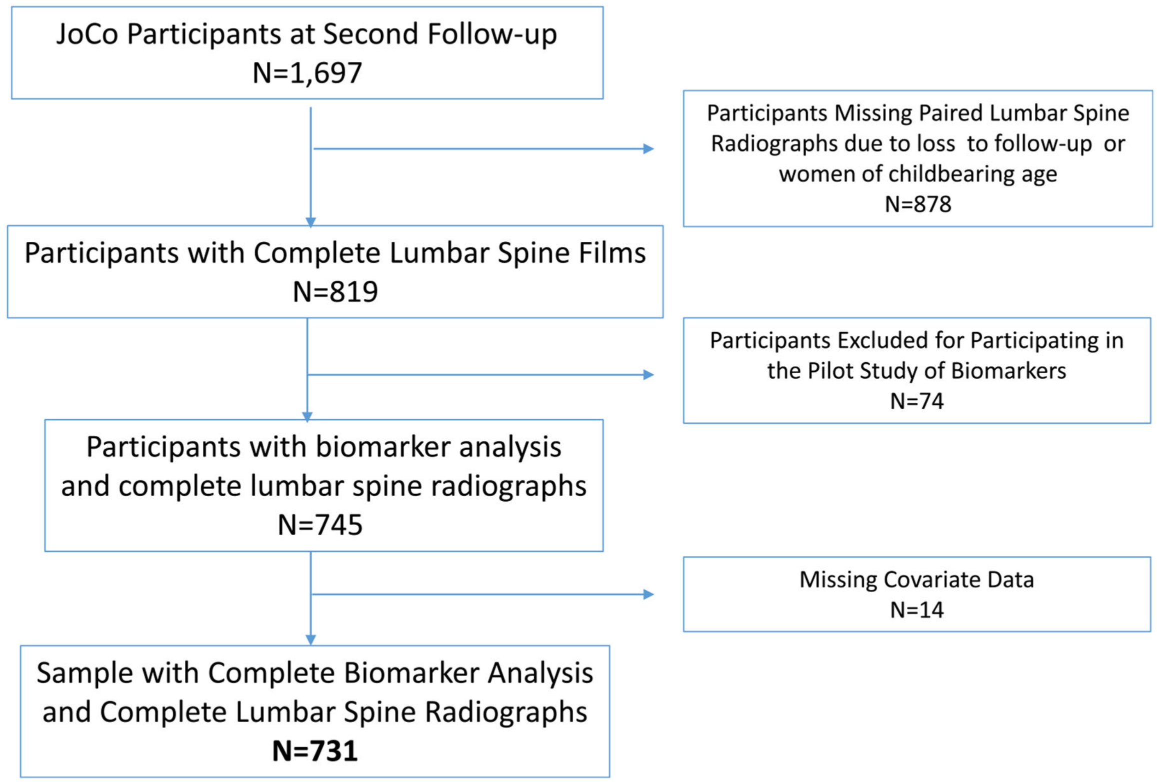

Fig. 1.
Selection of participants for the current study.

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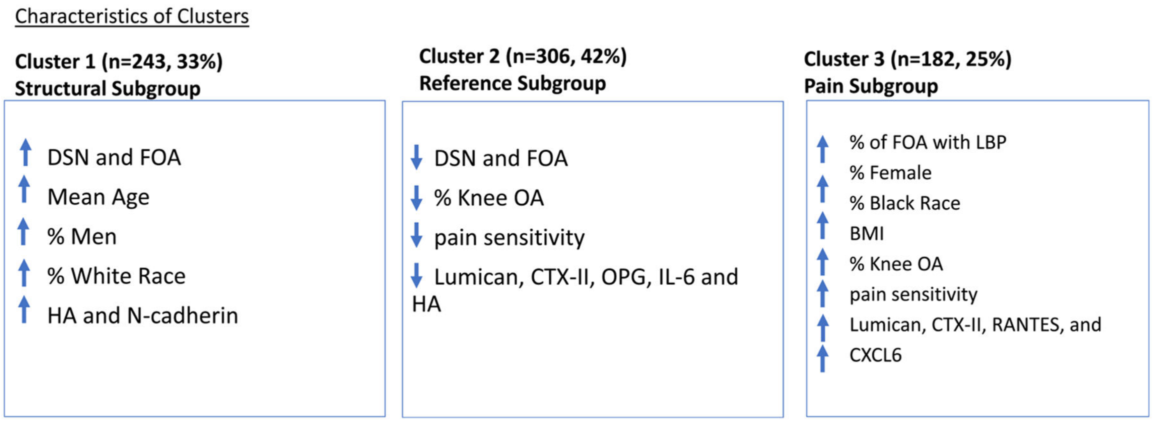

Fig. 2.

Overview of biomarker clusters.

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Table 1

Distribution of demographics, clinical characteristics, and biomarkers across each lumbar spine radiographic feature and low back pain.

Variable	Osteophytes		Disc Space Narrowing		Facet Joint Osteoarthritis		Low Back Pain	
	Present	**Absent**	**Present**	**Absent**	**Present**	**Absent**	**Present**	**Absent**
Demographics and Clinical Characteristics								
Age	66.2 (7.5)	65.7 (7.8)	67.1 (7.4)*	63.9 (7.3)	66.6 (7.5)*	64.4 (7.3)	65.9 (7.5)	66.1 (7.5)
Female, n (%)	448 (64.8%)	108 (84.4%)	403 (69.6%)	153 (63.7%)	443 (69.0%)	113 (63.8%)	207 (74.5%)	331 (63.6%)
Male, n (%)	243 (35.2%)*	20 (15.6%)	176 (30.4%)	87 (36.2%)	199 (31.0%)	64 (36.2%)	71 (25.5%)*	189 (36.4%)
White, n (%)	479 (69.3%)	80 (62.5%)	409 (70.6%)**	150 (62.5%)	447 (69.6%)	112 (63.3%)	187 (67.3%)	360 (69.2%)
Black, n (%)	212 (30.7%)	48 (37.5%)	170 (29.4%)	90 (37.5%)	195 (30.4%)	65 (36.7%)	91 (32.7%)	160 (30.8%)
Body mass index	31.8 (6)*	29.8 (6.4)	31.6 (6.1)	31.3 (6.2)	31.7 (6)**	30.6 (6.5)	32.9 (6.5)*	30.7 (5.7)
Knee osteoarthritis, n (%)	282 (41.6%)*	36 (28.8%)	248 (43.7%)*	70 (29.8%)	269 (42.7%)*	49 (28.3%)	119 (44.1%)	195 (38.1%)
Depression, n (%)	116 (17.3%)	17 (13.6%)	90 (16.0%)	43 (18.4%)	100 (16.0%)	33 (19.2%)	71 (26.3%)	59 (11.55%)
PPT ≤4 kg, n (%)	496 (71.8%)	81 (63.3%)	411 (71.0%)	166 (69.2%)	448 (69.8%)	129 (72.9%)	158 (59.6%)	402 (79.9%)
Biomarkers								
Structural								
N-cadherin, ng/ml	113 (23)	111.5 (30.1)	113.1 (25)	111.9 (22.2)	113.2 (23.1)	111.1 (28.2)	114.0 (26.2)	112.2 (23.3)
CTX-II, ng/mmol Cr	415 (556.7)	400.2 (619.8)	432.6 (585.6)	357.3 (507.8)	405.1 (423.4)	441.2 (929.9)	430.5 (485.7)	409.4 (615.6)
Lumican, ng/ml	132.8 (25.2)	137.4 (26.4)	133.3 (27)	134.3 (20.4)	133.8 (24.9)	132.7 (27.5)	135.4 (23.5)	132.5 (26.6)
Inflammation								
OPG, pg/ml	98.5 (41.4)	93 (46.4)	99.8 (41.8)**	91.6 (43.1)	96.8 (40.5)	100.8 (48.2)	102.8 (43.0)*	94.3 (41.5)
CXCL6, pg/ml	295 (726.1)	287.6 (198.8)	292.3 (770.3)	298 (202.3)	297.3 (748.7)	280.7 (190.3)	357.3 (1126.6)	259.7 (164.9)
HA, ng/ml	73 (90)	64.1 (52.6)	74.3 (92.2)	63.9 (60.3)	75.8 (92.9)*	56.1 (43.4)	71.4 (57.4)	72.0 (98.0)
IL-6, pg/ml	2.0 (3.9)	2.7 (6.7)	1.8 (2.2)	2.9 (7.9)	2.1 (4.8)	2.0 (3.1)	2.5 (6.7)	1.9 (2.8)
RANTES, pg/ml	182686.8 (96264.9)	173315.6 (92935.3)	177235.8 (92285.9)	192294.5 (104311.7)	181929.2 (96367.9)	178406.6 (93622.3)	189937 (102796)	176112 (91740.3)
Pain/Stress NPY, pg/ml	22.9 (8.9)	23.3 (8.8)	23 (8.9)	22.9 (9)	22.9 (8.9)	23.2 (9)	22.9 (8.9)	23.1 (9.0)
Free BDNF, pg/ml	30622.4 (9129.4)**	32870.9 (9086.4)	30307.4 (8527.7)*	32894.6 (10516.3)	30480 (8893)*	32844.2 (9865.5)	31139.3 (9060.1)	30894.5 (9189.6)

Data shown are mean (SD) except where indicated.

* $p < 0.001$,

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** $p < 0.01$.

CTX-II = type II collagen; OPG = osteoprotegerin; CXCL6 = C-X-C Motif Chemokine Ligand 6; HA = hyaluronic acid; IL-6 = interleukin-6; NPY = neuropeptide-Y; BDNF = brain-derived neurotrophic factor; RANTES = C–C Motif Chemokine Ligand 5.

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Table 2

Associations between biomarkers and lumbar spine radiographic degeneration regardless of the presence of low back pain (structural change) and lumbar spine degeneration with low back pain (structural change and symptoms).

	Osteophytes Present vs Absent	Osteophytes and LBP Present vs Absent	Disc Space Narrowing Present vs Absent	Disc Space Narrowing and LBP Present vs Absent	Facet Joint Osteoarthritis Present vs Absent	Facet Joint Osteoarthritis and LBP Present vs Absent	LBP Present vs Absent
	Odds Ratio (95% CI)	**Odds Ratio (95% CI)**	**Odds Ratio (95% CI)**	**Odds Ratio (95% CI)**	**Odds Ratio (95% CI)**	**Odds Ratio (95% CI)**	**Odds Ratio (95% CI)**
Biomarkers							
Structural							
N-cadherin, ng/ml	1.61 (0.58–4.43)	0.90 (0.37–2.19)	0.86 (0.37–2.01)	1.24 (0.49–3.11)	1.37 (0.56–3.36)	0.90 (0.36–2.24)	1.10 (0.49–2.45)
Lumican, ng/ml	0.33 (0.10–1.07)	1.41 (0.48–4.12)	0.45 (0.16–1.29)	1.63 (0.54–4.93)	1.42 (0.45–4.48)	2.08 (0.68–6.39)	1.91 (0.72–5.09)
CTX-II, ng/mmol	1.20 (0.88–1.63)	0.98 (0.76–1.27)	**1.39 (1.07–1.80)**	0.95 (0.73–1.25)	1.03 (0.78–1.36)	0.96 (0.73–1.25)	1.04 (0.82–1.31)
Inflammation							
OPG, pg/ml	**1.98 (1.17–3.35)**	**1.66 (1.05–2.63)**	**1.80 (1.16–2.78)**	1.47 (0.89–2.41)	**0.62 (0.38–0.99)**	**1.82 (1.15–2.89)**	**1.66 (1.10–2.51)**
CXCL6, pg/ml	0.99 (0.62–1.59)	1.45 (0.95–2.22)	1.05 (0.70–1.59)	1.31 (0.83–2.07)	1.09 (0.70–1.69)	**2.07 (1.30–3.28)**	**1.61 (1.08–2.39)**
RANTES, pg/ml	**1.83 (1.15–2.90)**	1.27 (0.85–1.88)	1.05 (0.71–1.56)	1.17 (0.76–1.79)	1.26 (0.84–1.90)	1.39 (0.93–2.07)	1.24 (0.86–1.78)
IL-6, pg/ml	0.86 (0.65–1.13)	1.24 (0.96–1.62)	0.87 (0.68–1.11)	1.13 (0.84–1.51)	0.99 (0.76–1.28)	1.09 (0.85–1.40)	1.23 (0.98–1.54)
HA, pg/ml	0.89 (0.65–1.23)	1.04 (0.79–1.37)	1.06 (0.80–1.39)	1.17 (0.87–1.58)	**1.54 (1.14–2.08)**	1.08 (0.82–1.43)	1.08 (0.84–1.39)
Pain/Stress							
BDNF, pg/ml	0.65 (0.31–1.39)	1.18 (0.64–2.20)	0.71 (0.38–1.32)	0.66 (0.32–1.35)	**0.49 (0.26–0.95)**	1.21 (0.64–2.28)	1.06 (0.59–1.88)
NPY, pg/ml	0.99 (0.55–1.79)	1.10 (0.67–1.83)	0.88 (0.54–1.46)	0.94 (0.55–1.61)	0.90 (0.53–1.52)	1.13 (0.68–1.87)	1.02 (0.65–1.61)
PPT, ≤4 kg vs > 4 kg	0.77 (0.49–1.20)	2.17 (1.45–3.22)	0.75 (0.50–1.10)	2.33 (1.54–3.57)	1.05 (0.68–1.64)	**2.56 (1.69–3.85)**	**1.89 (1.49–2.44)**

Bold values indicate statistical significance. All models include age, race, sex, knee osteoarthritis, depressive symptoms, pressure-pain threshold (PPT), and body mass index.

* Also adjusted for facet joint osteoarthritis.

** Also adjusted for osteophytes and disc space narrowing.

LBP = low back pain; CTX-II = type II collagen; OPG = osteoprotegerin; CXCL6 = C-X-C Motif Chemokine Ligand 6; RANTES = C–C Motif Chemokine Ligand 5; IL-6 = interleukin-6; HA = hyaluronic acid; BDNF = brain derived neurotrophic factor; NPY = neuropeptide-Y.

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Table 3

Distribution of outcomes, demographics, clinical characteristics, and biomarkers across identified k-means clusters.

Variable	Cluster 1 (n = 243)	Cluster 2 (n = 306)	Cluster 3 (n = 182)	p-value
Outcomes				
OST, n (%)	214 (88%)	255 (83%)	146 (80%)	0.0801
DSN, n (%)	196 (81%)	209 (68%)	135 (74%)	**0.0047** *ABC*
FOA, n (%)	202 (83%)	227 (74%)	149 (82%)	**0.0213** *AB*
OST with LBP, n (%)	72 (31%)	76 (26%)	58 (33%)	0.1967
DSN with LBP, n (%)	65 (28%)	66 (22%)	50 (28%)	0.2245
FOA with LBP, n (%)	65 (28%)	75 (25%)	65 (37%)	**0.0234** *BC*
LBP, n (%)				0.337
None	155 (66%)	207 (69%)	103 (58%)	
Mild	27 (11%)	30 (10%)	26 (15%)	
Moderate	35 (15%)	42 (14%)	34 (19%)	
Severe	19 (8%)	19 (6%)	14 (8%)	
Demographics and Clinical Characteristics				
Mean age (SD)	69.5 (7.54)	64.2 (6.78)	65.5 (7.31)	**<0.0001** *AC*
Sex, n (%)				**<0.0001** *ABC*
Female	149 (61%)	207 (68%)	152 (84%)	
Male	94 (39%)	99 (32%)	30 (16%)	
Race, n (%)				
White	202 (83%)	208 (68%)	77 (42%)	**<0.0001** *ABC*
Black	41 (17%)	98 (32%)	105 (58%)	
Knee osteoarthritis, n (%)	105 (44%)	93 (31%)	86 (49%)	**<0.0001** *ABC*
Mean body mass index (SD)	31.3 (6.24)	30.6 (5.62)	33.2 (6.47)	**0.0001** *BC*
Depressive symptoms present, n (%)	37 (16%)	45 (15%)	36 (20%)	0.3023
Pressure-pain threshold (≤4 kg), n (%)	65 (28%)	69 (23%)	62 (36%)	**0.0148** *ABC*
Biomarkers, mean (SD)				

Variable	Cluster 1 (n = 243)	Cluster 2 (n = 306)	Cluster 3 (n = 182)	p-value
Structural				
N-cadherin	120.8 (24.18)	106.1 (18.78)	113.9 (28.75)	**<0.0001** ^{AC}
Lumican	132.2 (18.75)	125.9 (17.62)	148.4 (36.35)	**<0.0001** ^{ABC}
CTX-II	421 (390.27)	236.3 (131.05)	705.9 (975.86)	**<0.0001** ^{ABC}
Inflammatory				
OPG	112.5 (44.98)	80 (31.46)	106.2 (38)	**<0.0001** ^{AB}
RANTES	126051.5 (64739.59)	187199.5 (87143.3)	243385.8 (102088.31)	**<0.0001** ^{ABC}
IL-6	2.7 (5.4)	1.4 (1.21)	2.4 (6.32)	**<0.0001** ^{AB}
CXCL6	201.3 (107.65)	265.9 (174.52)	466.7 (1316.27)	**<0.0001** ^{ABC}
HA	108.6 (133.01)	45.3 (27.48)	67.8 (42.2)	**<0.0001** ^{ABC}
Pain				
NPY	23.7 (7.78)	24.0 (10.18)	20.4 (7.24)	**<0.0001** ^{BC}
BDNF	24803.4 (6082.02)	32705.4 (8028.68)	36312.8 (9689.92)	**<0.0001** ^{ABC}

OST = vertebral osteophytes; DSN = disc space narrowing; FOA = facet joint osteoarthritis; LBP = low back pain; CTX-II = type II collagen; OPG = osteoprotegerin; RANTES = C–C Motif Chemokine Ligand 5; IL-6 = interleukin-6; CXCL6 = C-X-C Motif Chemokine Ligand 6; HA = hyaluronic acid; NPY = neuropeptide-Y; BDNF = brain derived neurotrophicfactor.

Pairwise comparisons:

A = p-value for Cluster 1 vs Cluster 2;

B = p-value for Cluster 2 vs Cluster 3;

C = p-value for Cluster 1 vs Cluster 3.

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Table 4

Associations among the three identified k-means clusters with lumbar spine degeneration and low back pain.

Outcomes	Structural Change Subgroup (Cluster 1) versus Reference Subgroup (Cluster 2)	Pain and Inflammation Subgroup (Cluster 3) versus Reference Subgroup (Cluster 2)
OST	1.48 (0.90–2.41)	0.81 (0.51–1.30)
OST with LBP	1.20 (0.81–1.78)	**1.60 (1.04–2.46)**
DSN	**1.94 (1.30–2.90)**	1.33 (0.89–2.01)
DSN with LBP	1.10 (0.73–1.68)	1.30 (0.82–2.06)
FOA	**1.72 (1.12–2.62)**	1.57 (0.99–2.48)
FOA with LBP	0.99 (0.66–1.48)	**1.59 (1.04–2.45)**
LBP	1.19 (0.83–1.71)	**1.63 (1.11–2.41)**

OST = vertebral osteophytes; DSN = disc space narrowing; FOA = facet joint osteoarthritis; LBP = low back pain.