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Gender Influences Radicular Pain Perception in Patients with Lumbar Disc Herniation

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Abstract

Background: Previous studies have demonstrated gender differences in pain perception in quantitative sensory testing. Thus, we hypothesized that there are differences in men and women with lumbar disc herniation awaiting lumbar sequestrectomy. To elucidate the differences in pain perception between men and women, we carried out a prospective clinical monocentric trial using quantitative sensory testing.
Methods: With institutional ethical approval, patients with radiculopathy awaiting lumbar sequestrectomy were examined the day before surgery. Preoperative pain was assessed using quantitative sensory testing and a series of questionnaires including Beck Depression Inventory and a numeric rating scale (NRS) for back and leg pain. Statistical analysis was performed using the Kolmogorov-Smirnov test for normal distribution. The unpaired Student's *t*-test, Mann-Whitney U test, and Fisher's exact test were used to analyze intergroup differences in the clinical and demographic characteristics and in clinical outcome variables.
Results: Fifty patients (20 women and 30 men) were included in the study. The groups did not differ in NRS for back and leg pain. Heat and pressure pain thresholds were found to be lower in women than in men ($p \leq 0.05$). Subgroup analyses revealed decreased wind-up ratio in male patients with prior periradicular steroid application ($p \leq 0.05$).
Conclusions: Our results clearly indicate that sex differences in pain perception not only exist in healthy subjects, but also in patients with lumbar disc herniation. Therefore, it is essential to provide different treatment modalities to women and men.

Introduction

The vast majority of low back pain is self-limited or successfully treated conservatively, whereas a small proportion of patients develop chronic low back pain intractable to nonsurgical treatments. These patients present an increasing medical and socioeconomical problem. The annual costs in terms of morbidity, lost productivity, medical expenses and worker's compensation benefits are significant.[1] Gender differences in pain and disability and heightened recognition of the role that gender can play in influencing the pain experience and treatment response have been a topic of increased interest in recent years. Large-scale epidemiological studies across multiple geographic regions demonstrate greater pain prevalence among women relative to men.[2] Studies of experimentally induced pain have produced a very consistent pattern of results, with women exhibiting greater pain sensitivity, enhanced pain facilitation, and reduced pain inhibition, though the magnitude of these sex differences varies across studies.[3–5] Therefore, women may be at higher risk than men for developing chronic pain disorders.[6]

Quantitative sensory testing (QST) is a psychophysical measurement, relying on the subjective perception of a physical stimulus in healthy humans and patients and offers the possibility to quantify pain.[7] It allows to evaluate the function of large- and small-fiber sensory modalities in both peripheral nerve fibers and their corresponding central nervous system pathways.[8] Aß-fibers are represented by the mechanical detection threshold to von Frey filaments and vibration, whereas Aδ-fibers conduct cold sensation. Furthermore, C-fiber function is represented by warm detection and heat pain thresholds.[9,10] Cold pain threshold may be attributed to C- and Aδ-fibers. The German Research Network on Neuropathic Pain aimed to characterize the somatosensory profile of patients with neuropathic pain. For this purpose,

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Rolke et al. established gender-matched QST reference values from 180 healthy subjects, assessed bilaterally over face, hand and foot.[10] QST then has mostly been used in patients with neuropathic pain,[7] and several studies examined the sensory function in lumbar disc herniation showing evidence of pain hyperintensitivity in patients with acute or chronic spinal pain compared with healthy control subjects.[8,11–17] Nevertheless, to the best of our knowledge, there have been no studies evaluating possible gender differences in radiculopathy using quantitative sensory testing. Considering gender differences in pain perception in healthy humans, there are likely differences in pain perception between men and women with lumbar disc herniation. This is of major importance, as the outcome of spine surgery differs with gender.[18]

Thus, we hypothesized that women with lumbar disc herniation might have accentuated pain perception and greater related disability than do men with lumbar disc herniation. The purpose of this prospective study was to compare different pain patterns in men and women with radiculopathy caused by a lumbar disc herniation using quantitative sensory testing.

Material and Methods

The study was purely observational, and there were no recommendations for additional diagnostic measures of interventions. Pain management was not delayed or altered by participation in this study. All patients were on best medical pain treatment, but sufficient pain release was not achieved. According to our institution's pain medication standard, all patients received standard preoperative doses of nonsteroidal anti-inflammatory drugs and weak opioid analgesics. The study was approved by the Local Ethics Committee of the Innsbruck Medical University in accordance with the ethical principles originating from the Declaration of Helsinki and in compliance with Good Clinical Practice. All subjects signed the informed consent form. Consecutive patients were considered for inclusion if they had a single-level disc herniation confirmed on magnetic resonance imaging and a radiating pain in the corresponding nerve root distribution area of L3 to S1. All patients had an indication for sequestrectomy according to the guidelines of German Society of Neurosurgery (DGNC) and German Society of Orthopedics and Orthopedic Surgery (DGOOC). No previous back surgery had been performed in any of the patients. None of the included patients presented a history of peripheral nervous system or mental disorders, especially major illness depression. Neither metabolic nor toxic damage to the peripheral nerves was revealed. In female patients, no adjustment for menstrual phase was made at the time of testing. The study group consisted of 20 women and 30 men.

Quantitative sensory testing

The QST was performed preoperatively by a single investigator. Patients were not distracted during the testing and were given clear and identical instructions. Thresholds were determined in the affected dermatome L3 to S1. A detection threshold (DT) was defined as the feeling of a new sensation, and a pain perception threshold (PT) as the threshold when the stimulus becomes uncomfortable. The thermal tests were performed using a computer-controlled Sensory Analyzer TSA-II (Medoc), a thermode that increases or decreases its temperature at a rate of 1°C/s. Patients were asked to press a button as soon as they perceived a new sensation and the values are recorded on a computer. After determination of perception, the thermode returned back to baseline (32°C). The outer temperature limits were set at 0°C for cold and 50°C for heat, to avoid tissue damage. Cold and warm detection thresholds were measured first (CDT, WDT), then cold pain and heat pain thresholds (CPT, HPT). The mechanical detection threshold (MDT) was measured with a standardized set of modified von Frey hairs (Somedic) with different diameters that exert forces upon bending between 0.25 and 512 mN, starting with a clearly noticeable filament. The vibration detection threshold (VDT) was performed with a Rydel-Seifer tuning fork (64 Hz, 8/8 scale) measuring the disappearance of vibratory sensation. The mechanical pain threshold was measured by a custom-made pinprick set with forces from 8 to 512 mN, starting with a usually nonpainful pinprick stimulator of 8 mN. Mechanical pain sensitivity (MPS) was assessed using the same pinprick stimuli to obtain a stimulus response function for pinprick-evoked pain. Subjects were asked to give a pain rating for each stimulus on a 0 to 10 numerical rating scale (0 = no pain; 10 = the most intense pain imaginable). The wind-up ratio (WUR) was acquired by applying a single pinprick stimulus (256 mN) and a subsequent series of 10 pinprick stimuli. The mean pain rating of trains divided by the mean pain rating to single stimulus (MPS) was calculated as WUR. WUR is a frequency dependent increase in excitability of spinal cord neurons. The absence of WUR is indicated as normal,[10,19,20] whereas various studies reported an enhanced WUR in chronic pain conditions.[21–23] A pressure gauge device (FDK 20, Wagner Instruments) was used to measure the pressure pain threshold (PPT). It is defined as the amount of pressure first perceived to be painful by the subject.[10,24]

Assessments

Prospectively planned evaluation included a detailed medical history, a physical examination, and completion of a series of questionnaires, including the Beck Depression Inventory (BDI)[25] and a numeric rating scale (NRS) for back and leg pain. The BDI is a multiple-choice self-reported inventory for measuring the severity of depression and responsiveness to treatment. A four-point scale indicates the degree of severity. Outcome is as follows: 0–9, minimal depression; 10–18, mild depression; 19–29, moderate depression; and 30–63, severe depression.[25] All data were recorded on the day before surgery.

Statistical analysis

Study data generation at the study site was clearly separated from data storage, processing, and statistical analysis at the Department of Medical Statistics, Informatics, and Health Economics. All values were expressed as mean ± standard deviation or (relative) frequencies. The Kolmogorov-Smirnov test was used for testing normal distribution. The unpaired Student's *t*-test, Mann-Whitney U test, and Fisher's exact test were used to analyze intergroup differences in the clinical and demographic characteristics and in clinical outcome variables; p-values < 0.05 were considered statistically significant. All statistical computations were performed with SPSS Version 21.0 (for Windows; IBM Corp.). Figures were designed using GraphPad Prism (version 5.0 for Mac OS X; GraphPad Software).

Results

The demographic details and preoperative characteristics of the patients are presented in Table 1. Fifty patients, twenty women and thirty men with a single lumbar disc herniation causing a radiculopathy, were prospectively included in the study. In women, the most common affected nerve root was S1, and in men, L5. There were no significant intergroup differences in the preoperative demographic data. The mean duration of symptoms was 136 ± 159 days in women and 168 ± 304 days in men, respectively (difference not significant). Pain characteristics are shown in Figure 1. At admission, the mean NRS for back pain was 3.6 ± 2.3 for women and 4.2 ± 2.7 for men (difference not significant); the mean NRS for leg pain at rest was 6.4 ± 2.5 for women and 6.1 ± 2.5 for men (difference not significant).

The results of quantitative sensory testing are presented in Table 2. HPT and PPT were found to be lower in female than in male patients ($p \leq 0.005$). Dynamic mechanical allodynia (ALL) did not occur in any of the patients. There were also trends that women were more sensitive than men for the thermal detection thresholds (CDT and WDT), but these did not reach statistical significance. Similarly, thermal and mechanical pain thresholds were, on average, lower in women than in men (difference not significant) (Fig. 2). Subgroup analyses revealed differences in wind-up ratio in male patients with (0.0 ± 0.0) and without (0.9 ± 1.5) periradicular steroid application ($p = 0.040$) within 30 to 90 days before testing, but there was a wide individual variation and no statistical difference in female patients (Fig. 3). Analysis of BDI data demonstrated no significant gender differences (8.0 ± 5.5 for women, 6.7 ± 6.5 for men).

Table 1. Demographic and Clinical Characteristics of Female and Male Patients with Low Back Pain and Radiculopathy

Characteristics	*Female patients* n = *20*	*Male patients* n = *30*
Mean age, years (SD)	44.0 (±9.4)	45.5 (±11.4)
Mean BMI (SD)	26.8 (±5.0)	26.8 (±3.2)
Smoking, *n* (%)	12/20 (60)	16/30 (53.3)
Physical activity		
None *n* (%)	5/20 (25)	8/30 (26.7)
Daily, *n* (%)	5/20 (25)	10/30 (33.3)
Weekly, *n* (%)	5/20 (25)	6/30 (20)
Incidentally, *n* (%)	5/20 (25)	6/30 (20)
Periradicular infiltration with steroid, *n* (%)	4/20 (20)	8/30 (26.7)
ASA score		
1, *n* (%)	12/20 (60)	18/30 (60)
2, *n* (%)	8/20 (40)	12/30 (40)
Mean duration of pain in days (SD)	136.9 (±159.5)	168.6 (±304.0)
Leg-raising test		
Negative, *n* (%)	6 (30)	5 (16.7)
Positive, *n* (%)	14 (70)	25 (83.3)
Radicular pain		
L3, *n* (%)	0/20 (0)	3/30 (10)
L4, *n* (%)	3/20 (15)	2/30 (6.7)
L5, *n* (%)	7/20 (35)	13/30 (43.3)
S1, *n* (%)	10/20 (50)	12/30 (40)

ASA, American Society of Anesthesiology; BMI, body mass index; L, lumbar; *n*, number of patients; S, sacral; SD, standard deviation.

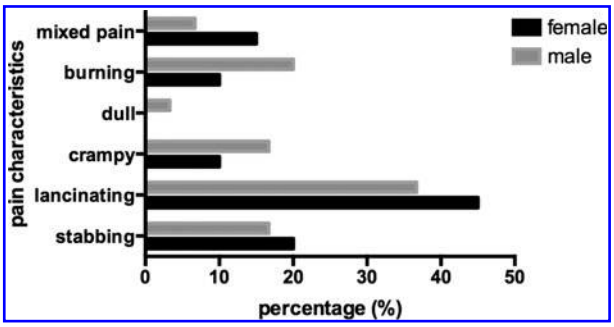

FIG. 1. Different pain characteristics between women and men with radiculopathy caused by lumbar disc herniation. The predominant pain characteristic was a lancinating pain in both women (45%) and men (36.7%).

Discussion

We present the results of the first prospective study comparing gender differences in patients with radiculopathy awaiting lumbar sequestrectomy using QST. Our analysis showed differences in heat and pressure pain thresholds between men and women, presenting lower pain thresholds in female patients.

Previous studies showed that QST values from patients with radicular pain ranged pathologically outside the German Research Network on Neuropathic Pain reference values.[12] Pain perception thresholds were found to be significantly lower on the clinically affected lower limb compared with the contralateral side.[13] Based on this former data and in order to validate our QST findings as precisely as possible, we did not compare our data with a healthy control group. Instead, we

Table 2. Preoperative Gender Differences in Thermal and Mechanical Thresholds on the Symptomatic Side

QST parameters	*Female* (n = *20*)	*Male* (n = *30*)	p-*Value*
CDT, mean ± SD	24.5 ± 5.0	23.1 ± 7.6	n.s.
WDT, mean ± SD	41.7 ± 4.2	42.5 ± 4.8	n.s.
CPT, mean ± SD	10.2 ± 9.5	8.7 ± 9.4	n.s.
HPT, mean ± SD	46.3 ± 8.2	48.8 ± 2.2	**0.039**
MDT, mean ± SD	13.5 ± 9.6	20.7 ± 22.6	n.s.
DMA, mean ± SD	did not occur in any of the patients		
VDT, mean ± SD	5.5 ± 1.6	5.4 ± 2.5	n.s.
PPT, mean ± SD	5.8 ± 2.0	7.5 ± 2.7	**0.036**
WUR, mean ± SD	0.9 ± 1.8	0.6 ± 1.4	n.s.
MPS, mean ± SD	1.4 ± 1.9	1.4 ± 2.1	n.s.

Quantitative sensory testing (QST) data are presented as means ± SD

CDT, cold detection threshold; CPT, cold pain pain threshold; DMA, dynamic mechanical allodynia; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; n.s., not significant; PPT, pressure pain threshold; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio.

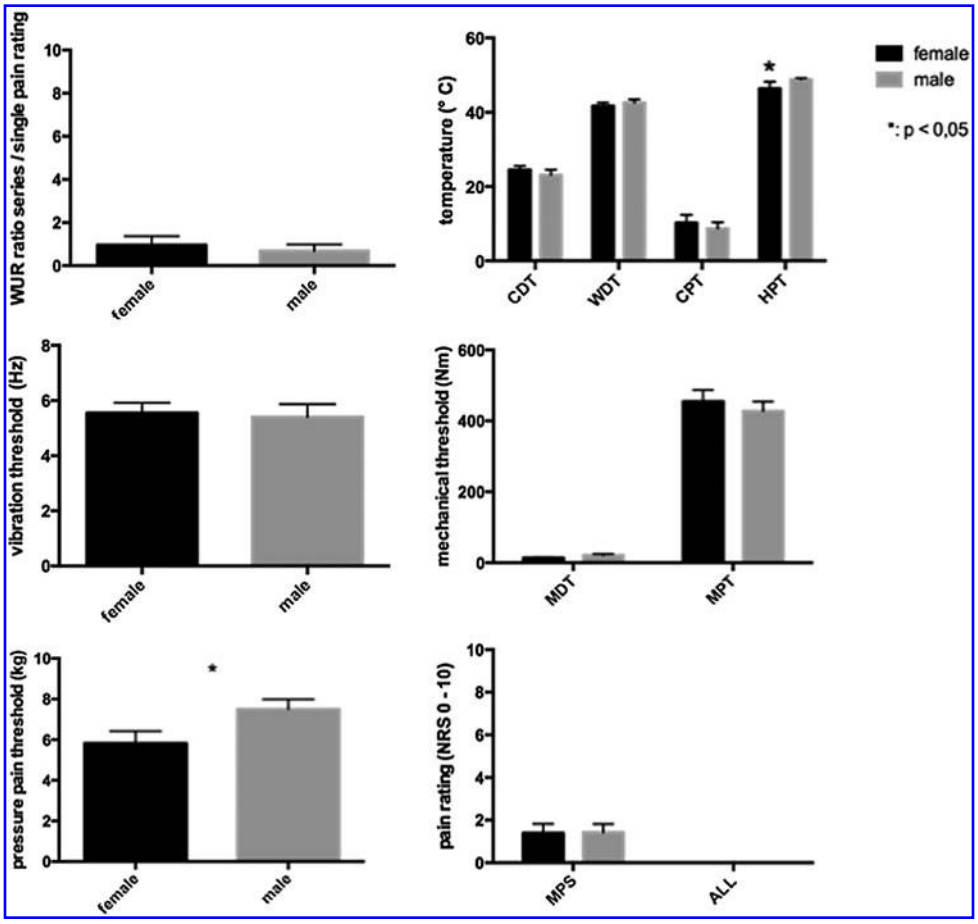

FIG. 2. Gender dependence of pain in patients with radiculopathy caused by a lumbar disc herniation. Heat pain threshold (HPT) and pressure pain threshold (PPT) differed between male and female patients. WUR, wind-up ratio; CDT, cold detection threshold; WDT, warm detection threshold; CPT, cold pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; ALL, allodynia. Data is presented as mean and standard error of the mean; $*p < 0.05$ (statistically significant).

focused on different somatosensory profiles in male and female patients with radiculopathy.

Recent research has emphasized that the presence of depression is an important factor which influences pain and also function after surgery.[26] Patients with mental disorders were excluded from our trial, and also, BDI scores between men and women were not statistically different. Thus, we could exclude depression as a possible influencing factor on pain perception in our study group.

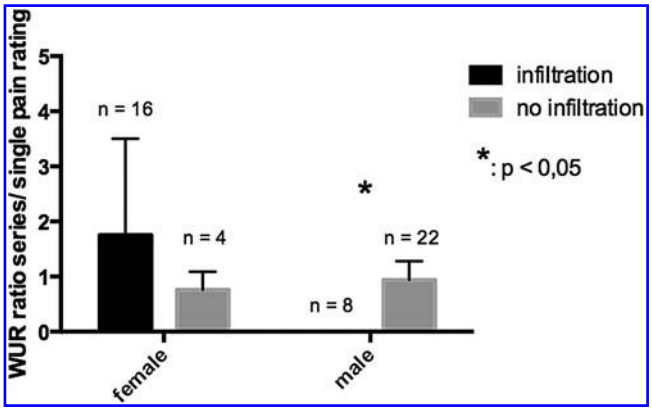

FIG. 3. Subgroup analyses of WUR in patients with and without periradicular steroid infiltration within 30 to 90 days prior to surgery. Data is presented as mean and standard error of the mean; *n*, number of patients; $*p < 0.05$ (statistically significant).

Multiple studies have examined gender differences in experimentally induced pain, and previous publications concluded that women display greater sensitivity to multiple pain modalities compared with men.[2,5,10,27] Rolke et al. investigated 180 healthy subjects by QST, assessed bilaterally over face, hand, and foot. They determined thermal detection and pain thresholds including a test for paradoxical heat sensation; mechanical detection threshold to Frey filaments and a 64 Hz tuning fork; mechanical pain threshold to pinprick stimuli and blunt pressure; stimulus/response-function for pinprick and dynamic mechanical allodynia; and wind-up ratio. QST parameters were region specific and age dependent. Similar to our results, pain thresholds were significantly lower in women than in men, whereas detection thresholds were generally independent of gender. Thermal detection thresholds, however, exhibited a significant gender-to-region interaction, indicating that the higher temperature sensitivity of women was only significant in the lower limbs.

The largest effect sizes for gender differences were found for heat pain (HPT), whereas cold pain (CPT) did not differ between women and men. C-fiber function is represented by the warm detection threshold (WDT) and HPT. The relative contribution of C- and Aδ-fiber nociceptors to CPT is less clear. Mechanisms of cold hyperalgesia are poorly understood including both peripheral sensitization and altered central processing. Furthermore, a large variability of CPT values was reported in the relevant literature.[10,28] This may explain the absence of significant gender differences for CPT.

While the results of our study show statistically significant differences between genders in mean HPT, the clinical relevance of such differences should also be considered. A review of the literature revealed no investigations devoted on this topic. It is important to note that further investigations are required to establish clinically relevant changes in HPT for both gender groups.[10]

QST has mostly been used in patients with neuropathic pain,[7] and several studies examined the sensory function in lumbar disc herniations.[8,12–17,29] It has already been shown that there is a preoperative association between clinical neurophysiological indices and the degree of lumbar nerve root compromise depicted on magnetic resonance imaging in patients awaiting lumbar discectomy.[13] Another group concluded that thermal testing had an acceptable reproducibility in patients with sciatica[8] but seemed to have the same poor predictive value for identifying the anatomic location of a herniated lumbar disc as conventional electrophysiological methods.[16] Further prospective clinical trials investigated quantitative sensory parameters after surgical decompression in lumbar radiculopathy by quantitative sensory testing.[14,15] Nevertheless, to the best of our knowledge, there is a lack of clear data on gender differences in radiculopathy caused by a lumbar disc herniation using QST.

Prolonged or intensely painful stimuli such as lumbar disc herniations can trigger chronic pain disorders and can lead to neuroplastic changes of the central nervous system.[30] WUR is a method to assess these changes and can be an important tool for studying chronic pain. The absence of WUR is indicated as normal,[10,19,20] whereas various studies reported an enhanced WUR in chronic pain conditions.[21–23] Although our results showed no statistical significant differences between men and women, a subgroup analysis revealed WUR to be different in male patients with and without periradicular steroid application within 30 to 90 days before surgery. There was no statistical difference in female patients. None of our male patients with preoperative steroid application showed a decreased WUR. Thus, we hypothesize that there are differences in pain responses to corticosteroid application between men and women, suggesting that men have a greater benefit than women from periradicular steroid interventions. A limitation of these findings is the small number of subjects in the subgroup that underwent this procedure. Additional studies with greater patient numbers are required for definitive confirmation. There are a number of further limitations, such as varying degrees of disc herniations or the uncertainty of the size of clinically significant differences, as mentioned above. In addition, all patients received preoperatively standard medication of nonsteroidal anti-inflammatory drugs and weak opioid analgesics. Possibly, women were being treated less effectively, which could have influenced their pain perception.

Conclusion

Our results and the literature reviewed above clearly indicate that sex differences in pain perception exist not only in healthy subjects, but also in patients with lumbar disc herniation. The current study provides insights for further research, especially regarding the influence in pain perception on the results of various treatment modalities between men and women. To provide optimal pain management for each patient, it is also essential to provide different treatment modalities to women and men. Particularly, our results indicate that we have to separately adapt standard medication regimes to both female and male patients with lumbar disc herniation.

Author Disclosure Statement

No competing financial interests exist.

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