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Original Research Article

Direct and Indirect Effects of Function in Associated Variables Such as Depression and Severity on Pain Intensity in Women with Carpal Tunnel Syndrome

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Abstract

Objective. To determine the direct and indirect effects of function on clinical variables such as age, pain intensity, years of the disease, severity of symptoms, and depression in women with electrodiagnostic and clinical diagnosis of carpal tunnel syndrome (CTS).

Design. A cross-sectional study.

Setting. Patients from an urban hospital referred to a university clinic.

Methods. Two hundred and forty-four (n = 224) women with CTS were included. Demographic and clinical data, duration of symptoms, function, symptom's severity of the symptoms, pain intensity, and depression were self-reported collected. Correlation and path analysis with maximum likelihood estimation were conducted to assess the direct and indirect effect of hand function on pain, age, years with the disease, symptoms severity, and depression.

Results. Significant positive correlations between function and pain intensity, years with pain and

symptoms severity were observed. The path analysis found direct effects from depression, symptoms severity, and years with pain to function (all, $P < 0.01$). Paths between function and depression on pain intensity (both, $P < 0.01$) were also observed. The amount of function explained by all predictors was 22%. The indirect effects in the path analysis revealed that function exerted an indirect effect from depression to pain intensity ($B = 0.18$; $P < 0.01$), and from symptoms severity to the intensity of pain ($B = 0.10$; $P < 0.01$). Overall, the amount of current pain intensity explained by all predictors in the model was $R^2 = 0.22$.

Conclusions. Our study demonstrated that function mediates the relationship between depression and symptoms severity with pain intensity in women with CTS. Future longitudinal studies will help to determine the clinical implications of these findings.

Key Words. Carpal Tunnel Syndrome; Function; Pain; Depression; Severity; Mediation

Introduction

Carpal tunnel syndrome (CTS) is the most common nerve entrapment of the upper extremity mainly featured by compression of the median nerve at the wrist. Thiese et al. recently found a prevalence of CTS ranging from 6.3 to 11.7%; however, these authors observed that the prevalence rate varies depending on the criteria included [1]. Women are most often affected than men (women/men ratio 3:1) [2]. Becker et al. reported that female gender (adjusted odd ratio [OR] 3.66–3.76) and age between 41 and 60 years old (adj OR: 1.81–1.92) were risk factors associated with CTS [3].

Pain and paresthesia within the median nerve related areas are the most common symptoms experienced by patients with CTS [4]. Pain is mainly determined by the activity of peripheral nerve nociceptors supporting a role of sensitization mechanism in this pain condition. In fact, continuous afferent bombardment from nerve nociceptors can lead to central and peripheral sensitization mechanisms observed in these patients [5,6]. These studies found that the intensity of pain was associated with higher central sensitization in women with CTS supporting the relevance of hand pain in this condition [7,8]. Other symptoms that individuals with CTS often report is pinch strength deficits, clumsiness during daily life activities and difficulty with grasping objects. Some studies had reported the presence of decreased function and fine motor deficits in women with CTS [7,8]. In fact, these deficits in fine motor control are not directly associated to electrodiagnostic findings or hand pain [9]. Tamburin et al. hypothesized that pain may modulate function in CTS and that nociceptive C-fibers can be involved in pain-motor interactions; however, no clear association between pain and function was observed [10].

A better understanding of the potential relationship between pain and function in individuals with CTS can assist clinicians in determining adequate therapeutic programs for these patients, as no clear relationship between these two factors exists. However, few studies have investigated the association between pain and function considering the potential influence of other variables in individuals with CTS. Nunez et al. observed that two psychological variables, that is, misinterpretation of nociception and depression, were associated with the intensity of pain in different hand pain conditions, including CTS [11]. Another study reported that the intensity of pain and depression were associated with hand function in women with CTS [12]. These studies would support a potential relationship between the intensity of hand pain, function and depression, among other variables; however, all these studies included an analysis without considering potential direct and indirect interactions between these variables.

Therefore, the purpose of this study was to determine the direct and indirect effects of function on clinical variables such as age, pain intensity, years of the disease, severity of the symptoms, and depression in women with electrodiagnostic and clinical diagnosis of CTS. It was hypothesized that the relationship between pain intensity and other clinical (i.e., age, years with pain, or symptoms severity) and psychological (i.e., depression) variables would be mediated by the effect of hand function.

Methods

Participants

Consecutive women diagnosed with CTS from January 2013 to December 2014 by different neurophysiologists with 10 years of clinical experience were screened for eligibility criteria. CTS was diagnosed based on both clinical and electrophysiological findings. To be eligible, they had to exhibit the following signs and symptoms: pain and paresthesia in the median nerve distribution, increasing symptoms during the night, positive Tinel sign, and positive Phalen sign. Symptoms had to have persisted for at least 6 months. In addition, the electrodiagnostic examination had to reveal deficits of sensory and motor median nerve conduction according to international guidelines of the American Association of Electrodiagnosis, American Academy of Neurology, and the American Physical Medicine and Rehabilitation Academy [13].

Patients were excluded if they exhibited any of the following criteria: 1) sensory/motor deficit in ulnar or radial nerve; 2) older than 65 years; 3) previous surgery or steroid injections; 4) multiple diagnoses on the upper extremity (e.g., cervical radiculopathy); 5) history of cervical, shoulder, or upper extremity trauma; 6) history of

a systemic disease causing CTS (e.g., diabetes mellitus, or thyroid disease); 7) history of musculoskeletal medical condition, for example, rheumatoid arthritis or fibromyalgia; 8) pregnancy; or 9) male gender. All subjects signed an informed consent before their inclusion. The local human research committee (HUFA-12/14) approved the study project.

Clinical Data

The clinical history included questions regarding the location of the symptoms, aggravating and relieving factors, intensity, duration, and previous treatments. The main outcome in this study was the intensity of hand pain. An 11-point Numerical Pain Rating Scale (0: no pain, 10: maximum pain) was used to determine the patients' current level of hand pain, and the worst and the lowest level of pain experienced in the preceding week [14]. The mean value of the three scores was used in the analysis as the main outcome.

Function and Symptoms Severity

The Spanish version [15] of the Boston Carpal Tunnel Questionnaire [16] (BCTQ) was used to determine functional status. The questionnaire evaluates two main domains: 1) the functional status scale evaluates ability to perform eight common hand-related tasks; 2) the symptoms severity scale consists of 11 items assessing pain severity, numbness, and weakness at night and during the day. Each question is answered on a 5-points scale (1: no complaint; 5: severe complaint), where higher scores indicate greater severity of the symptoms or worse function. The BCTQ has shown to be valid, reliable, and responsive for individuals with CTS [17].

Depression

Patients completed the Beck Depression Inventory (BDI-II) for reporting their level of depressive symptoms. The BDI-II is 21-item self-report questionnaire assessing affective, cognitive, and somatic symptoms of depression [18]. The BDI-II can be easily adapted in most clinical conditions for detecting major depression [19].

Statistical Analysis

Means, standard deviations, and confidence intervals were calculated to describe the sample. The Kolmogorov–Smirnov test revealed that all quantitative data exhibited a normal distribution. To determine the relationship between the dependent measure (the intensity of hand pain) and the remaining variables (age, symptoms severity, function, depression, and years with pain) different Pearson product-moment correlation coefficients were first assessed.

Second, a path model with maximum likelihood estimation was conducted to evaluate the direct and indirect effects of function between the variables using AMOS computer program [20]. A path model analysis is a regression model extension relating independent, intermediary, and dependent variables [21]. In the hypothesized model, pain intensity was the independent variable; age, years of pain, severity, and depression were predictors of function (independent outcomes), and function (intermediate variable) was specified as predictor of the intensity of hand pain. In a path analysis, single arrows indicate causation between intermediary and dependent variables, and double arrows indicate correlation between pairs of independent variables.

The path coefficient is a standardized regression coefficient (beta) showing the direct effect of an independent variable (function) on a dependent (pain) variable. These path coefficients may be used to decompose correlations in the model into direct and indirect effects, corresponding to direct and indirect path reflected in the arrows in the model. Indirect effects occur when the relationship between two variables (e.g., pain and depression) is mediated by one or more variables (i.e., function).

Evaluation of the path-model data was based on several recommended indexes. AMOS provides several fit of them that are largely independent of the sample size: chi-square statistic (X^2) [22,23]; the goodness of fit index (GFI) and adjusted goodness of fin index (AGFI) whose value reference is at 90 to consider an acceptable model [24], and the comparative fin index (CFI) which value is accepted if it is over 0.90 [25]. Finally, within parsimony adjustment indices, we also calculated the errors of the root mean square approximation (RMSEA) whose values <0.08 are good to accept the model [26]. Missing data were treated with maximum likelihood imputation.

Results

Three hundred ($n = 300$) women with diagnosis of CTS between January 2013 and December 2014 were screened for possible eligibility criteria. Of these, 224 women satisfied all the eligibility criteria, agreed to participate and signed the informed consent. The reasons for exclusion were: previous surgery ($n = 20$), previous steroid injections ($n = 18$), diabetes ($n = 12$), whiplash ($n = 9$), pregnancy ($n = 9$), and age above 65 ($n = 8$). Eighty- four (38%) reported unilateral symptoms (59 right side, 25 left side), and the remaining 140 (62%) had bilateral symptoms. Sixty-six (29%) presented minimal CTS, 75 (34%) moderate CTS and the remaining 83 (37%) severe CTS. Demographic data and mean outcome measure scores are listed in Table 1.

Correlation Analysis

Table 1 summarizes the Pearson's correlation coefficients between the variables included in the model. Significant positive correlations were observed between function score with the intensity of pain ($r = 0.44$;

Table 1 Demographic variables and Pearson-product moment correlation matrix for each study variable

	Mean	SD	95%CI	1	2	3	4	5
Age (years)	45.6	9.0	44.4–47.8					
Years with pain	3.6	3.1	3.2–4.0	n.s				
Pain intensity (0–10)	4.8	2.2	4.5–5.1	n.s.	n.s.			
Function (0–5)	2.4	0.8	2.3–2.5	n.s.	0.18**	0.44**		
Symptoms severity (0–5)	2.9	2.2	2.6–3.2	n.s.	n.s.	n.s	0.14*	
Depression (0–21)	4.5	2.9	4.1–4.9	n.s.	n.s.	0.31**	0.39**	n.s

SD = Standard deviation; 95% CI = 95% confidence interval.
* $P < 0.01$; ** $P < 0.001$.

$P < 0.01$), years with pain ($r = 0.18$; $P < 0.01$); and between function and symptoms severity ($r = 0.14$; $P < 0.05$): the higher the pain intensity, the longer the duration of the disease or the higher symptoms severity, the higher the functional score, that is, the worse function. Further, depression was positively associated with pain intensity ($r = 0.31$; $P < 0.01$) and symptoms severity ($r = 0.39$; $P < 0.01$): the higher the pain intensity or the symptoms severity, the higher the depression level.

Path Analysis

The hypothesized model fit the data was excellent, with $X^2 = 6.47$ $X^2/df = 4$; GFI: 0.99; AGFI: 0.95; CFI: 0.97. Further, RMSEA was 0.07. Figure 1 displays the parameter estimates (standardized solution).

According to the direct effects, significant paths were noted from depression ($B = 0.10$; $P < 0.01$), symptoms severity ($B = 0.14$; $P < 0.01$), years with pain ($B = 0.18$; $P < 0.01$) to function. Likewise, significant paths also were indicated between function ($B = 0.38$; $P < 0.01$) and depression ($B = 0.16$; $P < 0.01$) on the intensity of pain. The direct effects from age on function were not significant ($B = 0.05$; $P = 0.369$). The amount of function explained by all predictors in the model was $R^2 = 0.22$.

Furthermore, the indirect effects in the path analysis model were: the indirect effect from depression to pain intensity, exerted through function, was equal to $B = 0.18$, $P < 0.01$; from severity to pain intensity, exerted through function was $B = 0.10$; $P < 0.01$. The indirect effects of two predictors were not statistically related to the intensity of pain: age ($B = 0.02$; $P > 0.05$) and years of pain ($B = 0.08$; $P > 0.05$). Overall, the amount of pain intensity explained by all predictor in the model was $R^2 = 0.22$.

Discussion

This study demonstrated that function mediates the relationship between depression and symptoms severity

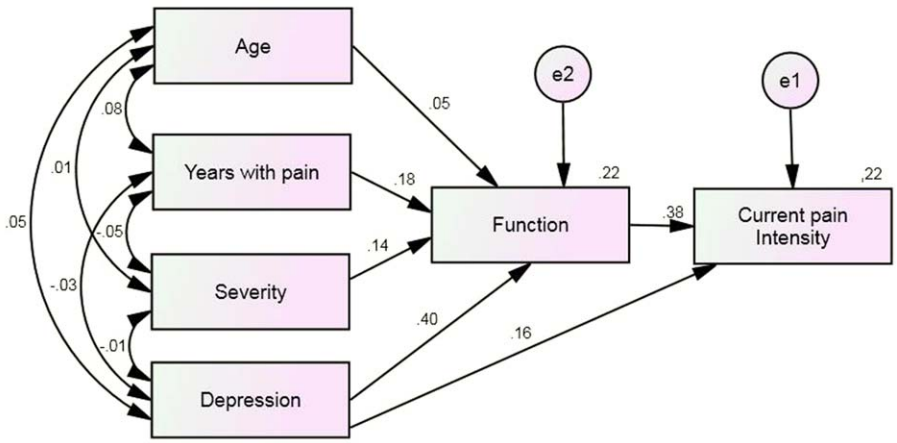

Figure 1 Path analyses relating the intensity of pain with age, years with pain, severity, and depression with the intermediate effect of function. Standardized direct path coefficients are presented. In this model, age, years with pain, severity, and depression all predict function, while the independent variable (pain intensity) is predicted by function and also directly by depression. The straight arrows represent regression paths for presumed causal relationships, which the curved double-headed arrows represent assumed correlations among the variables. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

with the intensity of hand pain in women with CTS. These results support the assumption that depression and pain intensity are intrinsically related but with an indirect effect of function.

The findings from this study show, first, and in accordance with prior literature that depression is a psychological factor clearly associated with the intensity of pain [27]. This finding is not new as an association between depression and intensity of pain in patients with CTS was previously reported by Nunez et al. [11]; however, this study did not investigate the indirect effects of other potential variables. Our study showed that function indirectly mediated the relationship between depression and the intensity of pain. Thus, while a significant amount of variance (22%) in the relationship between depression and pain intensity can be accounted for a reduction in function, the direct relationship between depression and pain remained significant. This suggests that depression also contributes to pain intensity via other factors. The role of depression in pain is an interesting finding as the level of depression in our sample was small. In fact, depression scores from our study can be considered as minimal or no clear signs of depression [18]. It is possible that the role of depression in pain would be greater in patients with higher levels of depression. Further, we should consider that the direction of the relationship between pain and depression seems to be bidirectional as pain may induce depression, but depression can also perpetuate or potentiate pain. Perhaps, proper management of depressive symptoms in subjects with CTS may help to improve, not only pain, but also hand function in this population.

The main result of this study was the role of function in the relationship between other variables such as depression and symptoms severity and the intensity of pain. A potential association between the intensity of pain and self-reported function in patients with neuropathic pain was previously reported by Seventer et al. [28]. Therefore, it seems clear that nociceptive pain has an effect on function in individuals with chronic pain [29] including CTS [10,12]. Some studies showed that the intensity of pain was a predictor of worse function in a variety of pain conditions, including low back pain [30] or sciatica [31]. Nevertheless, the methodology from our study allows few conclusions to be concluded regarding the mechanisms involved in the mediating relationship of function between depression and pain intensity. In fact, a decrease in function may be a consequence of pain pathways or may also perpetuate pain. For instance, nociceptive pain can induce a reorganization of motor strategy by a decrease activity of agonist musculature with the aim of limiting the velocity and force [32]; but motor output impairments may be also a perpetuating factor for pain mediated by pain-related fear or avoidance behaviors [33].

Uncertainty over biological mechanisms withstanding in these interactions, the current results have important clinical implications. Nijs et al. concluded, from a review of the current literature, that chronic nociceptive stimuli result in a reduced motor output activity of the affected area and that nociception-induced motor inhibition might prevent effective motor retraining [29]. Our results indicate that function, that is, motor output, plays a relevant role in the relationship between depression and symptoms severity and the intensity of pain in women with CTS. Therefore, current results suggest three main possibilities for clinical management of these patients: 1) an improvement in depression may induce better outcomes in hand function and thereby a decrease in the intensity of pain; 2) proper management of hand pain could improve hand function and therefore a decrease in depressive symptoms; or 3) proper management of function could also have indirect therapeutic effects on pain intensity and depression. Our study supports that proper management of subjects with CTS should include multimodal therapeutic interventions aimed to decrease pain intensity (i.e., manual therapies), improve function (e.g., exercises), and decrease depressive symptoms (i.e., psychological approaches).

There are a number of limitations that should be recognized. First, we used a cross-sectional design; therefore, although relationships between depression, symptoms severity, function, and the intensity of pain were examined, the mediation analyses were correlational precluding any causal inference. Second, our sample only included women with CTS, younger than 65-years old, and derived from an urban outpatient neurological population; therefore, extrapolation of current results should be considered with caution at this stage. Although, we do not currently know if our results would be similar in men with CTS or women older than 65 years old, we should consider that women aged from 41 to 60 years exhibit higher risk of suffering from CTS [3]. Therefore, this study covers the population spectrum most affected by this condition. Finally, other potential variables, for example, anxiety, sleep disturbances, or fear to movement, which could give a more broad vision of the biopsychosocial model approach were not included.

Conclusions

This study found that a significant amount of variance (22%) in the relationship between depression and symptoms severity with the intensity of pain was indirectly mediated by hand function in women with CTS. Our results suggest that function, that is, motor output, plays a relevant role in the relationship between depression and symptoms severity with pain in women with CTS. Future longitudinal studies will help to determine the clinical implications of these findings.

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