RESEARCH ARTICLE

Pain threshold by pressure algometry in the Carpal Tunnel Syndrome

Authors

Bernardino SN[1], Martins HAL[2], Martins RS[3], Heise CO[4], Souza FHM[5], Araújo MBL[6], Souza INB[7], Souza RNB[7], Malheiros RA[7], Lima PTMB[8]

[1] Department of Neurophysiology of Hospital Getúlio Vargas, Recife, Brazil.

[2] Department of Neuropsychiatry of Universidade Federal de Pernambuco, Recife, Brazil

[3] Department of Neurosurgery, Universidade de São Paulo, São Paulo, Brazil.

[4] Department of Neurophysiology, Universidade de São Paulo, São Paulo, Brazil.

[5] Department of Neurosurgery of Hospital da Restauração, Recife, Brazil.

[6] Department of Pathology, IMIP, Recife, Brazil

[7] Universidade de Pernambuco, Recife, Brazil

[8] Universidade Federal de Pernambuco, Recife, Brazil

Correspondence:
Silvya Nery Bernardino, PhD MD
Rua Amaro Coutinho, 531/3402, CEP: 52041-305, Recife, PE, Brazil
Tel. +55 81 3223-4891 / +55 81986776949
E-mail: s-nery@hotmail.com

Abstract

Background: Pain threshold evaluation in compressive neuropathy is very useful for explaining generalized symptoms. About peripheral sensitization process in the release of bradykinin and prostaglandin alters specific TRPV1 receptors leading to reduction of nerve fiber firing threshold. This repetition leads to a brain receptive field expansion with consequent central sensitization.

Methods: We have evaluated 160 female subdivided according to the neurophysiologic impairment of median nerve. Pressure algometry as well as discriminatory sensitivity between two points and The Boston Questionnaire were applied.

Results: The comparison of algometry data showed extremely significant differences between control group and another groups. Therefore, pain thresholds showed direct relation to mononeuropathy severity to a certain point. When sensory or motor potential were no longer obtained, painful thresholds returned close to normal values. We suggest this result could be due to small fibers destruction, when hyperalgesia would be replaced by hypoesthesia.

Conclusion: Pain threshold is lower in patients with carpal tunnel syndrome, either the median nerve innervated area or another areas.

Key-word: Pain measurement. Pain threshold. Compressive neuropathy. Carpal tunnel syndrome.

INTRODUCTION

Central sensitization can be defined as a response mediated by pain increase to nociceptive stimulation through signal amplification in the central nervous system and is characterized by different somatosensory changes (DE-LA-LLAVE-RINCÓN *et al.*, 2012). Over the last years there has been an increased interest in understanding nociceptive mechanisms in patients with Carpal Tunnel Syndrome (CTS), studying the sensitivity through pain threshold to pressure (CHESTERTON, 2003; ROLKE, 2005).

The main determinants of pathophysiology the following: 1. Increased intra-carpal pressure (WERNER; ANDARY, 2002); 2. Focal demyelination followed by axonal degeneration, macrophage activation and inflammatory cytokine and nitric oxide release, that can lead to 'Chemical neuritis', as an outcome of this vicious cycle (IBRAHIM *et al.*, 2012); 3. Neural adherence: Chronic compression results in nerve adherence to surrounding tissue, creating traction force during movement. (MACDERMID; DOHERTY, 2004); 4. Ischemia: Increased intra-fascicular pressure, capillary damage with edema and arterial blood flow obstruction (WERNER; ANDARY, 2002); 5.Blood-neural barrier injury, which leads to the inflammatory cells and protein accumulation, and ultimately intra-fascicular edema. (MACDERMID; DOHERTY, 2004); 6.Synovial tissue thickening increases fluid pressure inside the tunnel (WERNER; ANDARY, 2002). As a result, biochemical changes can occur on the synovial tissue (e.g., increase in proteoglycan content in the tendon stroma and hypertrophy) (YOON; HALPER, 2005); 7. Flexor tendon's synovial tissue inflammation can increase pressure inside the carpal tunnel, arising from a boost in Prostaglandin E2 and Vascular Endothelial Growth Factor (VEGF) (HIRATA *et al.*, 2004).

CTS is characterized by signs and symptoms associated with nerve compression through its course in an osseous-fibrous canal in the wrist named a carpal tunnel (ATROSHI *et al.*, 1999). It is the most frequently diagnosed neuropathy, being usually related to any pathophysiological condition or anatomical abnormality that leads to an increase in volume of the components of this canal, reduces its transversal diameter or raises pressure inside it (AKELMAN; WEISS, 1995). CTS affects 1,8 of every 1.000 people (3-6% of the general population) (LEBLANC; CESTIA, 2011). More women are affected by CTS that men, with 3 women affected for every men (BONGERS *et al.*, 2007). More commonly, individuals with a high Body mass index (BMI), age over 30 years, and some particular systemic conditions (BECKER *et al.*, 2002), such as: diabetes (KIANI *et al.*, 2014), nephropathies (MBARKI *et al.*, 2013), thyroid disorders (SHIRI, 2014), pregnancy (ATZMON *et al.*, 2014) and repetitive motor activities (DALE *et al.*, 2013).

Classic symptoms of CTS include pain and paresthesia in the distribution area of the median nerve (palmar face of the fingers I, II, III and radial side of the IV finger) that increase in intensity at night (SOLOMON *et al.*, 2005). With the evolution of compression, grip strength and hand function may be affected (ZYLUK; KOSOVETS, 2010). Occasionally the "flick" sign is referred to, during which the patient shakes up fists to relieve symptoms (Krendel *et al.*, 1986).

In peripheral sensitization, the tissue damage caused by trauma or inflammation releases chemical substances known as 'algogenic', which can lead to nociceptor sensitization. These substances include:

acetylcholine, bradykinin, prostaglandin, serotonin, leukotriene, P substance, platelet activation factor, neural growth factor, thromboxane, adenosine monophosphate (WOOD, 2004). They contribute to the inflammatory process start and sustaining, taking up an important role in the peripheral pain sensitization mechanism. Bradykinin leads to increased capillary permeability, whilst P substance and neurokinin leads to vasodilatation and increases vascular permeability, contributing to the inflammation spread. Prostaglandin and bradykinin cause changes in specific receptors: transient receptor potential cation channel subfamily V member 1 (TRPV1), reducing the neural membrane post-hyperpolarization time and, consequently reducing the neuronal fiber trigger-threshold (SCHMIDT, 2008).

Central sensitization implies peripheral impulses modifications. That leads either to a pain threshold decrease or an increased response to afferent *stimuli*. Repeated stimulation causes persistent discharges, which leads to the dorsal horn neurons' receptive field expansion. Repeated impulses on C fibers amplify sensory signals in spinal neurons, relaying messages to the brain (ZHUO, 2007).

Growing evidences shows CTS patients also exhibit symptoms not related to sensitivity (ZANETTE *et al.*, 2006) and proximal irradiation pain (ZANETTE *et al.*., 2007), suggesting involvement of central nociceptive mechanisms and plasticity. (Campbell and Meyer, 2006).

In 2010, Zanette *et al.*. sought to obtain psychophysical evidence of sensitization in CTS patients with extraterritorial symptoms. Quantitative sensory test (QST) was performed in 48 patients on the compromised territory and in territories unrelated to the median nerve, to document signs of sensitization (hyperalgesia and allodynia). Unrelated median nerve pattern was found in 33.3% of patients and proximal pain 37.5% of patients.

This same researchers group conducted a study in 2006 that reported typical symptoms distribution in about 60.6% of the hands, identifying glove distribution in 35.2% and ulnar distribution in 4.2% (ZANETTE *et al.*, 2006). Another study conducted in 2007 reported 45% of patients with CTS exhibited proximal pain associated with hand sensory symptoms. Proximal pain was most frequently reported at night, reaching 21% and occurred more frequently in patients with less severe median nerve injury (ZANETTE *et al.*, 2007).

Parallel research was performed on women with strictly unilateral CTS. Results revealed bilateral hyperalgesia in both median and extraterritorial areas when compared to healthy subjects. These results have shown the presence of thermal conduction deficit in C fibers (heat) and Aδ fibers (cold). That confirms the existence of a central nervous system disorder (i.e. a central sensitization process in patients with CTS) (DE-LA-LLAVE-RINCÓN *et al.*, 2009).

In 2010, Fernández-de-las-Peñas *et al.*. conducted a study in 20 women using topographic mapping of strictly unilateral CTS hands and comparing it to other 20 healthy women of similar age. Pressure pain thresholds were measured on 30 sites on each hands palm. Results revealed that the pain thresholds were lower in all points when compared to the control group. There was no difference regarding the hands pain intensity or symptom duration (FERNÁNDEZ-DE-LAS-PEÑAS *et al.*, 2010).

METHODOLOGY

This research received by the Hospital da Restauração in Recife, Brazil, ethics

committee authorization: 09278812.0.0000.5198. The sample was non-probabilistic by judgment. The patients included had symptoms suggestive of CTS between 18 and 85 years old. Women with any type of pathology that interferes with pain perception were excluded, such as: cognitive impairment of any kind, psychiatric disorders, dermatological disorders (e.g.: psoriasis, herpes zoster, leprosy, among others), sensory neuropathy (congenital insensitivity to pain), fibromyalgia bearer, patients who suffered a fracture or undergone any surgical procedure of the upper limbs or cervical spine, as well as patients with metabolic disorders that increase the possibility of polyneuropathy (diabetes, thyroid disorder). Patients who used analgesics in the previous five days were instructed to return without medication.

The groups were divided into: A) Control (n=40): Healthy volunteers with electrophysiological integrity of the median nerve through the wrist. B) Clinically suggestive CTS patients (n=120) were subdivided according to the median nerve's degree of neurophysiological involvement in the wrist, in accordance to Padua's classification (PADUA *et al.,* 1997), in Group I (n=20): Clinically suggestive patients without median nerve neuropathy proximal to wrist (MNNW); Group II (n= 20) discrete MNNW – only detectable by high sensitivity tests—In the current study we used the Robinson Sensitive Index, defined as the sum of the following three latency differences: median-ulnar nerves in the fourth finger; median-ulnar nerves in the ring finger; and median-radial nerves in the thumb (ROBINSON *et al.,* 1998); Group III (n = 20): mild MNNW--reduction of sensory conduction velocity in both palm-wrist and wrist-second finger segments (under 50 m/s); Group IV (n = 20): moderate MNNW – motor distal latency increase over 4ms; Group V (n = 20): Severe MNNW - indeterminable sensory potentials or motor range reduction (less than 5mV); Group VI (n = 20): extreme MNNW - indeterminable motor potentials (Table 1).

Table 1: Mononeuropathy Classification – Median nerve proximal do wrist. According PADUA *et al* (1997)

Grade 0	Negative	normal ENMG
Grade 1	Minimal	only detectable by high sensitivity tests
Grade 2	Mild	Decrease in sensory nerve conduction velocities
Grade 3	Moderate	increased motor distal latency
Grade 4	Severe	undeterminable sensory potentials
		decreased motor potential amplitude
Grade 5	Extreme	Undetermined potentials motors

In order to avoid the possibility of induction a higher pressure speed with the algometer, due to a patient's diagnosis knowledge, algometry was initially performed. After that, the discriminatory sensitivity between two points preceding the ENMG was evaluated and, consequently, knowledge of the degree of nerve involvement.

The participants rested for ten minutes, considered sufficient time for relaxation, before the algometer measurement started (PIOVESAN, 2001). A Wagner® digital algometer with 5 digit liquid crystal display, 0.5'' and calibration certificate was used (A). Obtaining a ninety degree approach between the stimulation surface and the stimulated point. Constant approach speed was administered. Participants were instructed to report the first unpleasant pain sensation (painful perception). Immediately after this information, the stimulus was interrupted and the values in Kg/cm^2 were recorded. The stimulated areas were divided into: B1) related to the median nerve territory in the hand after passage through the carpal tunnel, B2) related to the palmar cutaneous nerve, B3) related to the ulnar nerve in the hand and B4) areas proximal to the carpal tunnel.

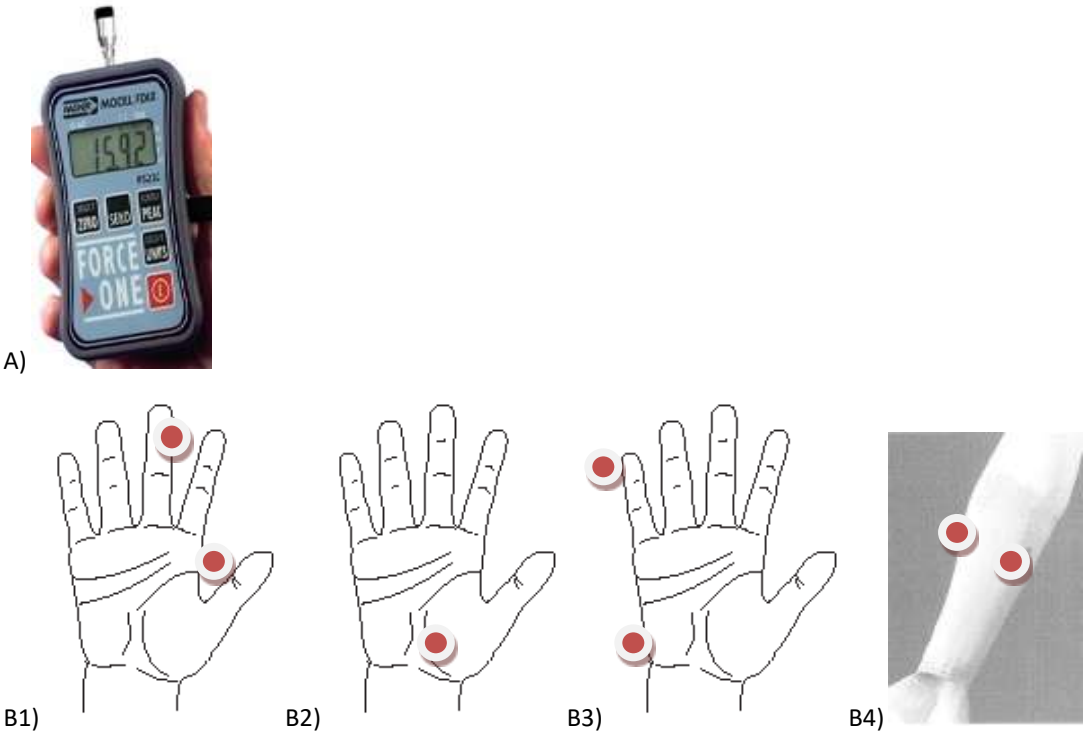

Figure 10 - Areas stimulated by pressure algometry
A) Wagner® Digital algometer
B1) Median nerve territorial areas after passage through the carpal tunnel: digital pulp of the I and II fingers.
B2) Median nerve before carpal tunnel innervated areas (palmar cutaneous nerve) in *abductor pollicis brevis* muscle.
B3) Areas innervated by the ulnar nerve: digital pulp of the V finger and *abductor digiti minimi*
B4) Extraterritorial areas of the median nerve proximal to the carpal tunnel: medial and lateral portion of the upper third of the forearm.

In the evaluation of the symptom severity scale (SSS) was used two parts of the questionnaire "Boston Questionnaire Symptom Severity" frequently used in the literature to quantify symptoms in CTS and already validated for Brazilian reality (LEVINE et al., 1993; CAMPOS et al., 2003; MEIRELLES et al., 2006). In this study was coded from 1 to 5 with a numerical progression of complaints.

STATISTICAL ANALYSIS

Statistical analysis was performed by descriptive analysis of parameters such as: arithmetic mean, standard deviation, and 25% and 75% percentiles. The parameters were tested for normality characterization by the Shapiro-Wilk test in the comparison between groups. For data with nonparametric distribution, the Kruskal-Wallis test was used with type 1 error <0.05. In case of a significant difference, paired comparisons were performed with Dunn's posthoc test. Although not normally distributed, we chose to use the arithmetic mean instead of the median.

RESULTS

SAMPLE CHARACTERIZATION TO PATIENT AGE

The patients recruited for the study were between 18 and 85 years old. The arithmetic mean age of all patients was 49,7 years (±14,6) (Table 2).

Regarding the age of the patients and the degree of nerve involvement, the higher the MNNW, the higher the mean age of the patients. Only significant between control and groups V e VI.

Table 2: Mean age of the groups expressed in years, standard deviation, coefficient of variation and analysis of variance by Kruskal Waliis test, comparing the control and each group according to the nerve involvement degree.

	n	Age (years)	Variation Coefficient (%)	Kruskal Wallis
Control	40	46,8±14,6	31,3	-
GI: sint s/ MNNW	20	41,4±9,9	23,98	(p= 0,22) ns
GII: Minimal MNNW	20	42±12,3	29,22	(p= 0,24) ns
GIII: Mild MNNW	20	45,5±12,3	27,11	(p= 0,77) ns
GIV: moderate MNNW	20	50,3±8,6	17,03	(p= 0,18) ns
GV: Severe MNNW	20	57,9±11,3	19,48	**
GVI: Extreme MNNW	20	67±13,7	20,42	***

ns:not significant, * = p< 0,05, ** = p< 0,01 e *** = p< 0,001.

SAMPLE CHARACTERIZATION IN RELATION TO PAIN THRESHOLD

Pressure algometry was performed on 320 hands and forearms of all 160 women participants. To compare the algometric data between the groups, the data were non-parametric (Shapiro-Wilkp test= 0,1955), therefore the Kruskal-Wallis test was used. The following were separated by innervation territory: 1) area innervated by the median nerve after passage through the carpal tunnel, comprising the digital pulp of the first finger

right and left (I finger R, I finger L) and the digital pulp of the second finger (II finger R, II finger L); 2) area innervated by the palmar cutaneous nerve, uptake in the *Abductor Pollicis Brevis* (APB R, APB L); 3) area innervated by the ulnar nerve that involves both the fifth finger digital pulp (V finger R, V finger L) and the *Abductor Digiti Minimi muscle* (ADM R, ADM L); 4) carpal tunnel proximal areas, involving the medial (Prx med R, Prx med L) and lateral regions of the forearm (Prx lat R, Prox lat L).

When pain threshold values were related to the degree of nerve involvement, it was observed that the threshold decrease as the pathology begins and progresses to some extent. There was an extremely significant difference between the control and groups II, III, IV, and V in all stimulated points. However, there was no significant difference between the control group and groups I and VI at some stimulated points.

Table 3 shows the pain threshold values obtained by pressure algometry in the territory innervated by the median nerve after passage through the carpal tunnel.

Table 3: Pain threshold value (expressed in kg / cm²) recorded by pressure algometry in each group classified according to the degree of nerve involvement. The measurement in the median nerve innervated territory after passage through the carpal tunnel, comprised of digital pulp of the first finger (I finger R, I finger L) and second finger (II finger R, II finger L). The variance analysis between the groups was performed by Kruskal Wallis test.

	I finger R	**I finger L**	**II finger R**	**II finger L**
Control	3,908	3,891	3,920	3,936
GI: sint s/ MNNW	3,661 *	3,624 *	3,673 *	3,668 *
GII:Minimal MNNW	3,214 ***	3,195 ***	3,256 ***	3,208 ***
GIII:Mild MNNW	3,037 ***	2,924 ***	3,026 ***	2,989 ***
GIV:moderate MNNW	2,693 ***	2,716 ***	2,700 ***	2,719 ***
GV:Severe MNNW	3,043 ***	3,074 ***	3,103 ***	3,076 ***
GVI:Extreme MNNW	3,357 **	3,429 **	3,434 **	3,429 **

ns:not significant, * = p< 0,05, ** = p< 0,01 e *** = p< 0,001.

Table 4 shows the values of pain thresholds obtained by pressure algometry in the area innervated by the palmar cutaneous nerve.

Table 4: Pain threshold value (expressed in kg / cm²) recorded by pressure algometry in each group classified according to the nerve involvement degree. Measurement was done in the territory innervated by the palmar-cutaneous nerve in the *Abductor Pollicis Brevis* (APB R, APB L). The comparison between groups was performed with Kruskal Wallis variance analysis.

	APB R	**APB L**
Control	3,888	3,895
GI: sint s/ MNNW	3,683 (p=0,24) ns	3,668 (p=0,12) ns
GII:Minimal MNNW	3,230 ***	3,261 ***
GIII:Mild MNNW	3,018 ***	3,099 ***
GIV:Moderate MNNW	2,673 ***	2,709 ***
GV:Severe MNNW	3,107 ***	3,054 ***
GVI:Extreme MNNW	3,388 **	3,336 **

ns:not significant, * = p< 0,05, ** = p< 0,01 e *** = p< 0,001.

Table 5 shows the values of pain thresholds obtained by pressure algometry in the area innervated by the ulnar nerve.

Table 5: Pain threshold value (expressed in kg / cm²) recorded by pressure algometry in each group classified according to the degree of nerve involvement. Measurement in the territory innervated by the ulnar nerve involving both the fifth finger digital pulp (V finger R, V finger L) and the *Abductor Digiti Minimi muscle* (ADM D, ADM E). The comparison between groups was performed with Kruskal Wallis variance analysis.

	V Finger R	**V Finger L**	**ADM R**	**ADM L**
Control	3,901	3,887	3,904	3,899
GI: sint s/ MNNW	3,697 (p= 0,09)ns	3,659 (p= 0,05)ns	3,645 (p= 0,07)ns	3,603 *
GII:Minimal MNNW	3,191 ***	3,209 ***	3,256 ***	3,244 ***
GIII:Mild MNNW	2,981 ***	2,969 ***	3,027 ***	3,018 ***
GIV:Moderate MNNW	2,680 ***	2,741 ***	2,742 ***	2,730 ***
GV:Severe MNNW	3,075 ***	2,978 ***	3,209 ***	3,094 ***
GVI:Extreme MNNW	3,514 **	3.528 *	3.520 **	3,475 *

ns:not significant, * = p< 0,05, ** = p< 0,01 e *** = p< 0,001.

Table 6 shows the values of pain thresholds obtained by pressure algometry in the carpal tunnel proximal areas.

Table 6: Pain threshold value (expressed in kg / cm²) recorded by pressure algometry in each group classified according to the degree of nerve involvement. Measurement was done in the carpal tunnel proximal areas, involving the medial (Prx med R, Prx med L) and lateral regions of the forearm (Prx lat R, Prox lat L). The comparison between groups was performed with Kruskal Wallis variance analysis.

	Prx med R	Prx med L	Prx lat R	Prx lat L
Control	3,704	3,732	3,721	3,718
GI: sint s/ MNNW	3,451 (p= 0,08)ns	3.462 *	3.479 *	3.480 *
GII:Minimal MNNW	3,083 ***	3,137 ***	3,143 ***	3,120 ***
GIII: Mild MNNW	2,868 ***	2,852 ***	2,937 ***	2,897 ***
GIV:Moderate MNNW	2,663 ***	2,599 ***	2,619 ***	2,620 ***
GV:Severe MNNW	2,860 ***	2,914 ***	2,875 ***	2,8905 ***
GVI:Extreme MNNW	3.296 *	3.384 (p= 0,09)ns	3,298 *	3,245 **

ns:not significant, * = p< 0,05, ** = p< 0,01 e *** = p< 0,001.

SAMPLE CHARACTERIZATION TO TWO POINT DISCRIMINATING SENSITIVITY

Weber-Moberg's static technique was used bilaterally to measure discriminatory sensitivity between two points in the digital pulps of the first and second fingers (I finger R, II finger R, I finger L, II finger L). Our data shows the more pronounced MNNW, higher the discriminatory sensitivity values are, with a significant difference between the control and groups III, IV, V and VI (Table 7).

Table 7: Discriminatory sensitivity (mean) in each group expressed in millimeters, measured on the digital pulps of the first and second fingers bilaterally (I finger R, II finger R, I finger L, II finger L) and the variance analysis by the Kruskal Waliis test, comparing Control and each group according to the degree of nerve involvement.

	I Finger R	I Finger L	II Finger R	II Finger L
Control	2,5	2,6	2,6	2,7
GI: sint s/ MNNW	2,5 (p= 0,79)ns	2,3 (p= 0,06)ns	2,2 (p= 0,22)ns	2,8 (p= 0,64)ns
GII: Minimal MNNW	2,8 (p= 0,12)ns	2,5 (p= 0,41)ns	2,4 (p= 0,18)ns	2,4 (p= 0,18)ns
GIII: Mild MNNW	4,8 ***	4,0 ***	3,9 ***	4,1 ***
GIV:Moderate MNNW	5,1 ***	5,1 ***	5 ***	4,8 ***
GV: Severe MNNW	5,7 ***	4,8 ***	5,3 ***	4,5 ***
GVI:Extreme MNNW	6,2 ***	6,1 ***	5,9 ***	6,0 ***

ns:not significant, * = p< 0,05, ** = p< 0,01 e *** = p< 0,001.

SAMPLE CHARACTERIZATION TO SYMPTOMS GRAVITY SCALE

In the nighttime pain (BA1) intensity assessment, it was group IV (moderate MNNW) that most complained. However, there was no significant difference between group IV and groups III (mild MNNW) and V (Severe MNNW).

Group V (Severe MNNW) had the most complaints about pain frequency at night (BA2). However, it did not differ significantly from groups III (mild MNNW) and IV (moderate MNNW).

In the daytime pain (BA3) intensity assessment, it was group IV (moderate MNNW) that most complained. However, there was no significant difference from group I (symptoms without MNNW), III (mild MNNW) and V (Severe MNNW).

The daytime pain frequency (BA4) had group IV (moderate MNNW) with the most complaints. There was no significant difference between this and group V (Severe MNNW).

The groups with most complaints of daytime pain (BA5) duration were IV (moderate MNNW) and V (Severe MNNW). However, there was no significant difference between these groups and group I (symptomatology without MNNW) and III (mild MNNW) (Table 8).

Table 8: Values obtained regarding pain intensity, frequency and duration in the typical 24-hour period during the last two weeks: BA1: nighttime pain intensity. BA2: frequency with which the patient wakes up with pain at night. BA3: daytime pain intensity. BA4: daytime pain frequency. BA5: daytime pain duration. The comparison between groups was performed with Kruskal Wallis variance analysis.

	BA1	BA2	BA3	BA4	BA5
GI:sint s/ MNNW	3,3 **	3,3 *	3,3 (p= 0,05)ns	3,3 **	3,5 (p= 0,61)ns
GII:Minimal MNNW	2,4 ***	2,3 ***	2,6 ***	2,9 ***	2,9 **
GIII:Mild MNNW	3,6 (p= 0,09)ns	3,6 (p= 0,07) ns	3,5 (p= 0,08) ns	3,6 **	3,1 (p= 0,07)ns
GIV:Moderate MNNW	4,0 -	4,1 (p= 0,82) ns	4,0 -	4,4 -	3,6 -
GV:Severe MNNW	3,6 (p= 0,25)ns	4,2 -	3,7 (p= 0,68) ns	4,3 (p= 0,50)ns	3,6 -
GVI:Extreme MNNW	2,7 ***	2,4 ***	2,8 ***	2,9 ***	2,7 **

ns:not significant, * = p< 0,05, ** = p< 0,01 e *** = p< 0,001.

Regarding numbness intensity (BA6), group IV (moderate MNNW) complained the most. However, no significant difference between this group and groups I (symptomatology without NMMP) and V (mild MNNW).

For tingling intensity (BA7), it was groups I (symptomatology without MNNW) and V (Severe MNNW) that complained the most, with no significant difference when compared to group IV (moderate MNNW).

In regards to nighttime numbness intensity or tingling (BA8), group V (Severe

MNNW) had the most complaints. However, there was no significant difference when compared to groups I (symptomatology without MNNW) and IV (moderate MNNW).

In the nighttime numbness frequency or tingling (BA9), group V (Severe MNNW) had the most complaints. However, there was no significant difference when compared to groups I (symptomatology without MNNW) and IV (moderate MNNW) (Table 9).

Table 9: Values obtained regarding intensity and frequency of numbness and / or tingling in the typical 24-hour period during the last two weeks. BA6: presence of numbness. BA7: tingling intensity. BA8: numbness or tingling intensity at night. BA9: Frequency of numbness / tingling at night. The comparison between groups was performed with Kruskal Wallis variance analysis.

	BA6	**BA7**	**BA8**	**BA9**
GI:sint s/ MNNW	4,1 (p= 0,07)ns	4,5 -	4,3 (p= 1,16)ns	4,3 (p= 0,08)ns
GII:Minimal MNNW	3,7 *	3,6 **	3,3 ***	3,6 ***
GIII:Mild MNNW	4,0 **	4,0 *	4,1 *	4,1 **
GIV:Moderate MNNW	4,5 -	4,4 (p= 0,37)ns	4,2 (p= 0,64)ns	4,6 (p= 0,08)ns
GV:Severe MNNW	4,1 (p= 0,08)ns	4,5 -	4,5 -	4,7 -
GVI:Extreme MNNW	3,4 ***	3,5 ***	3,4 ***	3,5 ***

ns:not significant, * = p< 0,05, ** = p< 0,01 e *** = p< 0,001.

Writing disability (BB1) was most commonly reported in group V (Severe MNNW). But, there was no significant difference when compared to groups III (mild MNNW) and IV (moderate MNNW).

As for buttoning clothes (BB2) group V (accented MNNW) complained the most.

To hold a book while reading (BB3), group V patients (Severe MNNW) reported the most difficulty. However, there was no significant difference when compared to groups III (mild MNNW) and IV (moderate MNNW).

To hold a telephone (BB4), group V had the most complaints (Severe MNNW). However, no significant difference when compared to group IV (moderate MNNW) (Table 10).

Table 10: Values obtained regarding the ability to perform daily activities (or interrupt them by increasing sensory complaints) on a typical day during the last two weeks. BB1: write. BB2: Button clothes. BB3: Hold a book while reading. BB4: Hold a telephone. The comparison between groups was performed with Kruskal Wallis variance analysis.

	BB1	**BB2**	**BB3**	**BB4**
GI:sint s/ MNNW	1,4 ***	1,8 ***	3,2 ***	3,7**
GII:Minimal MNNW	1,5 **	1,7 ***	2,1 ***	2,7 ***
GIII:Mild MNNW	2,4 (p= 0,07)ns	2,3 **	3,5 (p= 0,05)ns	4,0 *
GIV:Moderate MNNW	2,7 (p= 0,20)ns	2,6)**	3,8 (p= 0,15)ns	3,8 (p= 0,11)ns
GV:Severe MNNW	3,2 -	3,4 -	4,3 -	4,6 -
GVI:Extreme MNNW	2,2 *	2,2 ***	2,7 ***	3,1 ***

ns:not significant, * = p< 0,05, ** = p< 0,01 e *** = p< 0,001.

The patients in group V (Severe MNNW) had the most difficulty opening a pot (BB5). However, there was no significant difference between these and group IV (moderate MNNW).

To perform housework (BB6), it was group V (Severe MNNW) that reported the most disability, without statistically differing from group IV (moderate MNNW).

As for the inability to carry grocery bags (BB7), group V (Severe MNNW) complained the most. However, there was no significant difference compared to group IV (moderate MNNW).

For bathing and dressing up (BB8), the patients in group V (Severe NMMP) presented this difficulty the most. However, without significantly differing from group IV (moderate MNNW) (Table 11)

Table 11: Values obtained regarding the ability to perform daily activities (or interrupt them by increasing sensory complaints) on a typical day during the last two weeks. BB5: Open a pot's lid. BB6: Do housework. BB7: Carry grocery bags and BB8: Take a shower and get dressed. The comparison between groups was performed with Kruskal Wallis variance analysis.

	BB5	**BB6**	**BB7**	**BB8**
GI:sint s/ MNNW	4,0 ***	3,7 ***	2,5 ***	1,4 **
GII:Minimal MNNW	2,9 ***	3,3 ***	2,1 ***	1,4 **
GIII:Mild MNNW	4,2 *	3,3 ***	3,2 **	1,7 *
GIV:Moderate MNNW	4,7 (p= 0,28)ns	4,0 (p= 0,82)ns	3,8 (p= 0,07)ns	2,2 (p= 0,37)ns
GV:Severe MNNW	4,8 -	4,4 -	4,4 -	2,5 -
GVI:Extreme MNNW	3,5 ***	3,6 **	2,4 ***	2,0 *

ns:not significant, * = p< 0,05, ** = p< 0,01 e *** = p< 0,001.

DISCUSSION

In this cross-sectional study, 160 women were evaluated. A total of 320 hands were analyzed by pressure algometry and two points discriminatory sensitivity in the first and second finger digital pulps. A symptom severity scale questionnaire and a nerve conduction studies were also performed. It is considered a significant sample when compared to the literature. (ZANETTE *et al.*, 2006; ZANETTE *et al.*, 2007; ZANETTE *et al.*, 2010; DE-LA-LLAVE-RINCÓN *et al.*, 2009; FERNÁNDEZ-DE-LAS-PEÑAS *et al.*, 2010, FERNÁNDEZ-DE-LAS-PEÑAS *et al.*, 2013).

We observed the more pronounced the MNNW, the higher the mean age of the patients. Such data was concordant with previous study (POVLSEN *et al*., 2010).

As for the Weber-Moberg two points static discriminatory sensitivity (WEBER, 1835), (MOBERG, 1958), our data show the more pronounced the MNNW, higher are the discriminatory sensitivity values. Albeit the test does not have adequate sensitivity, its good specificity has already been proven (MACDERMID; WESSEL, 2004).

Over the last years there has been an increased interest in uncovering the underlying pain mechanisms in CTS patients, investigating sensitivity through pressure pain threshold (CHESTERTON, 2003), (ROLKE, 2005). Despite that, literature's still scarce in algometric studies performed on peripheral nerves. Other studies have identified complaints proximal to the carpal tunnel in patients with CTS, but without using algometry (ZANETTE *et al*., 2010).

In the present study, pain threshold values were correlated with the degree of nerve involvement. We observed that the thresholds decrease as pathology begins and progresses to a certain extent. Overall, our data also show similarity to the algometric hand topographic mapping study, where thresholds were lower at all points compared to the control group (FERNÁNDEZ-DE-LAS-PEÑAS *et al.,* 2010). Also, it was noted a pain threshold reduction in areas innervated by the palmar-cutaneous, ulnar and areas proximal to the carpal tunnel, in agreement with Zanette et al. 2010 findings. In which his patients reported pain with non-median nerve pattern, as well as proximal pain (forearm, elbow, arm, and shoulder) (ZANETTE *et al*., 2010).

In group VI (extreme MNNW), when sensory or motor potentials were no longer obtained in nerve conduction studies, pain thresholds returned to values closer to the control. This result is attributed to the probable destruction of fine fibers, in which there may be hypoesthesia replacing hyperalgesia. This is based on the theory that secondary hyperalgesia is due to an involvement of neural and nonneural tissues adjacent to the primary lesion and is associated with central sensitization. Thus, patients with neuropathic pain may experience mechanical allodynia in the skin related to Aβ fiber nerve transmission. Thus, patients with neuropathic pain may experience mechanical allodynia related to Aβ fiber transmission. When Noxious *stimuli* from Aδ fibers reach the spinal cords dorsal horn (lamina I), cells of wide dynamic range (lamina V) can be activated, increasing Aβ fiber's synaptic efficacy. So, loss of tactile function in patients with neuropathic pain may extinguish allodynia (MEYER *et al*., 2006).

These data concur with recent research, which in CTS there's functional and structural neuroplasticity of the brain's primary somatosensory cortex, but this linkage between neuroplasticity and functional deficits in CTS remains unknown. In order to evaluate this parameter, a group of scholars simultaneously

used functional MRI and tactile stimulation in the median nerve territory. Compared to healthy individuals, those with CTS demonstrated alterations in each finger's representation in the contralateral primary somatosensory cortex, corroborating the idea that a maladaptation phenomenon underlies the functional deficits observed in these patients (MAEDA et al., 2014).

Other studies evaluated magnetoencephalography and digital stimulation in the median-innervated area and concluded that slower peripheral nerve conduction in CTS correlates with greater delays in the first somatosensory cortical response (DHOND *et al*., 2012).

Structural diffusion tensor imaging (DTI) and voxel-based morphometry (MBV) were used to identify clear morphometric changes in CTS patients' brain. These central morphometric changes are probably secondary to peripheral nerve pathology and, consequently, alteration in somatosensory afference (MAEDA et al., 2013).

Confirmation of cortical maladaptation in peripheral neuropathy has also been sought in order to suggest corrections through appropriate therapy. Functional MRI and clinical testing were performed on CTS patients at baseline and after five weeks of acupuncture treatment. A control group of healthy adults was also evaluated. During functional MRI, median nerve sensory stimulation in the second and third fingers and ulnar nerve stimulation in the fifth finger were performed. Activity in the contralateral Brodmann area was shown to be increased in those with CTS when compared to healthy adults. After acupuncture, there was a significant decrease in this contralateral area. So, the presence of cortical maladaptation was confirmed and acupuncture was suggested as a means to induce beneficial cortical plasticity (NAPADOW et al., 2007).

In the present study, the relationship between the symptom severity scale and the degree of the median nerve neurophysiological involvement resulted in several findings. Patients who reported greater pain intensity at night had moderate impairment followed by severe nerve impairment, while those with severe impairment reported a higher frequency of nocturnal pain, followed by those with moderate and mild impairment. Also, daytime pain was more frequent in cases of moderate impairment followed by severe impairment of the median nerve. In these cases, it's believed that pain occurs more frequently due to pressure increasing activities within the carpal tunnel, intensifying compression on the median nerve and increasing pain frequency. The same behavior was observed in the daytime pain duration, being mostly reported in cases of moderate and severe impairment, followed by mild cases or those merely symptomatic. These findings are in consonance with a previous study that found symptoms tend to worsen at night and there may be difficulty with activities that require wrist flexion during daytime (Dorwart, 1984).

Our data on numbness reveal greater intensity in patients with moderate impairment, followed by the severe degree impairment patients and those merely symptoms. Tingling caught the attention of both those with only symptomatology and those with severe impairment, followed by those with moderate impairment. those who had severe impairment also were the ones that most complained about the intensity of numbness or tingling at night. That was followed by those merely symptomatic or of moderate degree. Suggesting the complaint is exaggerated due to sensation never been experienced before. The nighttime

numbness frequency or tingling was most frequently reported by those with severe impairment, followed by moderate to mild symptoms.

Several studies have already demonstrated functional disability related to sensory symptoms exacerbation (MARTINS, 2008). Our study reveals greater difficulty for patients with severe impairment to perform activities (writing, holding a book while reading and holding a phone), followed by those with moderate and mild impairment. Equally, there was also predominance in the severely impaired group, followed by the moderately impaired in the difficulty to open a pot, do housework, carry grocery bags, take a shower and dress. Patients with extreme impairment had the lowest complaints in the vast majority of issues. Returning to the large axonal loss idea, including fine fibers, can generate hypoesthesia that leads to a reduction in hyperalgesia. (MEYER *et al*., 2006).

Our study corroborates that lesions in the nervous system lead to changes in cortical areas through a central sensitization phenomenon, leading to a pain threshold reduction in CTS patients. Nevertheless, this limit reduces only to a certain extent: in extreme cases, when sensors or motors potentials are no longer detected, the values approach control`s. suggesting that a large axonal loss, including the fine fibers, may generate a hypoesthesia that leads to a hyperalgesia reduction. Thus, further studies are needed in order to broaden this knowledge henceforth.

CONCLUSION

Pain threshold is lower in patients with carpal tunnel syndrome, either the median nerve innervated area or another areas.

REFERENCES

Akelman E, Weiss AC: Carpal tunnel syndrome. Etiology and endoscopic treatment. Orthop Clin North Am. 1995 Oct;26(4):769-78.

Atroshi I, Gummesson C, Johnsson R, Sprinchorn A. Symptoms, disability, and quality of life in patients with carpal tunnel syndrome. J Hand Surg.1999 Mar;24:398-404.

Atzmon R, Eger G, Lindner D, Assaraf E, Lin E, Avissar E. Carpal tunnel syndrome in pregnancy. Harefuah. 2014 Nov;153(11):663-6.

Becker J, Nora DB, Gomes I, Stringari FF, Seitensus R, Panosso JS, Ehlers JC. An evaluation of gender, obesity, age and diabetes mellitus as risk factors for carpal tunnel syndrome. Clin Neurophysiol. 2002 Sep;113(9):1429-34

Bernardino SN. Medidas dos limiares dolorosos por algometria de pressão em pacientes com cefaleia primária. Master Degree, Recife, Jun 2012, 25 p.

Bilgin SS, Olcay SE, Derincek A, Adiyaman S, Demirtas AM. Can simple release relieve symptoms of carpal tunnel syndrome caused by a persistent median artery? Clinical experience. Arch Orthop Trauma Surg. 2004 Apr;124(3):154-6. Epub 2004 Feb 6.

Bongers F, Schellevis F, Van Den Bosch W, Van Der Zee J. Carpal tunnel syndrome in general practice: incidence and the role of occupational and non-occupational factors. Br J Gen Pract. 2007 Jan 1; 57(534): 36–39.

Brain WR, Wright AD, Wilkinson M. Spontaneous compression of both median nerves inthe carpal tunnel: six cases treated surgically. Lancet. 1947 Mar 8;1(6443-6445):277-82

Buchthal F, Rosenfalck A. Sensory conduction from digit to palm and from palm to wrist in the carpal tunnel syndrome. J Neurol Neurosurg Psychiatry. 1971 Jun;34(3):243-52.

Campbell J N, Meyer RA. Mechanisms of neuropathic pain. Neuron. 2006 Oct; 5(52):77-92.

Campos CC, Manzano GM, Andrade LB, Castelo A, Nóbrega JAM. Tradução e validação do questionário de avaliação de gravidade dos sintomas e do estado funcional da síndrome do túnel do carpo. Arq. Neuro-Psiquiatr. 2003 Mar;61(1):51-5.

Cannon BW, Love JG, Gender differences in pressure pain threshold in healthy humans. Pain, 1946;20:210-6.

Chesterton LS, Barlas P, Foster NE, Baxter GD, Wright CC. Gender differences in pressure pain threshold in healthy humans. Pain. 2003 Feb;101(3):259-66.

Coq JO, Barr AE, Strata F, "et. al". Peripheral and central changes combine to induce motor behavioral deficits in a moderate repetition task. Exp Neurol. 2009 Dec;220(2):234-45. doi: 10.1016/j.expneurol.2009.08.008. Epub 2009 Aug 15.

Crymble B. Brachial Neuralgia and the Carpal Tunnel Syndrome. Br Med J. 1968 Aug 24;3(5616):470-1.

Dale AM, Harris-Adamson C, Rempel D, "et. al". Prevalence and incidence of carpal tunnel syndrome in US working populations: pooled analysis of six prospective studies. Scand J Work Environ Health. 2013 Sep 1;39(5):495-505. doi: 10.5271/sjweh.3351. Epub 2013 Feb 19.

Das SK, Brown HG. In search of complications in carpal tunnel decompression. Hand, Essex. 1976 Oct;8(3):243-9.

Dawson GD, Scott JW. The recording of nerve action potentials through skin in man. J Neurol Neurosurg Psychiatry. 1949;12(4):259-67.

De-la-Llave-Rincón AI, Puentedura EJ, Fernández-de-las-Peñas C. New advances in the mechanisms and etiology of carpal tunnel syndrome.. Discov Med. 2012 May;13(72):343-8.

Dellon AV. The moving two point discrimination test: clinical evaluation of the quicckly adapting fiber receptor system. J Hand Surg Am. 1978 Sep;3(5):474-81.

Demircay E, Civelek E, Cansever T, Kabatas S, Yilmaz C. Anatomic variations of the median nerve in the carpal tunnel: a brief review of the literature. Turk Neurosurg. 2011;21(3):388-96. doi: 10.5137/1019-5149.JTN.3073-10.1.

Dhond RP, Ruzich E, Witzel T, "et al". Spatio-temporal mapping cortical neuroplasticity in carpal tunnel syndrome. Brain. 2012 Oct; 135(10): 3062–3073.

Dorwart BB. Carpal tunnel syndrome: a review. Semin Arthritis Rheum. 1984 Nov;14(2):134-40.

El Miedany Y, El Gaafary M, Youssef S, Ahmed I, Nasr A. Ultrasound assessment of the median nerve: a biomarker that can help in setting a treat to target approach tailored for carpal tunnel syndrome patients. Springerplus. 2015 Jan 13;4:13. doi: 10.1186/s40064-014-0779-4. eCollection 2015.

Ettema AM, Amadio PC, Zhao C, Wold LE, An KN. A histological and immunohistochemical study of the subsynovial connective tissue in idiopathic carpal tunnel syndrome. J Bone Joint Surg Am. 2004 Jul;86(7):1458-66.

Fernández-de-Las-Peñas C, Madeleine P, Martínez-Perez A, Arendt-Nielsen L, Jiménez-García R, Pareja JA. Pressure pain sensitivity topographical maps reveal bilateral hyperalgesia of the hands in patients with unilateral carpal tunnel syndrome. Arthritis Care Res (Hoboken). 2010 Aug;62(8):1055-64. doi: 10.1002/acr.20189.

Fernández-de-Las-Peñas C, Cleland JA, Plaza-Manzano G, "et al". Clinical, physical, and neurophysiological impairments associated with decreased function in women with carpal tunnel syndrome, J Orthop Sports Phys Ther. 2013 Sep;43(9):641-9. doi: 10.2519/jospt.2013.4830.

Fowler JR, Gaughan JP, Ilyas AM.FOWLER, J.R.; GAUGHAN, J.P.; ILYAS, A.M.: The sensitivity and specificity of ultrasound for the diagnosis of carpal tunnel syndrome: a meta-analysis. Clin Orthop Relat Res. 2011 Apr;469(4):1089-94. doi: 10.1007/s11999-010-1637-5. Epub 2010 Oct 21.

Fu T, Cao M, Liu F, "et al". Carpal Tunnel Syndrome Assessment with Ultrasonography: Value of Inlet-to-Outlet Median Nerve Area Ratio in Patients versus Healthy Volunteers. PLoS One. 2015 Jan 24;10(1):e0116777. doi: 10.1371/journal.pone.0116777. eCollection 2015.

Gilliatt RW, Sears TA. Sensory nerve action potentials in patients with peripheral nerve lesions. J Neurol Neurosurg Psychiatry. 1958 May;21(2):109-18.

Gray H, Clemente CD. Anatomy of the human body. 13th ed. Lea & Febiger, Philadelphia. 1985, 531,542,551.

Greenslade JR, Mehta RL, Belward P, Warwick DJ. Dash and Boston questionnaire assessment of carpal tunnel syndrome outcome: what is the responsiveness of an outcome questionnaire? J Hand Surg Br. 2004 Apr;29(2):159-64.

Hirata H, Nagakura T, Tsujii M, Morita A, Fujisawa K, Uchida A. The relationship of

VEGF and PGE2 expression to extracellular matrix remodelling of the tenosynovium in the carpal tunnel syndrome. J Pathol. 2004 Dec;204(5):605-12.

Hollinshead WH. Anatomy for surgeons: The Back and Limbs, vol 3, 3rd, ed. Philadelphia, Harper & Row, 1982, 420.

Horng YS, Chang HC, Lin KE, Guo YL, Liu DH, Wang JD. Accuracy of ultrasonography and magnetic resonance imaging in diagnosing carpal tunel syndrome using rest and grasp positions of the hands. J Hand Surg Am. 2012 Aug;37(8):1591-8. Epub 2012 Jul 4.

Hunt JR. The neural atrophy of the muscles of the hand without sensory disturbances. Rev Neurol Psych, Edinburgh, 1914, v. 12, p. 137-48.

IASP- International Association for Study of Pain. Consensus development conference statement: the integrated approach to the management of pain. J Accid Emerg Med, Bethesda, National Institutes of Health. 1994;6(3):491-2.

Ibrahim I, Khan WS, Goddard N, Smitham P. Carpal Tunnel Syndrome: A Review of the Recent Literature. Open Orthop J. 2012;6:69-76. doi: 10.2174/1874325001206010069. Epub 2012 Feb 23.

Johnson EW, Wells RM, Duran RJ. Diagnosis of carpal tunnel syndrome. Arch Physi Med Rehabil. 1962;43:414–9.

Karolczak APB, Vaz MA, Freitas CR, Merlo ARC. Síndrome do Túnel do Carpo. Revista Brasileira de Fisioterapia. 2005;9(2):117-22.

Keele KD. Pain sensitivity tests: the pressure algometer. Lancet. 1954 Mar ;266 (6813): 636-9.

Kiani J, Goharifar H, Moghimbeigi A, Azizkhani H.Prevalence and risk factors of five most common upper extremity disorders in diabetics. J Res Health Sci. 2014 Winter;14(1):92-5.

Krendel DA, Jobsis M, Gaskell PCJr, Sanders DB. The flick sign in carpal tunnel syndrome. J Neurol-Neurosurg-Psychiatr. 1986 Feb;49(2);220-1.

Leblanc KE, Cestia W. Carpal tunnel syndrome. . 2011 Apr;83(8):952-8.

Levine DW, Simmons BP, Koris MJ, "et al". A self-administered questionnaire for the assessment of severity of symptons and funcional status in carpal tunnel syndrome. J Bone Joint Surg Am. 1993 Nov;75(11):1585-92.

Li J, Vause CV, Durham PL. Calcitonin gene-related peptide stimulation of nitric oxide synthesis and release from trigeminal ganglion glial cells. Brain Res.2008 Feb;1196: 22-32.

Macdermid JC,Doherty T. Clinical and electrodiagnostic testing of carpal tunnel syndrome: a narrative review. J Orthop Sports Phys Ther. 2004 Oct;34(10):565-88.

MacDermid JC, Wessel J. Clinical diagnosis of carpal tunnel syndrome: a systematic review. J Hand Ther. 2004 Apr-Jun;17(2):309-19.

Maeda Y, Kettner N, Holden J, "et al". Functional deficits in carpal tunnel syndrome reflect reorganization of primary somatosensory cortex. Brain. 2014 Jun;137(Pt 6):1741-52. doi: 10.1093/brain/awu096. Epub 2014 Apr 16.
Maeda Y, Kettner N, Sheehan J, "et al". Altered brain morphometry in carpal tunnel syndrome is associated with median nerve pathology. Neuroimage Clin. 2013;2:313-319.

Martins RS, Siqueira MG, Simplício H, Agapito D, Medeiros M. Magnetic resonance imaging of idiopathic carpal tunnel syndrome correlation with clinical findings and electrophysiological investigation. Clin Neurol

Neurosurg. 2008 Jan;110(1):38-45. Epub 2007 Oct 24.

Mbarki H, Akrichi A, Lazrak A, "et al". Carpal tunnel syndrome in chronic hemodialysis patients. Pan Afr Med J. 2013 Jan;14:19.

Meirelles LM, Santos JBG, Santos LL, "et al". Evaluation of Boston questionnaire applied at late post-operative period of carpal tunnel syndrome operated with the pain e retinaculatome through palmar port. Acta Ortop Bras.2006;14(3):123-32.

Meyer RA, Ringkamp M, Campbell JN. Peripheral Mechanisms of Cutaneous Nociception, em: McMahon SB, Koltzenburg M - Wall and Melzack's - Textbook of Pain. Elsevier. 2006:3-34.

Moberg E. Objective methods for determining the functional value of sensibility in the hand. J Bone Joint Surg Br.1958 Aug;40B(3):454-76.

Napadow V, Liu J, Li M, Kettner N, "et al". Somatosensory cortical plasticity in carpal tunnel syndrome treated by acupuncture. Hum Brain Mapp. 2007 Mar;28(3):159-71.

Padua L, LoMonaco M, Gregori B, Valente EM, Padua R, Tonali P. Neurophysiological classification and sensitivity in 500 carpal tunnel syndrome hands. Acta Neurol Scand. 1997 Oct;96(4):211-7.

Piovesan EC, Tatsui CE, Kowacs PA, Lange MC, Pacheco C, Werneck LC. Utilização da algometria de pressão na determinação dos limiares de percepção dolorosa trigeminal em voluntários sadios. Arq. Neuro- Psiquiatr. 2001 Mar;59(1):92-6.

Povlsen B, Aggelakis K, Koutroumanidis M. Effect of age on subjective complaints and objective severity of carpal tunnel syndrome: prospective study. JRSM Short Rep. 2010 Dec;1(7):62.

Robinson LR, Micklesen PJ, Wang L. Strategies for analyzing nerve conduction data: superiority of a summary index over single tests. Muscle Nerve. 1998 Sep;21(9):1166-71.

Rolke RA, Campbell K, Magerl W, Treede RD. Deep pain thresholds in the distal limbs of healthy human subjects. Eur J Pain. 2005 Fev;9(1);39-48.

Schmidt AP. Estudo sobre os mecanismos envolvidos na atividade antinociceptiva das purinas: o papel dos derivados da guanina. Doctorate Tesis. Porto Alegre. Universidade Federal do Rio Grande do Sul. 2008, 14-20 p.

Shiri R. Hypothyroidism and carpal tunnel syndrome: a meta-analysis. Muscle Nerve 2014;50(6):879-83.

Siqueira MG, Martins RS. Síndromes compressivas de nervos periféricos. Dilivros, 1ª Ed, 2008:31.

Solomon L, Warwick D.; Nayagam S. Apley's concise system of orthopaedics and fractures. 3rd ed. London: Hodder Arnold, 2005, 118-20 p.

Weber EH. Uber den tastsinn. Arch Anat Physiol. 1835;1:152.

Werner RA, Andary M. Carpal tunnel syndrome: pathophysiology and clinical neurophysiology. Clin Neurophysiol. 2002 Sep;113(9):1373-81.

Wood JN. Recent advances in understanding molecular mechanisms of primary afferent activation. Gut. 2004 Mar;53(2):9–12.

Yoon JH, Halper J. Tendon proteoglycans: biochemistry and function. J Musculoskelet Neuronal Interact. 2005 Mar;5(1):22-34.

Zanette G, Cacciatori C, Tamburin S. Central sensitization in carpal tunnel syndrome with

extraterritorial spread of sensory symptoms. Pain. 2010 Feb;148(2):227-36.

Zanette G, Marani S, Tamburin S. Proximal pain in patients with carpal tunnel syndrome: a clinical neuro-physiological study. J Peripher Nerv Syst.2007 Jun;12(2): 91-7.

Zanette G, Marani S, Tamburin S. Extra-median spread of sensory symptoms in carpal tunnel syndrome suggests the presence of pain-related mechanisms. Pain. 2006 Mar;122(3):264-70.

Zhuo M. Neuronal mechanism for neuropathic pain. Molecular Pain, On line published. 2007 Jun;3:14, jun. 2007.

Zyluk A; Kosovets L. An assessment of the sympathetic function within the hand in patients with carpal tunnel syndrome. J Hand Surg Eur. 2010 Jun;35(5):402-8.

