Fibromyalgia as a Predictor of Complex Regional Pain Syndrome After Distal Radius Fracture

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Abstract

Background: Complex regional pain syndrome (CRPS) can be a devastating complication following extremity injury, but risk factors are not well understood. The purpose of this study was to investigate the association between fibromyalgia and the development of CRPS after distal radius fracture. **Methods:** The PearlDiver Medicare database was queried using *International Classification of Diseases, 9th Revision* (ICD-9) and Current Procedural Terminology (CPT) codes for diagnoses and treatments of distal radius fractures. Patients were separated into fibromyalgia and control cohorts, and the prevalence of CRPS was measured at 3, 6, 9, and 12 months from the date of injury or procedure. Demographic factors, treatment modality, and comorbid conditions were analyzed by multivariable logistic regression to reduce confounding and identify additional risk factors. **Results:** Database queries yielded 853 186 patients diagnosed or treated for distal radius fracture, with 6% having previous diagnosis of fibromyalgia. The prevalence of CRPS following distal radius fracture was increased at 3, 6, 9, and 12 months in the fibromyalgia cohort compared with the control c, with a 1-year incidence of 0.51% compared with 0.20% (odds ratio [OR], 2.54, $P < .001$). Multivariable logistic regression supported the association, with estimated OR of 2.0 ($P < .001$). In addition, female gender, surgical or manipulative treatment, and anxiety were positively associated with CRPS, and age >65 , diabetes, and heart failure were negatively associated. **Conclusions:** While the basis of the association between fibromyalgia and CRPS is unknown, our data suggest that it could serve as a useful predictor of CRPS risk, promoting increased vigilance for CRPS symptoms and earlier recognition and treatment, thereby improving patient outcomes.

Keywords: complex regional pain syndrome, distal radius fracture, fibromyalgia, fracture complication, reflex sympathetic dystrophy

Introduction

Distal radius fractures are a common upper extremity fracture, accounting for 44% of the hand and forearm fractures seen in the emergency department (ED), or 0.7% of all ED visits.⁸ They are frequently associated with falls in older populations, with females over the age of 60 having a residual lifetime risk of 15% and men a risk of 1.7%.²⁰ Distal radius fractures are treated with open reduction and internal fixation, closed reduction and immobilization, or with immobilization alone, depending on the severity of fracture and displacement.

Complex regional pain syndrome (CRPS) type I is a potentially debilitating condition that has been observed following distal radius fracture, with reported rates that range from 1% to 22%.^{10,39} Complex regional pain syndrome typically occurs following a trauma, surgery, or period of immobilization, with type I defined by the absence

of a known nerve lesion, in contrast to type II. The disease presentation and progression are quite variable but may be characterized by any or all of the following: burning or aching pain, allodynia, edema, limited range of motion, and autonomic dysfunction.³³ Complex regional pain syndrome may progress through 3 stages, with worsening and less reversible skin changes, contractures, muscular atrophy, and bone demineralization in later stages, and has the potential to spread to, or recur at, sites other than the site of initial injury.^{3,34} Inherent limitations in accuracy of

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diagnosis and interobserver reliability certainly exist. The diagnosis was historically one of exclusion, with persistent and unexplained pain following trauma. The International Association for Study of Pain (IASP) criteria were introduced in 1994 to help standardize diagnosis, but subsequent validation studies showed overdiagnosis with sensitivity and specificity of 1.0 and 0.41, respectively. The updated Budapest Criteria, published in 2007, addressed the issue of overdiagnosis, with clinical criteria having sensitivity/specificity of 0.98/0.68 and tighter research criteria having 0.78/0.79.¹⁵ These criteria consist of persistent pain not explained by original insult or other diagnosis, with the presence of multiple signs and symptoms in the sensory, vasomotor, sudomotor/edema, and motor/trophic categories. The inconsistent use of criteria, or use of varying criteria, is likely an important factor in the broad range of CRPS incidences listed in the literature.

Fibromyalgia is a common cause of chronic generalized musculoskeletal pain affecting 2% to 3% of the US population,¹³ with a prevalence greater than 7% in females age 60 to 80.¹³ It is characterized by pain and tenderness at widespread musculoskeletal locations without inciting event. The 1990 American College of Rheumatology (ACR) classification criteria specified 18 anatomic locations commonly involved in fibromyalgia, which significantly improved the accuracy and reliability of diagnosis, and have continued to be updated, with the addition of somatic symptoms, including fatigue and difficulty concentrating in 2010, and adaptation to a completely patient-administered survey in 2011 with sensitivity and specificity of 0.97 and 0.92, respectively.³⁶

Fibromyalgia and CRPS share many commonalities. There is no laboratory or radiological test that can accurately identify either syndrome, so diagnosis is primarily by clinical presentation.²⁸ The etiology and pathogenesis of both syndromes are still unclear, though there have been several studies that have shown physiological changes in patients. Both conditions show alterations in areas of the central nervous system associated with the central processing and modulation of pain, including the sensory, cingulate, and insular cortices, as identified by functional magnetic resonance imaging and magnetic resonance spectroscopy.^{12,18} In addition to the central nervous system, peripheral nerve involvement has been suggested by elevated levels of neuropeptide substance P in both syndromes.^{26,27} Dysfunction of the autonomic nervous system is also present, as indicated by orthostatic hypotension and tachycardia in fibromyalgia,³¹ and increased resting sweat output, decreased skin blood flow and temperature, gastroparesis, and neurogenic bladder in CRPS.^{7,16} Although somewhat controversial, emotional disturbances may play a role in the onset of both fibromyalgia and CRPS.^{13,23}

Given the many similarities in disease presentation and proposed pathogenesis between fibromyalgia and CRPS, it

raises questions about the possibility of shared mechanisms or predispositions. This study was designed to assess for an association between fibromyalgia and the development of CRPS following a distal radius fracture.

Materials and Methods

The patient data was obtained from the PearlDiver Patient Records Database (www.pearldiverinc.com; PearlDiver Inc, Fort Wayne, Indiana), an insurance-based database accessible to paying subscribers. Access to the database was provided for academic research via a protected server maintained by PearlDiver Inc. The de-identified patient records contain the dates of record creation; associated *International Classification of Diseases, 9th Revision* (ICD-9) diagnosis and procedure codes; Current Procedural Terminology (CPT) codes; basic demographics, including age, gender, and region; and average charge information. The PearlDiver records examined in this study were derived from the Medicare Standard Analytical Files, which contain information on Medicare filings from 51 million patients between 2005 and 2012.

The database was queried for patients diagnosed with distal radius fracture, or treated for distal radius fracture either surgically or with closed reduction (Supplemental Figure S1, Table S1). Only the first instance of a diagnosis code was used, attempting to maximize the number of patients with acute injuries and minimize the number of patients with distal radius fracture codes related to malunion or chronic sequelae. In addition, patients treated with closed reduction exclude those who subsequently underwent surgical intervention. The patients identified were queried for a history of fibromyalgia prior to the distal radius fracture, as available within the observation period of 2005-2012, separating the group into fibromyalgia and control cohorts. The cohorts were then analyzed for the development of CRPS within 3, 6, 9, and 12 months from injury. The 1-year time frame was chosen based on the variable presentation of CRPS, which can be difficult to diagnose in the acute setting. Most patients will exhibit signs and symptoms within 1 year,²⁹ with previous studies demonstrating time to diagnosis of CRPS ranging from 3 to 18 months, average 5 to 7 months,^{27,32,34} and average time to confirmatory testing of 9.8 months.³⁸ Analysis was not continued beyond 1 year to minimize CRPS diagnoses related to new injury.

The 2 cohorts were analyzed for basic demographics, including age (in 5-year ranges between 65 and 85, as returned by the PearlDiver database) and gender, type of intervention (surgical or closed reduction, if any), and common general comorbidities diagnosed prior to injury, as summarized in Table 1. To evaluate for confounding factors, the 2 cohorts were combined and each of the aforementioned variables, including fibromyalgia, was subsequently analyzed for its association with the development of CRPS

Table 1. Basic Demographics, Treatment Modalities, and Comorbidities of Fibromyalgia and Control Cohorts.

	Control	FMS
Total	803 039	50 147
Gender ^a		
Male	17%	10%
Female	82%	90%
Age ^a		
<65	11%	24%
65-69	16%	13%
70-74	15%	16%
75-79	17%	16%
80-84	17%	15%
>84	22%	15%
Intervention		
Surgery	24%	27%
Reduction	15%	13%
Comorbidities		
Smoker	8%	20%
Obesity	5%	16%
DM	22%	35%
HTN	57%	82%
CAD	22%	37%
CHF	14%	24%
Anxiety	10%	33%
Depression	16%	45%

Note. FMS = fibromyalgia syndrome; DM = diabetes mellitus; HTN = hypertension; CAD = coronary artery disease; CHF = congestive heart failure.

^a1% of patient records without age or gender designation.

within 1 year of distal radius fracture using PearlDiver functions powered by back-end R statistical software to perform both bivariate and multivariable logistic regression, returned as estimated coefficients with calculated probability. Estimated odds ratios (ORs) were calculated through exponentiation of model coefficients, and $P < 0.05$ was considered statistically significant.

Results

The PearlDiver Medicare database contained records for 49 550 651 distinct patients. The total prevalence of distal radius fractures in the database was 1.7%, with an annual incidence of 0.2%. The total prevalence of CRPS was 0.13%, with an annual incidence of 0.016%. In fibromyalgia patients, the total prevalence of CRPS was 0.44%, with an annual incidence of 0.055%.

The database queries yielded a total of 853 186 patients diagnosed or treated for distal radius fracture between the years 2005 and 2012. Of those patients, 6% (50 147) had a previous diagnosis of fibromyalgia during the observation period, with the remaining 94% (803 039) being used as control. The prevalence of CRPS following distal radius

Figure 1. Prevalence of CRPS in fibromyalgia and control cohorts following distal radius fracture.

Note. CRPS = complex regional pain syndrome; FMS = fibromyalgia syndrome; OR = odds ratio.

fracture was increased at 3, 6, 9, and 12 months in the fibromyalgia cohort compared with the control, with a 1-year incidence of 0.51% compared with 0.20%, which is an OR of 2.54 ($P < .001$; Figure 1).

Demographic analysis of each cohort identified some notable differences between the fibromyalgia and control cohorts. (Table 1) The database queries yielded a predominantly female population, with a greater number of females sustaining distal radius fractures overall, as well as a greater percentage of females in the fibromyalgia cohort. The fibromyalgia cohort was also skewed toward younger ages, with 24% of fibromyalgia patients being younger than 65 compared with only 11% in the control, though average age could not be calculated due to limitations of the PearlDiver database. One percent of patient records were without age or gender designation. Additional discrepancies within Table 1 in summation to 100% are a result of rounding for aesthetic purposes. Querying for common comorbidities demonstrated an increased prevalence of all examined variables in the fibromyalgia cohort, including smoking, obesity, diabetes mellitus (DM), hypertension (HTN), coronary artery disease (CAD), congestive heart failure (CHF), anxiety, and depression. The proportions of patients undergoing surgery, closed reduction, or no procedural intervention were comparable in both fibromyalgia and control cohorts.

Performing bivariate logistic regression demonstrated a statistically significant correlation between all aforementioned variables and the development of CRPS within 1 year of distal radius fracture, with fibromyalgia, female gender, younger ages, surgery, closed reduction, smoking, obesity, anxiety, and depression being positively correlated, and male gender, older ages, DM, HTN, CAD, and CHF being negatively correlated. (Table 2) However, with multivariable

Table 2. Bivariate and Multivariable Logistic Regression of Fibromyalgia, Demographics, Treatment Modalities, and Comorbidities on the Development of CRPS Within 1 Year of Distal Radius Fracture.

	Bivariate			Multivariable		
	Estimated OR	Coefficient	P	Estimated OR	Coefficient	P
Gender						
Male	0.775	−0.255	<.001	0.593	−0.523	<.001
Female	1.290	0.255	<.001	1.687	0.523	<.001
Age						
<65	1.513	0.414	<.001	1.505	0.409	<.001
65-69	1.000 ^a	0.000	<.001	1.000^a	0.000	—
70-74	0.723	−0.324	<.001	0.721	−0.327	<.001
75-79	0.435	−0.833	<.001	0.435	−0.832	<.001
80-84	0.223	−1.502	<.001	0.224	−1.498	<.001
>84	0.116	−2.158	<.001	0.118	−2.136	<.001
Intervention						
Surgery	1.336	0.290	<.001	1.245	0.219	<.001
Reduction	1.126	0.119	.042	1.415	0.347	<.001
Comorbidities						
FMS	2.575	0.946	<.001	1.978	0.682	<.001
Smoker	1.784	0.579	<.001	1.009	0.009	.900
Obesity	1.395	0.333	<.001	0.974	−0.026	.766
DM	0.885	−0.122	.026	0.870	−0.139	.022
HTN	0.738	−0.304	<.001	0.917	−0.087	.095
CAD	0.705	−0.349	<.001	0.976	−0.024	.722
CHF	0.593	−0.523	<.001	0.811	−0.209	.013
Anxiety	1.527	0.423	<.001	1.178	0.164	.016
Depression	1.448	0.370	<.001	1.021	0.021	.742

Note. CRPS = complex regional pain syndrome; OR = odds ratio; FMS = fibromyalgia syndrome; DM = diabetes mellitus; HTN = hypertension; CAD = coronary artery disease; CHF = congestive heart failure. Bold-faced variables retained significance ($P < 0.05$) after multivariable regression.

^aAges 65 to 69 set as baseline OR of 1 for comparison across age groups.

regression modeling, the effects of smoking, obesity, HTN, CAD, and depression became statistically insignificant. Fibromyalgia, gender, age, treatment modality, DM, CHF, and anxiety maintained independent and statistically significant correlations with the development of CRPS.

Discussion

Complex regional pain syndrome is a serious complication following distal radius fractures that can considerably prolong the recovery process and result in permanent and disabling sequelae.^{3,34} Despite increased attention in recent years, the etiology, pathogenesis, and risk factors that may be helpful in predicting its incidence and promoting prompt recognition and treatment are still unclear.²³

Our data suggest a significant correlation between a previous diagnosis of fibromyalgia and the rate of CRPS following a distal radius fracture. In our study population, fibromyalgia patients were over 2.5 times more likely to develop CRPS within 1 year of a distal radius fracture than control. Multivariable analysis to account for confounding factors suggested an independent estimated OR closer to

2.0, though still statistically significant and greater in magnitude than any other examined comorbid condition, gender, or treatment modality. Considering that fibromyalgia patients may exhibit allodynia similar to CRPS, it is possible that an overdiagnosis of CRPS in the fibromyalgia population exists, but when CRPS diagnostic criteria are used appropriately, the inappropriate diagnosis of CRPS based on the pain that is seen in fibromyalgia should be relatively limited, though this cannot be proven in this study. In addition, given the previously noted similarities in presentation of fibromyalgia and CRPS, one might have expected an association of greater magnitude than demonstrated by this study. This could suggest disease etiologies less similar than originally hypothesized.

Gender and age analysis were consistent with previous studies examining the epidemiology and risk factors of CRPS. Female gender is one of the most accepted risk factors for both fibromyalgia and CRPS,^{23,35,37} and is supported by our data, with the development of CRPS in female patients being associated with an independent estimated OR of 1.7 ($P < .001$) compared with males. While CRPS can develop in any age group, previous epidemiological analysis

suggests that the highest incidence occurs between ages 61 and 70⁹ though some studies have suggested an average age as low as 43.² These age ranges would support our data, which showed a significant and progressive decrease in the risk of CRPS with increasing age over 65 (ages 65-70 used as baseline OR of 1, as dictated by PearlDiver functions).

Treatment modality has also been investigated as a possible risk factor for CRPS. Surgery alone has been associated with the development of CRPS, including a variety of upper extremity surgeries, regardless of the presence of traumatic injury.²⁵ The effects of fracture reduction have been disputed, though some studies suggest an association between forceful manipulation and the development of CRPS.⁴⁰ The controversy often revolves around the increased incidence of CRPS with high-energy injuries, increased severity of fracture, comminution, and displacement, and the ability to separate out those factors from the decision to proceed with more invasive management like open or closed reduction.²⁵ Our data showed an increased rate of CRPS following distal radius fracture when treated with surgery or closed reduction. However, patient mechanism of injury and severity of fracture are unknown, preventing further investigation into the controversy surrounding closed reduction.

Comorbid analysis of the cohorts in this study revealed that the fibromyalgia patients had higher rates of all comorbidities, including smoking, obesity, DM, HTN, CAD, CHF, depression, and anxiety. Fibromyalgia has a strong association with depression,¹³ which is associated with increased rates of smoking.²⁴ Obesity is another common comorbidity of fibromyalgia,²¹ and is a known risk factor for developing DM.¹⁹ Finally, smoking, obesity, diabetes, and depression have all been associated with cardiovascular disease.^{1,11,14,17} Given the intricate connections between each comorbidity, it is not surprising to see elevated rates of them all in the fibromyalgia cohort.

However, medical risk factors for CRPS are not well understood, and there is limited evidence about the comorbidities examined in this study. Smoking, obesity, and diabetes have been investigated, though none have been shown to be associated with an increased incidence of CRPS.^{25,40} While CRPS can lead to autonomic dysregulation of the heart and regional peripheral vasculature,^{4,22} neither HTN, CAD, nor heart failure have been identified as risk factors for CRPS. This study also did not find any association between smoking, obesity, HTN, or CAD with the development of CRPS. However, diabetes and CHF were actually found to have a small but statistically significant protective effect on the development of CRPS after distal radius fracture. Lastly, anxiety and depression, as part of a "Sudeck" personality, were some of the earliest risk factors suggested to be associated with the development of CRPS, though more recent reviews have questioned this notion.²³ Our data did not suggest an association between depression and

CRPS, but a history of anxiety corresponded with a slightly increased risk of CRPS.

The reported prevalence of CRPS following distal radius fractures varies greatly, making it difficult to establish a reference value. Studies have reported rates ranging from 1% to as high as 22%.^{10,39} The overall rate of CRPS at 1 year following distal radius fracture in this study was 0.2%, considerably lower than the proposed range. While it is possible that previous studies overestimated the prevalence, CRPS in the Medicare database may also be underdiagnosed or undercoded.

Previous studies have investigated the prevalence of fibromyalgia in the general population, with values ranging from 2% to 3%.¹³ A study by Wolfe et al examined a random sample of 3006 persons in Wichita, Kansas, concurring with an overall prevalence of 2.0%. However, more in-depth analysis showed a marked increase in prevalence with age, exceeding 7% in females between the ages of 60 and 80.³⁷ This more closely matches our calculated prevalence of 6%, given the older patient population represented in the Medicare database. Fibromyalgia is also more prevalent in females, with some studies suggesting a rate 6 times greater in females than males,³⁷ while others show a less dramatic difference. A survey-based study with 830 participants in Minnesota proposed a ratio between females and males with fibromyalgia of 1.6,³⁵ closely matching our calculated value of 1.8.

This study has several limitations related to the use of an administrative database for obtaining patient information. The PearlDiver database contains the entirety of the Medicare Standard Analytical Files between 2005 and 2012; therefore, our analysis relies on the accuracy of diagnosis and procedure coding by physicians and hospitals, with both miscoding and noncoding being potential sources of error. However, a recent improper payments report from 2012 cited an overall coding error rate of 1.3%.⁶ Therefore, although this is a potential limitation, the observed error rate is low. In addition, diagnoses that may not be frequently associated with billing may be undercoded in administrative databases. However, this undercoding is likely to be uniform across cohorts and would not interfere with the identification of associations, but may underestimate the prevalence of diagnosis and the magnitude of these associations. Last, given this study's time frame spanning from 2005 to 2012, there is likely to be changing variability in the diagnosis of both fibromyalgia and CRPS with the institution of new and updated criteria, though the effect on this study is unknown.

The treatment strategy in CRPS requires quick recognition and early intervention for the best prognosis.³⁰ Prevention of course yields the best outcome, and studies have shown decreased rates of CRPS with early mobilization and vitamin C supplementation.^{5,39} However, in the event of CRPS development, each progressive stage is associated

with a lesser response to therapy, more invasive treatments, and more permanent changes.³⁰ While the basis of the association between fibromyalgia and CRPS is unknown, our data suggest that it could serve as a useful predictor of CRPS risk, promoting increased vigilance for CRPS symptoms and earlier recognition and treatment, thereby improving patient outcomes.

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Ethical Approval

This study was approved by our institutional review board.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

All 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 2008 (5). No informed consent was required for this study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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