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ORIGINAL ARTICLE

Analysis and relationship between the volume of upper limb lymphoedema and pressure pain threshold, neural range of motion, pain intensity, kinesiophobia, pain hypervigilance and catastrophizing in breast cancer survivors

Isabel ALMAGRO-CÉSPEDES [1, 2, 3], Rosa M. TAPIA-HARO [2, 4] *, Antonio M. MESA-RUIZ [1], Natalia FERNÁNDEZ-SÁNCHEZ [3], Patrocinio ARIZA-VEGA [4, 5], María E. AGUILAR-FERRÁNDIZ [2, 4]

[1]Physical Medicine and Rehabilitation Service, Virgen de las Nieves University Hospital of Granada, Granada, Spain; [2]Instituto de Investigación Biosanitaria ibs.GRANADA, Granada, Spain; [3]Biomedicine Program (B 11.56.1) of the University of Granada, Granada, Spain; [4]Department of Physical Therapy, Faculty of Health Sciences, University of Granada, Granada, Spain; [5]PA-HELP "Physical Activity for HEaLth Promotion" Research Group, Department of Physical Therapy, Faculty of Health Sciences, University of Granada, Granada, Spain

*Corresponding author: Rosa M. Tapia-Haro, Department of Physical Therapy, Faculty of Health Sciences, University of Granada, Ave. de la Ilustración, 60, 18071, Granada, Spain. E-mail: rtapia@ugr.es

ABSTRACT

BACKGROUND: Lymphedema of the upper limbs and persistent pain are frequent sequelae after surgical treatment of breast cancer.
AIM: The aim of this paper was to analyze the upper limb volume, pressure pain threshold, neural range of motion, pain intensity, kinesiophobia, pain hypervigilance and catastrophizing in patients with and without lymphoedema after breast cancer surgery. Secondly, we aimed to investigated the association between upper limb volume and these variables.
DESIGN: Descriptive observational study.
SETTING: Faculty of Health Sciences of the University of Granada.
POPULATION: Fifty-eight post-surgical breast cancer survivors, 29 with upper limb lymphoedema and 29 without lymphoedema.
METHODS: We measured upper limb volume (perimetric method). Also, pressure pain thresholds were assessed with a digital algometer, neural range of motion (neurodynamic test for radial, ulnar and median nerves), pain intensity (visual analogue scale), kinesiophobia, pain hypervigilance and catastrophizing (validated tests). To detect differences between the groups for the measurement variables we performed a t-test for independent samples analysis. A simple linear regression analysis adjusting for age and body mass index was performed to check the association among upper limb volume and pain variables in the group with lymphoedema.
RESULTS: The analysis showed that lymphoedema group had lower pressure pain threshold bilaterally in the masseter (origin $P \leq 0.036$; insertion $P \leq 0.046$), temporalis (insertion $P \leq 0.021$), suboccipitalis ($P \leq 0.036$); second ($P \leq 0.014$), third ($P \leq 0.001$) and tenth rib ($P \leq 0.001$); affected side of the temporalis (origin $P=0.025$); temporomandibular joint ($P=0.024$); neural range of motion in the median nerve ($P=0.047$), ulnar ($P=0.042$) on the affected side and radial ($P=0.039$) on the unaffected side; and greater kinesiophobia ($P=0.042$). Linear regression analysis only showed a significant association between upper limb volume and neural range of motion in the radial nerve ($P=0.020$) in the lymphedema group. No significant associations were obtained for the rest of variables.
CONCLUSIONS: These findings suggest that the presence of lymphoedema may contribute to an increased level of generalized mechanosensitivity and fear to movement in this population.
CLINICAL REHABILITATION IMPACT: Upper limb lymphedema can lead to heightened mechanosensitivity and movement-related fear in breast cancer survivors. Therefore, fast track rehabilitation approach should be focus in screening and rehabilitation methods for detection and control this sequalae.

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KEY WORDS: Breast neoplasms; Chronic pain; Hypersensitivity; Lymphedema; Mastectomy; Women.

Breast cancer is the most frequent type of female cancer worldwide, surpassing lung cancer, with 2.3 million new cases by 2020 (representing 11.7% of cancers and 31% of cancers in women).[1, 2]

The risk of breast cancer increases with age, being the average age of diagnosis 61 years, and decreases after menopause. It ranks as the fifth cancer with the highest mortality rate worldwide (6.9%), being the leading cause of cancer death in women in more than 100 countries.[1, 2] However, there has been evidence of a progressive increase in the survival of patients with this type of cancer since the second half of the 20th century, with a survival rate of 86% currently,[2] and there has also been a decrease in the proportion of metastatic diagnoses. Increased screening protocols and continued advances in treatment for this type of cancer may be the causes of this decline.[3]

As breast cancer survival increases, the quality of life problems of these patients become increasingly relevant.[1, 4] Among the most frequent complications of surgical treatment is the development of upper limb lymphoedema.[4] A meta-analysis of 98 studies on the most frequent risk factors for developing lymphoedema in these patients concluded that the most important are mastectomy, radiotherapy, axillary dissection and axillary tumor nodules.[4] The incidence of lymphoedema in surviving women is still questionable, with studies showing that 20-30% of surgical patients have lymphoedema,[5] while others range from 6% to 70%.[6]

Despite the impact of this condition, lymphedema is underdiagnosed and undertreated.[6] Some studies claim that this is due to a lack of research into preventive measures and treatment approaches,[6, 7] poor hospital services, insufficient specialized clinics or the costs of treatment.[6] These studies also report that lymphoedema is understudied because it is not life-threatening, and that there is a need for improved evidence-based practices and high-quality patient and family education.[6-8]

Another common sequela in breast cancer survivors is the onset of persistent pain after breast cancer treatment (PPBCT), with a prevalence of 24-47%.[8] PPBCT has been identified as the most important predictor of deterioration in the quality of life of these patients after surgery, affecting daily, home and work activities considerably.[8, 9] Persistent pain is mainly neuropathic, due to nerve tissue injury during treatment.[9] This pain most commonly manifests in the breast, axilla, ipsilateral upper arm and anterior and/or lateral chest wall.[9, 10] Different symptoms such as paresthesias in scar and arm, strange sensations and muscle weakness in the ipsilateral arm appear more frequently accompanying the pain in the same area.[10] Furthermore, in response to nerve damage, neuropathic pain is frequently accompanied by a subsequent central sensitization.[11] Fernandez Lao *et al.*[12] suggested in their research that the bilateral and generalized pressure pain hypersensitivity found in the patients studied suggests a central sensitization present in any type of breast cancer surgery. In this line, different studies have reported the presence of hypersensitivity to pressure pain after treatment in patients with breast cancer seems to suggest a central sensitization after surgery.[12-15]

The relationship between upper limb lymphedema and pain-related outcomes in breast cancer survivors remains a topic of debate. Some studies suggest that lymphedema can lead to altered neural tissue mobility and increased neuropathic pain in these patients.[16-19] Conversely, a recent study found no correlation between the severity of lymphedema and increased neuropathic pain in the median nerve.[20]

Additionally, the association between kinesiophobia (fear of movement) and lymphedema remains controversial. While one study indicated a significant relationship between kinesiophobia and lymphedema,[21] other research did not find significant correlations between the volume of upper limb lymphedema and the degree of kinesiophobia in breast cancer survivors.[22, 23]

Overall, the evidence regarding the relationship between upper limb lymphedema and pain-related variables is limited and inconsistent, indicating a need for further research to clarify these associations.

Within this context, we proposed two objectives in the present study. Firstly, we established to analyze and compare upper limb volume, pressure pain threshold, neural range of motion, pain intensity, kinesiophobia, catastrophizing, and pain hypervigilance in breast cancer survivors with and without lymphedema.

Secondly, to investigate the association between the upper limb lymphedema volume and pressure pain threshold, neural range of motion, pain intensity, kinesiophobia, catastrophizing, and pain hypervigilance in the group of patients with lymphedema.

Materials and methods

Study design

A descriptive observational study was conducted with 58 post-surgical breast cancer survivors, including 29 participants with upper limb lymphoedema and 29 without lymphoedema. The study was approved by the Clinical Biomedical Research Ethics Committee of Granada (CEI-6hWMS795P) and was conducted in accordance with the amended version of the Declaration of Helsinki, 2013, obtaining informed consent from all participants.

The patients were evaluated in the clinical research facilities of the Faculty of Health Sciences of the University of Granada, carrying out a clinical examination and a personalized interview with each patient. Several variables were recorded, including sociodemographic data, upper limb volume as dependent variable, pressure pain threshold (PPT) as primary variable and upper limb volume, neural range of motion, pain intensity, kinesiophobia, hypervigilance and catastrophizing as secondary variables. Both groups of participants were assessed using the same procedures.

Participants and setting

Between February and April 2023, a total of 58 women who had undergone surgery after a diagnosis of breast cancer were recruited, all of them from the Association of Andalusian Mastectomized Women (AMAMA) in Granada. The diagnosis of lymphoedema was made previously by an oncologist of the Andalusian Health Service of the according to the criteria of the International Society of Lymphology, which establishes the presence of lymphoedema when an increase of 2 cm or more is detected in at least two consecutive perimeters of the affected upper limb compared to the healthy contralateral limb,[24] in addition confirmatory diagnosis of the lymphedema was made using lymphoscintigraphy. To be included in the study, patients had to meet the following criteria: 1) to be in cancer remission stage I-IIIA; 2) to be older than 20 years; 3) to have passed at least 6 months since surgery; 4) to have passed at least 3 months since radiotherapy or chemotherapy treatment, if received; 5) to have undergone mastectomy or lumpectomy surgery. Inclusion criteria for patients with lymphoedema were chronic lymphoedema (more than three months of evolution) of the upper limb due to neoplastic disease. Patients that have undergone bilateral surgery, patients with other health conditions that could interfere with the study variables such as recurrent neoplastic symptoms or a previous diagnosis of pathology with chronic pain were excluded.

Measures

Upper limb volume

To calculate the volume of the upper limb we use the perimetric method. In this method, the upper limb is divided in four segments with truncated cones.[25] The cones are placed taking into account anatomical reference points (wrist to the middle of the forearm, middle of the forearm to the elbow, elbow to the middle of the arm and limit of the middle of the arm to the upper part of the arm). We then calculated the segmental volume of each truncated cone using the following formula h (C2 +Cc + c2) /12π, where h is the height (distance between two measurements), C is the perimeter of the large circumference and c is the perimeter of the small circumference. Total upper limb volume was obtained by adding the volumes of the truncated cones, volume total=(V1+V2+V3+V4).[25] We have also calculated the relative volume of each segment. Assuming the total volume of the upper limb is 100%, we determined the percentage that each segment contributes to the total volume.

Mechanosensitivity

Pressure pain thresholds

The PPT is defined as the minimum amount of pressure that produces pain to the patient.[26, 27] To measure PPTs, we used a digital algometer (Wagner model FPX 25, Instruments Greenwich, CT), whose tip consisted of a 1 cm^2 rubber disc. The examiner applied a constant force perpendicularly to the skin of the participants, who were asked to indicate when the pressure sensation turned into mild painful discomfort. Three consecutive measurements were taken at each point, with a 30-second rest between each assessment, and the PPT value was calculated as the average result of the three measurements. Patients were instructed to avoid analgesics or muscle relaxants 48 hours before the evaluation process.[26-29]

PPTs were measured on the face along the course of the trigeminal nerve on its three branches. We also evalu-

ated PPTs bilaterally on the upper limbs at the level of the median, radial and ulnar nerves. Furthermore, the PPT were assessed on the masseter, temporalis, suboccipitalis, temporomandibular joint, second, third and tenth ribs, the proximal third of the sternum, and the joint space between C5-C6 and C7-T1.[27, 28]

Finally, the deltoid muscle, ulnar styloid and anterior tibialis muscle PPT were assessed.[26-31] (Supplementary Digital Material 1: Supplementary Table I).

Neural range of motion

Upper Limb Neurodynamic Tests (UPNT) of the radial, ulnar and median nerves were performed to assess neural tension in both upper limbs, with the aim of detecting neural range of motion.[32] Neurodynamic testing was considered positive if it reproduced the patient's pain symptoms, if the symptoms varied with neck position (feeling relief with homolateral lateroflexion, exaltation with contralateral lateroflexion) or if there was a difference of more than 10 degrees in goniometry between both upper limbs.[33-35]

The movement patterns established by Nee *et al.*[32] were used to individually evaluate the peripheral nerves of both upper limbs. The tests were performed while the patient was supine, in a relaxed position and with the cervical area in a neutral position, without reclining using a posterior pillow. The execution of the tests was slow and gentle, and the patients were instructed to identify and communicate any pain that prevented them from continuing with the movement. The assessment began by performing structural differentiation maneuvers while the patient was in the position described above, using cervical lateroflexion. If the patient was pain-free, the range of motion was continued until the maximum available range of motion was reached. The number of degrees of movement was measured by current goniometry when the optimal range of motion was reached. For the radial and ulnar tests, the degrees of shoulder abduction were measured by placing the axis of the goniometer over the acromion, the fixed arm aligned with the midaxillary line and parallel to the sternum, and the movable arm aligned with the longitudinal midline of the humerus. To assess the median nerve, degrees of elbow extension were measured by placing the axis of the goniometer over the epitrochlea, the fixed arm aligned with the longitudinal midline of the humerus and the movable arm aligned with the longitudinal midline of the forearm (Figure 1). Upper Limb Neurodynamic Tests in a participant with lymphedema.

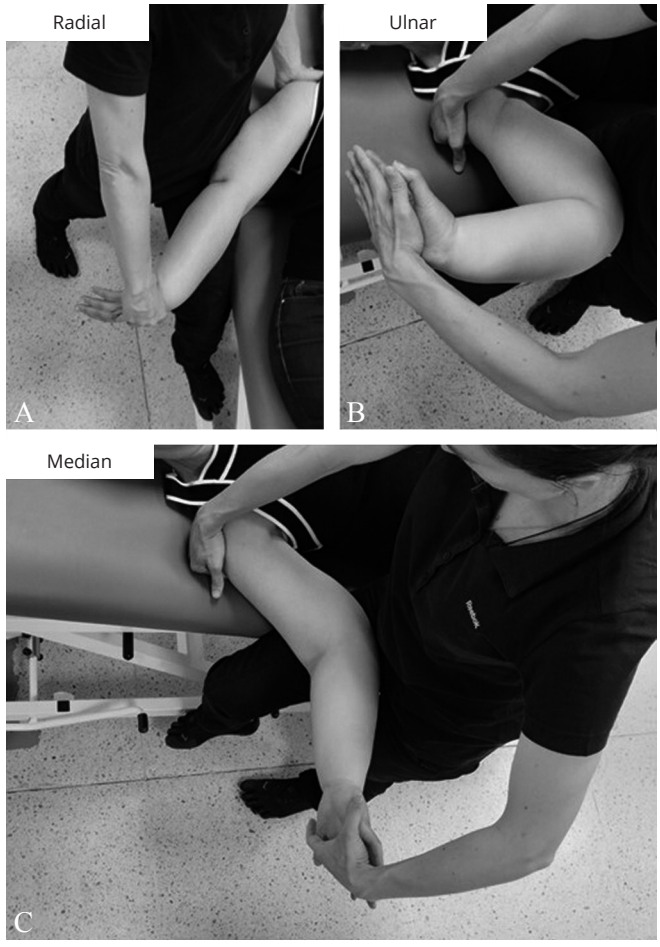

Figure 1.—Upper limb neurodynamic tests in a participant with lymphedema. A) Upper limb neurodynamic test for radial nerve; B) upper limb neurodynamic test for ulnar nerve; C) upper limb neurodynamic test for median nerve.

Pain intensity

We measured pain intensity with the Visual Analogue Scale (VAS). Patients were shown a horizontal line from 0 to 10 centimeters, with the terms "no pain" and "maximum pain" at the ends, and the words "mild, moderate and severe" distributed along the line,[36] patients were asked to indicate their degree of pain at the time of the examination. This scale has been shown to have good reliability with a Goodman-Kruskal coefficient of 0.70.[36]

Kinesiophobia

We used the Tampa Scale for Kinesiophobia (TSK-11), which is a widely used tool to evaluate fear of movement and fear of re-injury during movement. It consists of 11

items and is divided into two factors: "activity avoidance" (6 items), which refers to fear and avoidance of activities that may cause pain, and "somatic focus" (5 items), which refers to the belief that pain is a sign of serious harm or injury to the body.[37] The total score of the TSK-11 can range from 11 to 44 points, where higher scores indicate a greater fear of re-injury during movement.[37, 38] This test has been shown to have good test-retest reliability, convergent validity and sensitivity to change.[38]

Pain hypervigilance

Hypervigilance was measured using the Pain Vigilance and Awareness Questionnaire (PVAQ).[39] The PVAQ consists of 9 items assessing aspects of awareness, knowledge, vigilance and observation of pain. Patients are asked to consider their behavior over the past two weeks and to rate each item on a scale from 0 to 5, reporting how they perceive themselves.[40] The PVAQ total score can range from 0 to 45 points, indicating a greater degree of vigilance and awareness of pain when scores are higher.[40] The PVAQ has been shown to be reliable, with adequate internal consistency (Cronbach's alpha=0.86) and temporal stability over a short time interval.[40]

Pain catastrophizing

We used the Pain Catastrophizing Scale (PCS) in its Spanish adapted version[41, 42] to evaluate catastrophizing. This scale analyses three factors that patients perceive in relation to their pain control: rumination ("I can't stop thinking about how much it hurts"); magnification ("I worry that something serious might happen"); and helplessness ("There is nothing I can do to reduce the intensity of the pain").[42] It consists of a total of 13 items scored from 0 to 4, ranging from "Not at all" to "All the time," with a total score of 52.[42] A total score of 30 on the PCS indicates a significant level of pain catastrophizing from a clinical point of view.[41, 42] The PCS is a reliable and accurate tool with high internal consistency (Cronbach's α=0.87).[42]

Statistical analysis

We used the SPSS Statistics Version 29 for Windows (IBM Corporation, Armonk, NY, USA) for data analysis. Normality of the variables was verified with the Kolmogorov-Smirnov test (α value=0.05). Sociodemographic and clinical variables were tested by a one sample *t*-test for continuous variables and the Chi-square Test (χ^2) for categorical variables. The data for continuous variables were expressed as mean±standard deviation (SD) and for categorical variables as frequency (%). Subsequently, the groups were compared using a *t*-test for independent samples, to detect differences between the groups as means (with 95% confidential intervals) for the dependent, primary and secondary measurement variables. We performed a simple linear regression analysis to test the associations between the total volume of the upper limb as a dependent variable and the measurements of the different pain parameters as independent variables in the lymphedema group. In this way, the simple linear regression analysis was specifically carried out with the total volume of the upper limb as the dependent variable, adjusted for age and body mass index and specifically with each of the independent variables, neural range of motion (radial, ulnar and median nerves), pain intensity, kinesiophobia, hypervigilance and level of catastrophizing. The results of the linear regression analysis were expressed as beta estimate (β) with 95% CI and P value. $P<0.05$ was considered statistically significant.

Sample size

G*Power Version 3.1.9.7 software (Heinrich Heine University, Düsseldorf, Germany) was used to estimate the sample size. Based on a previous study[43] a clinically significant difference between groups of 20% was taken as the clinically significant difference between groups for the primary variable PPT of the upper limb (median nerve), resulting in a sample size estimate of 16 patients per arm to provide a 95% confidence interval, with a power of 80%, assuming a two-sided significance level (α) of 0.05. The sample was increased to 29 patients per arm to provide a loss to follow-up of 55%.

Results

Sociodemographic and clinical characteristics

For the present study, a total of 58 female breast cancer survivors were evaluated and classified into two groups, with the criterion being the occurrence of post-surgery lymphoedema in the affected arm (29 patients with lymphoedema and 29 without lymphoedema). The mean age of the participants was 61.59±11.76 years, of whom 30 had undergone lumpectomy and 28 had undergone mastectomy. All of them underwent radiotherapy and/or chemotherapy after surgery and in 35 of the participants the affected arm was the non-dominant one (Supplementary Digital Material 2: Supplementary Table II).

Differences in upper limb volume between lymphedema group and non-lymphedema group

Independent samples *t*-test analysis showed significant differences between the groups for the absolute segmental volume of the second cone (P=0.010), the third cone (P=0.009) and for the total absolute volume (P=0.032) of the affected upper limb, where the group with lymphoedema had a significantly higher mean for these perimeters than the group without lymphoedema. The result also showed significant differences between the groups in the relative volume of the third cone (P=0.006) of the unaffected upper limb and the relative volume of the affected upper limb (P=0.029) (Supplementary Digital Material 3: Supplementary Table III). Furthermore, independent samples t-test analysis showed significant differences between affected and non-affected mean differences between groups in all the variables for absolute volume (P≤0.049); and for the relative volume of the second (P=0.006) and fourth cone (P=0.048) (Supplementary Table III).

Differences in mechanosensitivity between lymphedema group and non-lymphedema group

Pressure pain thresholds

Independent samples *t*-test analysis showed significant differences between groups for pressure pain points on the unaffected side for masseter muscles at origin (P=0.036) and insertion (P=0.024); temporalis at insertion (P=0.006); suboccipitalis (P=0.036); second rib (P=0.014); third rib (P<0.001) and tenth rib (P<0.001). Significant differences between groups were also obtained on the affected side of the masseter muscles at origin (P=0.025) and insertion (P=0.046); temporalis at origin (P=0.025) and insertion (P=0.021); suboccipitalis (P=0.015); second rib (P=0.004); third rib (P=0.001), tenth rib (P<0.001) and temporomandibular joint (P=0.024). For all these points, the lymphoedema group had significantly lower mean values than the non-lymphoedema group (Supplementary Digital Material 4: Supplementary Table IV). No significant differences were obtained for the rest of the items evaluated (P≥0.057).

Neural range of motion

The t-test analysis for independent samples showed significant differences in ULNT for median nerve (P=0.047) and ulnar nerve (P=0.042) of the upper limb on the affected side and radial nerve of the upper limb on the unaffected side (P=0.039) between the groups. The lymphoedema group showed significantly lower mean ULNT in these variables compared to the non-lymphoedema group (Supplementary Table IV).

Differences in pain intensity, kinesiophobia, pain hypervigilance and pain catastrophizing between lymphedema group and non-lymphedema group

The *t*-test analysis for independent samples did not show significant differences for pain intensity between the groups (P=0.102) (Supplementary Digital Material 5: Supplementary Table V).

The *t*-test analysis for independent samples showed a significant difference in the kinesiophobia test between groups (P=0.042), with patients with lymphoedema scoring higher than those without. No significant differences were obtained between the groups for pain hypervigilance nor pain catastrophizing (P≥0.104) (Supplementary Table V).

Associations between upper limb volume and pressure pain thresholds, neural range of motion, pain intensity, kinesiophobia, pain hypervigilance and pain catastrophizing in the lymphoedema group

The linear regression analysis adjusting for age and BMI showed that upper limb volume in patients with lymphoedema were significantly associated with the radial neural range of motion (β=-7.248, 95% CI [-13.234, -1.261], P=0.020). However, there were no significant interactions between upper limb volume and the rest of mechanosensitivity (P≥0.132) and pain (P≥0.538) variables (Supplementary Digital Material 6: Supplementary Table VI). Finally, the linear regression analysis, adjusting for age and BMI, showed that the mean differences in upper limb volume between the affected and non-affected sides in patients with lymphedema were not significantly associated with any of the mechanosensitivity (P≥0.203) or pain (P≥0.263) variables (Supplementary Digital Material 7: Supplementary Table VII). Beta estimates, confidence intervals and p-values for the association between mean differences for affected vs non-affected side upper limb volume and clinical features in lymphoedema group).

Discussion

The results showed that female breast cancer survivors with lymphoedema had higher levels of bilateral mechanosensitivity, with greater hypersensitivity and alterations in neural range of motion and higher levels of kinesiophobia than patients without lymphoedema. However, we

did not find significant associations between upper limb lymphedema volume and, pressure pain threshold, pain intensity, kinesiophobia, hypervigilance and catastrophizing in women with lymphoedema.

According to our results, patients with lymphoedema had higher hypersensitivity to PPTs on both the affected and unaffected side (masseter, temporalis, suboccipitalis and second, third and tenth ribs) and in the temporomandibular joint on the affected side, compared to patients without lymphoedema. Also, patients with lymphoedema had altered neural ranges of motion for the median and ulnar nerve on the affected side and the radial nerve on the unaffected side. These findings suggest that the presence of lymphoedema may contribute to an increased level of generalised (bilateral) mechanosensitivity, which could affect the central sensitization process. The occurrence of central sensitization processes after treatment in breast cancer patients has been widely described.[12-14] The central nervous system sensitization that occurs in these patients may result in persistent pain, generalized pain sensations and hyperalgesia (increased pain and tenderness).[15] The findings of the present study are in line with those of previous studies that have indicated that the bilateral and generalized pressure pain hypersensitivity found in these patients seems to suggest a central sensitization after surgery,[12-14] which would also involve the non-operated side. However, in our sample, the presence of lymphoedema seems to contribute to an increase in general hypersensitivity. In this regard, Shinde *et al.* state that lymphoedema may progressively lead to entrapment neuropathy that may increase neuronal mechanosensitivity as a protective response to movement or traction.[16] Along these lines, a study by Smoot *et al.*,[17] where they analyzed mechanosensitivity and neural range of motion after treatment in women with breast cancer, determined that women with pain and lymphoedema may have altered neural mechanosensitivity related to upper limb lymphedema.[17] Neuropathic pain appears to be the result of nerve-trapping fibrosis due to scar tissue after mastectomy, chemotherapy or radiotherapy.[18] However, this pain has been reported to be more prevalent in those patients with lymphoedema[19] suggesting the involvement of upper limb lymphedema as a contributing factor.

On the other hand, pain levels could be influenced by the processes of kinesiophobia pain hypervigilance or catastrophizing. Based on our results, patients with lymphoedema have higher levels of kinesiophobia than those without lymphoedema, while they show similar values for the level of pain hypervigilance and pain catastrophizing. The study by Aleem *et al.*[22] in 2023 reported a mean TSK score of 24, measured immediate post-mastectomy, which, in line with our results, suggests high levels of kinesiophobia that are maintained over time. Similarly, previous studie[44, 45] have also shown high levels of kinesiophobia in women breast cancer survivors one year after treatment. These studies indicated that higher levels of kinesiophobia were associated with older age and lower levels of physical activity.[44, 45] Likewise, the study by Can et al[21] showed that TSK scores were higher in patients with lymphoedema than in those without, suggesting that the presence of lymphoedema is a determinant in the development of kinesiophobia.

Furthermore, the study conducted by De Groef *et al.*[15] in 2018 in breast cancer survivors found similar values to our study in terms of the level of catastrophizing, establishing that higher levels of catastrophizing correlated with greater levels of central sensitization. In a previous study,[46] along the same lines, they concluded that higher levels of central sensitization, pressure hypersensitivity, catastrophizing and hypervigilance were associated with higher levels of upper limb dysfunction in these patients, thus negatively affecting their quality of life.

Finally, our results fail to show a relationship between upper limb lymphedema volume and the variables studied, suggesting that there is no association between lymphoedema volume and mechanosensitivity, pain intensity, kinesiophobia, hypervigilance and catastrophizing. Only a negative correlation was found between upper limb volume and radial nerve neural range of motion, which seems to indicate that the grade of upper limb volume does not influence the neural range of motion alterations in our patients. In line with our results, a study by Ayhan *et al.*,[20] in which they analyzed the damage to the median nerve caused by lymphoedema, reported that the severity of carpal tunnel syndrome, detected in 41.37% of these patients, was not related to the severity of the upper limb lymphedema. Our results, however, contrast with those of the study by Shinde *et al.*,[16] where alterations in neural tissue mobility were directly proportional to the severity of lymphoedema. Patients with mild lymphoedema had a 48% impairment of neural tissue mobility; those with moderate lymphoedema, a 32% impairment and those with severe lymphoedema, a 20% impairment; where the median nerve was the most affected (52%), followed by the radial (20%) and ulnar (10%) nerves. However, consistent with our findings, a cross-sectional study[47] in women who underwent surgery after breast cancer did not find a correlation between the volume of upper limb lymphedema and loss of function of the upper limb, although there was a

correlation between pain levels and function. The authors suggested that pain is a stronger determinant of disability compared to swelling or grade of upper limb lymphedema.

Regarding fear of movement, our results do not agree with those of the study by Can *et al.*,[21] where they found a significant association between the presence of lymphoedema and kinesiophobia. These authors concluded that kinesiophobia increased the risk of lymphoedema, depression/anxiety and decreased upper extremity function in breast cancer survivors. In contrast, our results are supported by those of a recent study in post-mastectomized women,[22] which also found no significant correlation between lymphoedema volume and fear of movement in TSK post-surgery, concluding that this may indicate that the presence of kinesiophobia may not contribute to the development of early lymphoedema in these patients. In this same direction, in a cross-sectional study conducted in 2021,[23] they neither obtained significant correlations between upper limb function and relative upper arm volume excess. However, they found that higher pain intensity, catastrophizing and higher pain hypervigilance were associated with greater dysfunction at the affected upper limb in these patients. In other words, and in line with our results, it seems that the intensity of pain, factors related to cognition (catastrophizing, hypervigilance and kinesiophobia) and the presence of upper limb lymphedema are more important determinants than the volume of lymphoedema itself.

Limitations of the study

Finally, it is worth mentioning the limitations of this study. Firstly, although we have obtained a sample with adequate statistical power to detect differences between groups, a larger sample size would be needed in future studies to be able to extrapolate the results. Secondly, it would be interesting to include a pre-treatment evaluation of the patients, which would allow a pre-post intervention analysis to more comprehensively evaluate the impact of the surgical intervention. Thirdly, we did not include in our evaluation the difference in hand volume between the affected and unaffected side. Finally, we would like to highlight the difficulty in assessing lymphoedema. Although a standardized protocol has been selected for assessing upper limb lymphoedema, that is perimetric method, no complementary tests have been performed for evaluating volume which allow differentiate its irregular distribution. Therefore, it should be considered in future studies to include objective measures such as water displacement volumetry, electrical bioimpedance spectroscopy etc.[48-50]

Conclusions

In conclusion, the results of the present study seem to indicate that breast cancer survivors with upper limb lymphoedema had greater mechanosensitivity (PPT hypersensitivity and altered neural ranges of motion), as well as greater kinesiophobia compared to patients without lymphoedema. However, no clear association was found between upper limb lymphedema volume and most of the parameters assessed, which seems to indicate that lymphoedema volume would not influence mechanosensitivity, pain intensity, kinesiophobia, hypervigilance and catastrophizing in this population. Therefore, future studies that continue to analyze the relationship between the volume of upper limb edema and pain-related symptoms in these patients are necessary. Additionally, it is important to conduct studies that analyze the effects of specific therapeutic approaches aimed at improving lymphedema in breast cancer survivors.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
All authors meet the International Committee of Medical Journal Editors criteria for authorship for this article and contributed substantially to the study concept and design: all authors; acquisition of data: Isabel Almagro-Céspedes, Rosa M. Tapia-Haro and Antonio M. Mesa Ruiz; statistical analysis: Natalia Fernández-Sánchez, Patrocinio Ariza Vega and Mª Encarnación Aguilar-Ferrándiz, analysis and interpretation of data: all authors; drafting of manuscript: all authors. All authors read and approved the final version of the manuscript.

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SUPPLEMENTARY DIGITAL MATERIAL 1

Supplementary Table I.—Location of pressure pain thresholds measurements.

Pressure Pain Thresholds	Location
Branch 1 Trigeminal Nerve	In the orbital fissure of the superior orbital rim, in its internal third.
Branch 2 Trigeminal Nerve	In the maxillary bone, approximately 1.5 to 2.0 cm below the infraorbital margin and 1 cm lateral to the base of the nose.
Branch 3 Trigeminal Nerve	At the mentonian foramen, above the oblique line at the position of the second lower premolar tooth.
Median Nerve	In the medial cubital fossa, just next to the biceps tendon, without passing through the brachial artery
Radial Nerve	In the intermuscular septum between the medial and lateral portion of the biceps, at the lower portion of the humerus
Ulnar Nerve	In the groove between the medial epicondyle and the olecranon
Masseter Origin	At the anterior edge of the superficial portion of the muscle
Masseter Insertion	By palpation during maximal dental clenching, in the most prominent lower region
Temporalis Origin	Below the temporal line, in the temporal fossa
Temporalis Insertion	On the mandibular coronoid apophysis
Suboccipitalis	At the suboccipital insertions of the muscles
Temporomandibular Joint	At the lateral pole of the temporomandibular joint
Second Rib	At the second intercostal space
Third Rib	At the third middle clavicular rib
Tenth Rib	At the tenth middle clavicular rib
Sternum	In the middle of the sternum
C5-C6	In the joint space between C5 and C6
C7-T1	In the joint space between C7 and T1
Deltoid Muscle	In the middle portion of the deltoid muscle
Ulnar Styloid	At the bony prominence of the ulna distal end
Anterior Tibialis	In the upper third of the muscular belly

SUPPLEMENTARY DIGITAL MATERIAL 2

Supplementary Table II.—Sociodemographic and clinical data in participants.

Outcomes	Lymphoedema group (N=29)	Non-lymphoedema group (N=29)	
	Mean±SD/frequency (%)	Mean±SD/frequency (%)	95% CI
Age (years)	64.17±10.9	59±15.1	[-0.914, 11.259]
Height (cm)	164.7±0.1	167.1±0.1	[-0.073, 0.025]
Weight (kg)	73.1±10.3	72.1±14.8	[-5.724, 7.655]
BMI (kg/cm^2)	26.9±3.5	25.7±3.9	[-0.705, 3.235]
Affected arm (%)			
Dominant arm	10 (34.5)	13 (44.8)	
Non-dominant arm	19 (65.5)	16 (55.5)	
Type of surgery (%)			
Lumpectomy	14 (48.3)	16 (55.2)	
Mastectomy	15 (51.7)	13 (44.8)	
Type of treatment (%)			
Chemotherapy	28 (96.9)	28 (96.9)	
Radiotherapy	29 (100)	27 (93.1)	
Hormone Therapy	17 (58.6)	19 (65.5)	
Inmunotherapy	9 (31)	11 (37.9)	
Time since surgery	12.8 (7.6)	11.6 (7.3)	[-2.747, 5.092]
Time since lymphedema	7.8 (5.0)		

Data are expressed as mean±standard deviation (SD) for quantitative variables and as frequency (%) for qualitative variables.

BMI: Body Mass Index.

SUPPLEMENTARY DIGITAL MATERIAL 3

Supplementary Table III.—Mean±standard deviation for absolute and relative upper limb volume, mean differences (95% Confidence Interval) between affected and non-affected side in each group (lymphoedema and non-lymphoedema) and between-group change score of absolute and relative upper limb volume (95% Confidence Interval).

Volume		Lymphoedema group (N=29)	Mean differences Affected *vs.* unaffected (95% CI)	Non-lymphoedema group (N.=29)	Mean differences Affected *vs.* unaffected (95% CI)	Score change between-group (95% CI)	P-value
Segmental Volume Truncated Cone 1							
Unaffected UL	Absolute	295.09±42.86	68.44 (49.08, 87.80)†	309.04±66.51	18.56 (13.14, 23.99)†	-13.94 (-44.01, 16.12)	0.357
	Relative	13.91±1.29	0.28 (0.18, 0.74)	14.65±1.55	0.03 (-0.15, 0.21)	-0.74 (-1.49, 0.01)	0.052
Affected UL	Absolute	363.54±70.25		327.61±73.24		35.93 (-1.81, 73.68)	0.062
	Relative	14.20±1.80		14.69±1.61		-0.49 (-1.39, 0.41)	0.281
Segmental Volume Truncated Cone 2							
Unaffected UL	Absolute	447.81±68.60	127.17 (89.68, 164.65)†	462.32± 114.88	29.82 (20.13, 39.51)†	-14.51 (-64.53, 35.51)	0.562
	Relative	21.02±1.15	1.37 (0.52, 2.20)†	21.68±1.57	0.15 (0.11, 0.40)	-0.66 (-1.38, 0.07)	0.077
Affected UL	Absolute	574.98± 114.32		492.14± 122.88		82.83 (20.40, 145.27)	0.010*
	Relative	22.39±2.41		21.82±1,67		0.57 8-0.52, 1.67)	0.303
Segmental Volume Truncated Cone 3							
Unaffected UL	Absolute	612.38± 104.93	137.71 (108.55, 166.88)†	597.84± 154.57	43.36 (28.91, 57.81)†	14.54 (-54.96, 84.04)	0.677
	Relative	28.64±1.04	0.54 (0.17, 1.26)	27.94±0.81	0.36 (0.10, 0.62) †	0.70 (0.21, 1.19)	0.006*
Affected UL	Absolute	750.09± 137.79		641.20± 168.79		108.89 (27.83, 189.95)	0.009*
	Relative	29.18±1.92		28.30±0.89		0.88 (0.09, 1.77)	0.029*
Segmental Volume Truncated Cone 4							
Unaffected UL	Absolute	780.41± 143.51	99.57 (42.51, 156.62)†	768.29± 217.59	38.88 (17.00, 60.65)†	12.12 (-84.83, 109.08)	0.803
	Relative	36.43±2.07	-2.19 (-3.80,-0.59)†	35.73±2.54	-0.54 (-1.01, -0.63)†	0.70 (-0.52, 1.92)	0.257

Affected UL	Absolute	879.98±199.48		807.16± 255.01		72.81 (-47.62,193.25)	0.231
	Relative	34.23±5.01		35.19±2.99		-0.96 (-3.13, 1.21)	0.380
Total Upper Limb Volume							
Unaffected UL	Absolute	2135.70± 340.80	432.88 (323.38, 542.41)†	2137.49± 535.73	130.62 (85.48, 155.66)†	-1.79 (-237.98, 234.40)	0.988
	Relative	-	-	-			
Affected UL	Absolute	2568.60± 430.21		2268.11± 598.00		300.48 (-25.83,575.13)	0.032*
	Relative	-		-			

UL: upper limb.

†Significance level P<0.05 (t-test analysis for independent samples, score change between groups for mean differences for affected *vs.* non-affected side upper limb volume)

*Significance level P<0.05 (t-test analysis for independent samples, score change between groups for absolute and relative upper limb volume).

SUPPLEMENTARY DIGITAL MATERIAL 4

Supplementary Table IV.—Mean±Standard Deviation for pressure pain thresholds and neural range of motion and between-group mean change (95% CI).

Outcome	Lymphoedema group (N=29)	Non-lymphoedema group (N=29)	Score Change Between-group (95% CI)	**P-value**
Pressure Pain Threshold (Kg/cm^2)				
Branch 1 Trigeminal Nerve				
Unaffected side	1.83 ± 0.77	2.11 ± 0.92	-0.28 (-0.73, 0.16)	0.208
Affected side	1.80 ± 0.79	2.13 ± 0.93	-0.33 (-0.78, 0.12)	0.150
Branch 2 Trigeminal Nerve				
Unaffected side	1.93 ± 0.78	2.32 ± 0.90	-0.39 (-0.83, 0.05)	0.083
Affected side	1.95 ± 0.80	2.39 ± 0.91	-0.44 (-0.90, 0.01)	0.057
Branch 3 Trigeminal Nerve				
Unaffected side	1.74 ± 0.69	1.99 ± 0.66	-0.25 (-0.60, 0.10)	0.163
Affected side	1.63 ± 0.79	1.91 ± 0.75	-0.27 (-0.68, 0.13)	0.182
Median Nerve				
Unaffected UL	1.93 ± 0.69	2.02 ± 0.84	-0.09 (-0.49, 0.32)	0.664
Affected UL	1.90 ± 0.74	1.70 ± 0.78	0.20 (-0.20, 0.60)	0.317
Radial Nerve				
Unaffected UL	1.90 ± 0.78	2.01 ± 0.97	-0.11 (-0.57, 0.35)	0.637
Affected UL	1.95 ± 0.86	1.70 ± 0.86	0.25 (-0.20, 0.70)	0.274
Ulnar Nerve				
Unaffected UL	2.63 ± 0.90	2.79 ± 0.90	-0.16 (-0.63, 0.31)	0.496
Affected UL	2.89 ± 0.99	2.50 ± 0.79	0.40 (-0.08, 0.87)	0.099
Masseter Origin				
Unaffected side	1.95 ± 0.70	2.38 ± 0.83	-0.43 (-0.84, -0.30)	0.036*
Affected side	1.92 ± 0.70	2.37 ± 0.80	-0.45 (-0.85, -0.59)	0.025*
Masseter Insertion				
Unaffected side	1.71 ± 0.56	2.09 ± 0.68	-0.38 (-0.71, -0.05)	0.024*
Affected side	1.59 ± 0.60	1.93 ± 0.66	-0.34 (-0.67, -0.01)	0.046*
Temporalis Origin				
Unaffected side	1.48 ± 0.55	1.81 ± 0.68	-0.33 (-0.65, 0.00)	0.050
Affected side	1.34 ± 0.56	1.73 ± 0.72	-0.39 (-0.73, -0.05)	0.025*
Temporalis Insertion				
Unaffected side	1.77 ± 0.61	2.25 ± 0.67	-0.48 (-0.82, -0.14)	0.006*
Affected side	1.76 ± 0.64	2.19 ± 0.73	-0.43 (-0.79, -0.66)	0.021*
TMJ				
Unaffected side	1.86 ± 0.59	2.15 ± 0.63	-0.29 (-0.61, 0.04)	0.080

Affected side	1.75 ± 0.57	2.12 ± 0.67	-0.38 (-0.71, -0.05)	0.024*
Second Rib				
Unaffected side	2.28 ± 0.77	2.85 ± 0.94	-0.57 (-1.02, -0.12)	0.014*
Affected side	1.86 ± 0.73	2.47 ± 0.82	-0.62 (-1.03, -0.21)	0.004*
Third Rib				
Unaffected side	2.12 ± 0.75	2.92 ± 0.71	-0.80 (-1.18, -0.41)	<0.001*
Affected side	1.65 ± 0.66	2.26 ± 0.65	-0.61 (-0.95, -0.26)	0.001*
Tenth Rib				
Unaffected side	2.38 ± 0.75	3.31 ± 0.82	-0.94 (-1.35, -0.53)	<0.001*
Affected side	1.88 ± 0.66	2.70 ± 0.081	-0.82 (-1.21, -0.43)	<0.001*
Sternum	2.05 ± 0.71	2.44 ± 0.84	-0.39 (-0.80, 0.01)	0.058
Suboccipitalis				
Central	21.11 ± 0.83	2.51 ± 0.86	-0.40 (-0.84, 0.04)	0.077
Unaffected side	2.01 ± 0.93	2.52 ± 0.90	-0.51 (-0.99, -0.03)	0.036*
Affected side	1.93 ± 0.93	2.54 ± 0.92	-0.61 (-1.10, -0.12)	0.015*
Deltoid Muscle				
Unaffected UL	1.94 ± 0.71	2.01 ± 0.73	-0.07 (-0.44, 0.31)	0.727
Affected UL	1.88 ± 0.74	1.86 ± 0.77	0.01 (-0.38, 0.41)	0.948
Anterior Tibialis				
LL unaffected side	3.02 ± 1.10	2.88 ± 0.95	0.14 (-0.41, 0.68)	0.619
LL affected side	3.03 ± 1.17	2.83 ± 0.98	0.20 (-0.36, 0.77)	0.478
C5 – C6				
Unaffected side	1.79 ± 0.67	1.86 ± 0.71	-0.073 (-0.44, 0.29)	0.688
Affected side	1.67 ± 0.71	1.77 ± 0.69	-0.11 (-0.47, 0.26)	0.569
C7 – T1				
Unaffected side	1.72 ± 0.79	2.14 ± 0.88	-0.42 (-0.86, 0.03)	0.064
Affected side	1.68 ± 0.77	2.05 ± 0.87	-0.37 (-0.80, 0.06)	0.093
Ulnar Styloid				
Unaffected UL	1.53 ± 0.65	1.69 ± 0.70	-0.16 (-0.52, 0.19)	0.358
Affected UL	1.62 ± 0.75	1.44 ± 0.71	0.18 (-0.20, 0.57)	0.343
Upper Limb Neurodynamic Tests (º)				
Median Nerve				
Unaffected UL	135.14 ± 25.13	132.21 ±37.45	2.93 (-13.85, 19.71)	0.728
Affected UL	100.31 ± 30.05	119.03 ±39.54	-18.72 (-37.20, -0.25)	0.047*
Radial Nerve				
Unaffected UL	60.97 ± 17.45	73.59 ± 27.01	-12.62 (-24.58, -0.69)	0.039*
Affected UL	47.55 ± 23.27	54.83 ± 24.51	-7.28 (-19.85, 5.29)	0.251
Ulnar Nerve				
Unaffected UL	90.93 ± 27.16	92.66 ± 21.45	-1.72 (-14.60, 11.15)	0.789
Affected UL	61.90 ± 26.00	74.90 ± 21.32	-13.00 (-25.51, -0.49)	0.042*

*Significance level $p<0.05$

Abbreviations. TMJ: Temporomandibular Joint; UL: Upper Limb; LL: Lower Limb.

SUPPLEMENTARY DIGITAL MATERIAL 5

Supplementary Table V.—Mean±standard deviation for pain intensity, kinesiophobia, pain hypervigilance and pain catastrophizing, and between-group mean change (95% confidence interval).

Outcome	Lymphoedema group (N=29)	Non-lymphoedema group (N=29)	Score Change Between-group (95% IC)	P-value
Pain Intensity (cm)	5.38±2.35	4.38±2.23	1.00 (-0.20, 2.20)	0.102
Kinesiophobia	28.52±8.60	24.07±7.63	4.45 (0.17, 8.73)	0.042*
Pain hypervigilance	20.72±7.66	17.17±8.69	3.55 (-0.76, 7.86)	0.104
Pain catastrophizing	17.41±10.33	13.21±10.87	4.21 (-1.37, 9.79)	0.137

*Significance level P<0.05.

SUPPLEMENTARY DIGITAL MATERIAL 6

Supplementary Table VI.—Beta estimates, confidence intervals and P-values for the association between upper limb volume and clinical features in lymphoedema group.

Variable	Lymphedema group (N.=29)		
	Upper limb volume		
	β	95 % CI	P-value
Pressure pain thresholds			
Branch 1 trigeminal nerve	125.170	[-77.750, 328.090]	0.216
Branch 2 trigeminal nerve	47.963	[-152.511, 248.436]	0.626
Branch 3 trigeminal nerve	69.962	[-139.264, 297.188]	0.497
Median nerve	2.132	[-204.197, 208.371]	0.983
Radial nerve	-27.009	[-113,342, 85,738]	0.609
Ulnar nerve	-60.199	[-207.219, 86.821]	0.407
Masseter origin	111.058	[-114.313, 336.430]	0.320
Masseter insertion	190.829	[-69.345, 451.003]	0.143
Temporalis origin	67.983	[-215.883, 351.849]	0.626
Temporalis insertion	12.775	[-238.286, 263.796]	0.917
Suboccipitalis	35.972	[-149.028, 220.612]	0.693
TMJ	50.347	[-233.239, 333.898]	0.718
Second rib	122.765	[-90.064, 335.595]	0.246
Third rib	97.922	[-127.546, 323.390]	0.380
Tenth rib	81.058	[-147.950, 310.065]	0.473
Sternum	155.645	[-50.202,361.492]	0.132
C5-C6	-27.885	[-246.439, 190.669]	0.795
C7-T1	38.493	[-157.621, 234.608]	0.689
Deltoid muscle	-16.367	[-266.471, 129.166]	0.481
Ulnar styloid	-9.506	[-205.763, 186.750]	0.921
Anterior tibialis	-25.972	[-160.090, 108.146]	0.693
Upper limb neurodynamic tests			
Median nerve	-1.047	[-6.432,4.338]	0.692
Radial nerve	-7.248	[-13.234, -1.261]	0.020*
Ulnar nerve	-1.671	[-7.833, 4.490]	0.581
Pain intensity	17.687	[-44.550, 79.923]	0.564
Kinesiophobia	5.186	[-11.905, 22.277]	0.538
Pain hypervigilance	1.968	[-17.240, 21.176]	0.835
Pain catastrophizing	-2.833	[-17.127, 11.461]	0.687

*Significance level: P<0.05

TMJ: temporomandibular joint.

[β]Regression coefficient adjusted for age and body mass index; 95% CI: 95% confidence interval.

SUPPLEMENTARY DIGITAL MATERIAL 7

Supplementary Table VII.—Beta estimates, confidence intervals and P-values for the association between mean differences for affected vs non-affected side upper limb volume and clinical features in lymphedema group.

Variable	Lymphoedema group (N.=29)		
	Mean differences affected *vs.* unaffectedupper limb volumE		
	β	95 % CI	P-value
Pressure pain thresholds			
Branch 1 trigeminal nerve	23.343	[-135.855, 181.541]	0.764
Branch 2 trigeminal nerve	38.917	[-112.730, 190.565]	0.602
Branch 3 trigeminal nerve	21.212	[-138.437, 180.852]	0.787
Median nerve	-15.174	[-171.173, 140.824]	0.843
Radial nerve	10.337	[-124.249, 144.923]	0.876
Ulnar nerve	-5.176	[-118.021,107.670]	0.925
Masseter origin	51.954	[-120.810, 224.718]	0.541
Masseter insertion	55.527	[-148.943, 259.992]	0.581
Temporalis origin	30.647	[-184.912, 246.206]	0.772
Temporalis insertion	-11.795	[-201.811, 178.221]	0.892
Suboccipitalis	-24.274	[-164.269, 115.722]	0.724
TMJ	29.089	[-185.063, 244.682]	0.777
Second rib	30.630	[-134.485, 195.744]	0.706
Third rib	3.701	[-169.680, 177.082]	0.965
Tenth rib	-12.492	[-187.607, 162.623]	0.884
Sternum	45.545	[-116.581,207.671]	0.568
C5-C6	-16.292	[-181.828, 149.245]	0.841
C7-T1	-41.699	[-189.647, 106.249]	0.567
Deltoid muscle	-35.899	[-186.445, 114.646]	0.628
Ulnar styloid	-46.741	[-194.083, 100.601]	0.520
Anterior tibialis	-12.550	[-114.268, 89.168]	0.801
Upper limb neurodynamic tests			
Median nerve	-2.510	[-6.467, 1.477]	0.203
Radial nerve	-4.207	[-8.966, 0.551]	0.081
Ulnar nerve	-1.839	[-6.471, 2.793]	0.421
Pain intensity	25.729	[-20.505, 71.965]	0.263
Kinesiophobia	4.654	[-8.243, 17.550]	0.464
Pain hypervigilance	-0.156	[-15.068, 14.036]	0.942
Pain catastrophizing	-0.279	[-11.135, 10.577]	0.958

TMJ: temporomandibular joint.

*****Significance level: P<0.05; $^{\beta}$regression coefficient adjusted for age and Body Mass Index; 95% CI: 95% confidence interval.