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Pilot Study: Characteristics of Lumbar Disc Disease in Patients Who Centralize their Symptoms

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Abstract

Background: Despite increases in healthcare cost for back pain (BP), there is little improvement in patient outcomes. Although BP is most commonly linked with lumbar disc disease (LDD), diagnosis remains unclear, making cost-effective care difficult. However, BP patients reporting centralization of symptoms (CS) have demonstrated improved outcomes; these patients may also have LDD. This pilot's purpose was, referencing LDD-linked genetic markers (*MMP2-1306, VDR-352T, IL6-597A_G*) and MRI (Modic changes), to describe LDD characteristics in patients with CS.

Methods: Genetic marker, MRI and clinical (CS, historical, laboratory) data from 12 patients with BP were compared with 10 previously-studied controls.

Results: All subjects were similar in age, height and activity levels. 9 of 12 patients and all controls showed negligible pathology on MRI. Patients showed greatest prevalence of *MMP2-1306C*= 1.00 (1.00, 1.00); *VDR-352T*= 0.67 (0.35, 0.98); and *IL6-597A_G*= 0.58 (0.26, 0.91) genetic variants; all controls showed an absence of *IL6-597A* variant, but similar prevalence of the *MMP2-1306C* and *VDR-352T* variants to patients. Patients had greater BMI (p= 0.018) and number offalls/accidents (p= 0.015). 10 patient's reporting CS also had zero-to-negligible pathological bone (CTx) or cartilage (COMP) degradation, inflammation (Hs-CRP) or bone production (BAP) compared to patients without CS or controls.

Conclusions: Expanded study is warranted to employ the described MRI/genetic reference criteria proposed for LDD in patients with CS, obesity, and biomechanical trauma.

Keywords: Lumbar disc disease; Low back pain; Centralization; Genetics; MRI

Abbreviations

BAP: Bone Alkaline Phosphatase; BP: Back Pain; COMP: Cartilage Olgomeric Matrix Protein; CI: Confidence Interval; CS: Centralize Symptoms; CTx: C-terminal Telopeptide; HsCRP: High sensitivity C - reactive protein; LDD: Lumbar Disc Disease; MRI: Magnetic Resonance Imaging; VAS: Visual Analog Scale

Introduction

Back pain (BP) is the most common and debilitating musculoskeletal condition experienced by adults [1]. Annual total costs have increased [2] without evidence of improvement in patient management [3, 4] because there is little agreement on the etiology of this condition. Back pain remains a challenge to classify. Intervertebral disc degradation, also known as lumbar disc disease (LDD) [5], is one of the most common underlying causes of BP [6] and yet clear diagnosis remains elusive. Misclassification results in inappropriate and costly treatment, thus to effectively differentiate BP related to LDD from what is not LDD would better inform BP management.

Patients with LDD present with stenosis (central canal and for aminal narrowing), sciatica (radiculopathy of the lumbar spine) or disc bulge (and its sequelae). Collectively, these conditions have been operationally defined as lumbar disc disease (LDD) [5]. Therefore, people with LDD comprise a subset of individuals with BP. The intervertebral disc normally ages early in life [7, 8], due to a progressively diminishing nutrient supply from the vertebral endplate [8]. Some believe degeneration due to age is not pathologic. Further, they assert that signs of aging can be differentiated from pathological degradation of the disc (i.e., LDD) with MRI [9]. Others contend that this degradation process may be a substantive reason for back pain [9-12].

Many factors can influence accurate clinical classification of LDD. Environmental and personal risk factors include occupational load [13], whole body vibration [14], anxiety and fear avoidance [15, 16], smoking, age [8, 17], sex [18], height, and weight [19]. However, no single environmental or personal factor can distinguish BP specifically due to LDD from BP due to another risk factor.

Reference Criteria for Lumbar Disc Disease

Magnetic resonance imaging (MRI) is a commonly used diagnostic imaging tool for patients with BP. MRI shows disc morphology [20]. However, MRI of the back can yield confusing and inconclusive results. People with seemingly pathologic changes observed on MRI may report no BP while others with normal MRI results can describe

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significant BP and disability [13]. Some challenge the diagnostic value of MRI in patients with BP because of its decreased ability to explain MRI findings against the patients' symptom histories [21]. Hancock, et al. [22] conducted a systematic review to help identify the source of BP and determine the diagnostic accuracy of commonly used diagnostic imaging, such as MRI. Of the 28 studies concerning the disc included the systematic review, features of LDD seen on MRI (high intensity zone, endplate changes, disc degeneration) showed a positive likelihood ratio =2, indicating the disc as source for the BP. But, the researchers challenged the LR, due to the large confidence intervals found in the studies reviewed. Absence of the degeneration on MRI was the only test found to reduce the likelihood that the disc was the source of BP [22]. There are 3 categories in the classification of the intervertebral disc on MRI, called Modic classification: one associated with acute inflammation in the disc, the second associated with chronic degenerative changes, and third associated with severe vertebral endplate changes [20]. For the current study, all participants underwent magnetic diagnostic imaging and were classified using Modic classification.

Up until recently, it atypical to employ genetics to diagnosis a pathologic condition. From the research literature, the investigators selected 8 genetic variants linked to LDD. Markers of interleukin genes (e.g., *IL1A-889T_C, IL1B-3954C_T,IL6-174G_C*, and *IL6-597A_G*) that encode pro-inflammatory cytokines produced in response to infection, injury or antigen challenge have been linked to disc degradation. This gene has been shown to regulate the destruction of the disc matrix [23, 24]. Variants in collagen IX gene (e.g., *COL9A2-976C*, *COL9A3-307C_T*) have been linked with LDD and sciatica [25, 26]. Polymorphisms (abnormal mutations) in the vitamin D receptor gene (*VDR-352 T_C*) [26, 27] and metalloproteinase-2 gene (*MMP2 1306C_T*) [28] have also been associated with disc degeneration. An imposing challenge to the investigators was that most previous research was focused on a single variant on a specified ethnic or racial population. To address the racial diversity in the population sampled in the current study, the investigators employed a set of LDD-linked genetic variants as a second reference criterion for LDD. If any of the participants ranked positive in any of the genetic markers tested, then they were considered "with LDD." Thus, MRI and genetic testing together as reference criteria were employed to determine presence of LDD characteristics in symptomatic patients and compared those characteristics with previously-studied asymptomatic control subjects [29].

The association between genetic factors and LDD opens an avenue for investigation that may have clinical implications for diagnosis, classification, and management of patients with BP in general, and LDD specifically. Genetically testing individuals with BP should add more critical evidence to those findings identified in currently ongoing study. And, in all of the genetic studies concerning LDD, MRI was used to confirm presence of LDD. Thus, MRIs and genetic testing should be assessed to determine presence and extent of characteristics of LDD in symptomatic subjects. Further, the investigators contend that it is crucially important to determine the presence and extent of genetic and MRI evidence of LDD in symptomatic individuals with CS, to improve the ability in distinguishing genetic and MRI characteristics between patient subgroups.

Clinical Factors

There is little agreement on a "gold standard" clinically-based test to diagnose BP. In 1987, the Quebec Task Force established basic diagnostic and prognostic guidelines for BP management [30]. These guidelines have been challenged by others who favor guidelines more predictive of outcome [31, 32]. One indicator found to be predictive of successful outcome [31] in those with BP is the "centralization phenomenon" which was formatively based on an intervertebral disc model [32]. The centralization phenomenon (centralization of symptoms, CS) in the lumbar spine occurs when pain in the buttock or leg progressively moves toward the center of the back during or as a result of specific loading strategies such as repeated lumbar movements or assumption of postures [32]. McKenzie and May [32] proposed that these loading strategies cause a mechanical change within the disc that result in reduction in internal disc derangement and reported pain. Further, Hancock et al [22] found that centralization of symptoms (CS) was the sole clinical feature found to increase the likelihood that the disc was the pain generator (+LR=2.8 [95% CI, 1.4-5.3]).

Many diagnostic guidelines are based on the presence of factors assumed to cause BP. The factors are numerous, further compounding the challenge of classifying patients accurately. Some researchers study risk factors while others focus on causal factors. Risk factors such as characteristics of anxiety and fear-avoidance have been associated with severity of BP disability that results in poorer clinical outcomes [15]. Demographic factors such as age [8, 16] and sex [17] influence risk of painful LDD. However, the results of a large retrospective study conducted by the Dionne and others [33] on 3, 212 patients with BP revealed that those clinically diagnosed with disc related BP reported a history of a related accident, a longer elapsed symptom onset-to-treatment time and were less likely to report anxiety, than those diagnosed with non-disc related diagnoses. These factors' usefulness to diagnose BP attributable to LDD and differentiate between BP due to LDD or not (not LDD) needed be prospectively tested with comparison data from symptomatic adults with CS.

The investigators contend that the clinical factors from our retrospective work (i.e., elapsed symptom onset-to-treatment time, accident history, presence of anxiety), tested in combination with the presence of centralization of symptoms, should most likely distinguish patients classified with LDD from those with non-disc related BP (not LDD). One study [32] framed a potential comprehensive profile of asymptomatic adults with no history of BP. The current study would examine the diagnostic accuracy of these signs and symptoms to differentiate if those with CS are indeed a subset of the LDD group.

Developing a classification model based on clinical signs and symptoms requires a large number of participants because of the etiologic heterogeneity of BP (LDD, not LDD) and the number of those factors that may interact with one another. Investigational methods must be well established prior to undertaking such an endeavor as designed in the current pilot project. Results from the current study would determine the presence and extent of genetic and MRI findings that may be characteristic of LDD in symptomatic adults with centralization of symptoms, i.e., framing a profile for "CS." The investigators would also be better informed on the presence

Table 1: Sample size estimation based on alpha level of 0.05.

Outcome	P_0(Prevalence from literature)	P_1(Prevalence from pilot study)	Power			
			.80	.85	.90	.95
IL6-597A	.45	.00	5	5	5	5
VDR Taq1	.09	.40	10	12	15	20
MMP3	.20	.69	6	7	8	10

Ref: Introduction to Sample Size Determination and Power Analysis for Clinical Trials. Controlled Clinical Trials 2, 93-113 (1981). John M. Lachin.

Table 2: Symptomatic and control descriptive data.

Descriptor	Total n=22	Symptomatic n=12	Controls [32] n=10
Sex Men	10	6	4
Women	12	6 (no CS=2)	6
Mean Age years (SD)	37.5 (13.8)	40.83(12.6)	33.5 (14.9)
Mean Height inches (SD)	66.64 (4.23)	67.3(4.5)	65.20 (3.55)
Mean Weight pounds (SD)	168.95(42.37)	193.9(38.63)*	139 (23.19)
Mean BMI(in/lbs^2)*703(SD)	26.87 (7.4)	30.18(8.52)**	22.9 (2.68)
Smoking history	1	1	0
History of Accidents			
Yes	17	11***	6
No	5	1	4
Activity Level			
Sedentary	1	0	1
Light	4	1	3
Moderate	17	11	6
Biomarker (inflammation CRP)			
Normal	18	8	10
Abnormal	2	2	0
Missing data	2	2	0
Biomarker (collagen turnover COMP)			
Normal	18	8	10
Abnormal	2	2	0
Missing data	2	2	0
Biomarker (bone turnover CTX)			
Normal	20	10	10
Abnormal	0	0	0
Missing data	2	2	0
Biomarker (bone formation BAP)			
Normal	14	4	10
Abnormal	6	6	0
Missing data	2	2	0

*p =0.001, CI=(25.8, 84.03); **p=0.018, CI=(1.403,13.14); ***p=0.015

of biomarkers associated with LDD and can determine the scores in specific clinical measures related to BP in symptomatic adults with CS. This pilot's purpose was, using genetic and MRI reference criteria, to identify LDD characteristics in patients with centralization of symptoms.

Methods

This cross-sectional descriptive study was approved by a university-based institutional review board for protection of human subjects. Participants were recruited from a greater metropolitan area in the mid-western United States. All participants gave formal consent prior to participation in the study. Participants were included if they were: 1) English-speaking; 2) men and women with back pain; 3) between 21 and 64 years of age; 4) who were able to independently ambulate without an assistive device. Subjects were excluded if they had: 1) acute or sub acute [34] postoperative pain from back surgery; 2) significant co-morbidities of the cardiopulmonary or neuromuscular systems; 3) any contraindication subject to exposure to MRI; 4) confirmed pregnancy. Selection criteria for the control group previously studied were identical except those subjects were asymptomatic at the time of testing without a history of back pain[33].

Procedures

All investigators were blinded during data collection to limit bias. All participants completed an intake sheet for demographic information as well as VAS-Pain score [29], the Fear-Avoidance Beliefs Questionnaire [15] and the Oswestry Disability Index [35]. Participants also underwent blood draws for gene marker testing and biomarkers associated with lumbar disc degeneration for collagen/ bone turnover (cartilage olgomeric matrix protein [COMP]), bone turnover (CTX), bone formation (BAP), and systemic inflammation (HsCRP) [36]. Biomarker testing and interpretation were conducted by a biochemist investigator [37]. The investigators considered subjects "positive for LDD" when there was presence of 1) Modic changes on MRI at lumbar intervertebral discs L3-4, L4-5, and L5-S1 and 2) genetic presence of variants of the *VDR, COL9* or *IL-1*genetic markers. The radiologist investigator examined for Modic changes; genetic testing and interpretation were conducted by the geneticist investigator.

Table 3: Questionnaires Table.

Questionnaire	Symptomatic-no CS(SD) n=10	Symptomatic-no CS(SD) n=2	Controls [35] (SD) n=10
VAS Pain score (0-10cm)	2.335 (2.43)	1.025 (.813)	0 (0)
$FABQ_W$ ($FABQ_W$<19)[15]	12.8 (10.33)	13.0 (7.07)	.2 (.4216)
Oswestry Disability Index Minimal Perceived Disability, ODI, 0-20) [35]	8.9 (6.64)	12.00(8.48)	0(0)

Table 4: Genetic markers tested in symptomatic and asymptomatic participants.

Genetic Marker	Symptomatic n=12 (CS=10, no CS=2) Prevalence (CL)	Asymptomatic [35] n=10 Prevalence (CL)
IL1 Role: pro-inflammatory cytokine produced in response to infection, injury or antigen challenge [23]		
IL1A-889T_C	0.33 (0.02,0.65)	0.70 (.35,1.0)
IL1B-3954C_T	0.42 (0.09, 0.74)	0.50 (0.12, 0.88)
IL6 Role: encodes pro-inflammatory cytokine, linked to disc degeneration by regulating the destruction of disc matrix [24]		
IL6-174G_C	0.25 (0, 0.54)	0.20 (0,0.50)
IL6-597A_G	0.58 (0.26, 0.91)	0 (0,0)*
COL9A Role: have been linked with: LDD and sciatica; disc bulges; alterations between collagen IX and other matrix molecules [25]		
COL9A2-976C	0.08 (0,0.27)	0 (0,0)
COL9A3-307C_T	0.17 (0,0.41)	0.30 (0,0.65)
VDR Role: Linked with bone mineralization and remodeling [26,27]		
VDR-352 T_C	0.67 (0.35, 0.98)	0.60 (0.23, 0.97)
MMP Role: linked with destruction of the extracellular matrix of IVD; major proteolytic enzymes responsible 3x at risk; MMP are modulated by a combination mechanical, inflammatory, oxidative stress factors; *MMP2* is mechanical [26,28] *MMP2 1306C_T*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)

*p=0.005

The investigators hypothesized that clinical factors such as accident history and absence of fear-avoidance, in combination with the presence of centralization of symptoms (CS), would distinguish patients classified with LDD-CS from those with LDD without CS. A positive clinical indication to be tested for LDD-CS included: presence of centralization of symptoms [22, 32] positive history of an accident [31], a score of 19 or below on the FABQw to denote negligible fear-avoidance [15]. The investigators also assumed that classification of centralization of symptoms would be established within a 5-visit span [38]; all participants underwent 5 visits for MDT classification by one clinician investigator with a credential in MDT [38].

Data Analysis

All collected data were placed on secured encrypted external hard drive. All data analyses were run by the biostatistician investigator using statistical software (SPSS). All patient demographic, genetic and prevalence data were descriptively analyzed and compared with controls. Significance was set at 0.05.

Results and Discussion

Out of 20 subjects recruited, a total of 12 symptomatic subjects consented and completed the study (Table 2). All but 2 participants were classified into the centralization group by an experienced, credentialed clinician [38]. Although similar in age, and both groups met selection criteria, the BP group, compared with controls, had a mean body weight of 193.9 lbs (p=0.001, CI= [25.8, 84.03]) and body mass index of 30.18 (p=0.018, CI= [1.403, 13.14]). All but one participant had a history of an accident (p=0.015) and a moderately active lifestyle. Biomarker data were missing from 2 participants. Of the 10 remaining, all 10 tested non-pathological for bone turnover (CTX) and 8 tested non-pathological for inflammation (HsCRP) and collagen turnover (COMP) biomarkers. However, 6 tested abnormally elevated in bone formation (BAP). All symptomatic participants reported minimal pain levels, low fear avoidance, and minimal perceived disability (Table 3).

For genetic LDD markers, prevalence and confidence limits (CL) were calculated on the symptomatic group as a whole (Table 4). Because there were only 2 in the no-CS subgroup, differences between symptomatic subgroups (CS=10, no CS=2) were not ascertained. Investigators found genetic markers with greatest prevalence in the overall BP group were: *MMP2-1306C*=1.00 (1.00, 1.00); *VDR-352T*= 0.67(0.35, 0.98); and *IL6-597A_G*= 0.58 (0.26, 0.91). Investigators compared between the symptomatic group and previously-studied controls and found very similar prevalence of the *MMP2-1306C*=1.00 (1.00, 1.00) and *VDR-352T*=0.60 (0.23, 0.97) markers, but difference in the *IL6-597A_G* marker (p=0.005). Seven of 12 symptomatic participants had no discernable Modic changes on any lumbar level evaluated (Table 5). As expected, centralization and Modic changes were more frequently found (p=.002; [0.125, 0.735]) in the BP group.

The over arching aim of the study was to rule in presence of reference criteria for lumbar disc disease (LDD) in symptomatic adults with centralization of symptoms. Specifically, we aimed to quantify the presence of genotypic markers and the presence of disc degradation on MRI that are associated with LDD. We found that the prevalence of the *MMP2 1306C_T* exceeded the prevalence estimated at 70 percent by Batté, Videman and Parent [19]. However, so did the asymptomatic controls (Table 4). The *VDR-352T_C* genetic marker approached the established prevalence at 67% and is supported in the literature [26]. However, the prevalence was at 60% in the control group, similar to the symptomatic group prevalence. It was interesting that there was an absence of the *IL6-597A_G* marker in the asymptomatic control group, and that genetic marker was ranked third most prevalent in the symptomatic group. This particular marker has been associated with the destruction of matrix structure within intervertebral disc tissue linked with untoward mechanical

Table 5: Magnetic Resonance Imaging Modic Classification for LDD by lumbar segment per group and symptomatic subgroup.

Lumbar Segment	All Symptomatic n=12	Centralization Subgroup n=10	No Centralization Subgroup n=2	Controls [35] n=10
L3-L4				
Normal	9	7	2	10
Active inflammation	1	1	0	0
Modicchanges	2	2	0	0
L4-L5				
Normal	9	7	2	10
Active inflammation	0	0	0	0
Modic changes	3	3	0	0
L5-S1				
Normal	9	7	2	10
Acute inflammation	1	1	0	0
Modicchanges	2	2	0	0

loading on the intervertebral disc matrix material [24]. Further study is warranted to direct investigation on the genetic markers in the top rankings in a similar, though much larger, cohort to confirm these suppositions.

Three out of 12symptomatic participants were ranked as either demonstrating acute inflammation or degenerative changes on MRI. This indicates that, in those with centralization of symptoms in this study, were more likely to have morphologically robust intervertebral discs. These results imply potential overuse of costly MRI when patients centralize symptoms. Much larger study is required.

Of all of the clinical, demographic and historical data collected, centralization of symptoms, body weight, BMI, and history of accidents were found more frequent in the participants with BP. Personal and historical factors (evidence of obesity with increased body mass index) and history of a related accident, a potential source of untoward biomechanical force, may indeed be linked to mechanically-influenced back pain seen in clinic and warrants further investigation. Previous study supports the number in this study with CS, that at least 6 out of 10 outpatients with back pain mechanically assessed demonstrates this phenomenon [39].

Little-to-no differences in biomarker findings were found among those with back pain- in inflammation (CRP) collagen (COP) or bone (CTX) turnover, and bone formation (BAP)-very similar to the asymptomatic controls (Table 2). This informs us that, in the subjects tested, there was negligible indication for bone, collagen-related or inflammatory pathology. Specifically, however, there was an absence of bone degradation or inflammation in the CS subgroup compared to the BP without CS subgroup or controls. This robust bone and disc health is indirectly reflected in the self-reported pain scale score, low fear avoidance, and perceived disability scores (Table 3). Lack of biochemical-related pathology supports the contention of those with back pain and centralization of symptoms may have mechanically-mediated pain, as the phenomenon occurred as a result of systematically-imparted loads on lumbar intervertebral disc tissues during the mechanical lumbar assessment.

However, this preliminary study has limitations. Overall number of participants was limited, and most centralized symptoms. Thus, we could not observe statistical differences between the CS and not-CS patient subgroups. However, absence of centralization may inform clinicians of other conditions that can refer to the back. For example, one of the two without CS had a non-lumbar pathology exposed on MRI and was immediately referred to another medical service for care. The second subject was classified as mechanically inconclusive without appreciable Modic changes on MRI. A larger number of subjects would further elucidate this observation. Additionally the descriptive biomarker(Hs-CRP, CTx, COMP, BAP) data were categorically organized as "pathological" or "not pathological" as per the specifications of the serous sample processing(as opposed to tabling the raw data), which may have been more information but more identifiable by individual subject. Thus, the investigators reported these data in categorical aggregate and it could be viewed as a limitation. In view of small sample size, the investigators caution readers from drawing any sweeping generalizations from this preliminary work, but several interesting findings should be noted. Yet, as illustrated in Table 1, the power summary table based on 3 of the genetic markers associated with LDD shows that a sample size in this preliminary study has adequate power with 12 participants with LDD (power=.80 or .85), indicating that results should be informative to larger, future study.

Conclusion

From the information gathered on the 12 participants with BP (10 with CS and 2 with no CS), the investigators found elevated or similar prevalence of the *IL6, VDR,* and *MMP2* genetic markers for LDD in participants with BP, as LDD in the general population. But, more than 50% had no appreciable Modic changes on MRI. Back pain (LDD, not LDD) is heterogeneous in nature. Many indicators for LDD may also be found in symptomatic individuals with CS. We described genetic, MRI, clinical (e.g., mechanical), and physiologic characteristics of LDD in symptomatic adults with CS. The results could inform investigators and clinicians to better distinguish characteristics of "back pain" from "back pain with CS," reducing formation of false positive conclusions, potentially creating a more robust diagnostic model, as well as adding credence to the clinical usefulness of the centralization phenomenon. Further study on the relationships between centralization of symptoms and the non-inflammatory/mechanical properties of the intervertebral disc tissue (genetic markers [*MMP2, IL6,* and *VDR*], and MRI [inflammation Modic changes]; absence of biomarker [Hs-CRP]); with the clinical presentation of obesity and history of related trauma is warranted.

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