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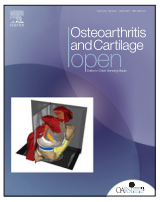

A multi-modal evaluation of experimental pain and psychological function in women with carpometacarpal osteoarthritis

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ABSTRACT

Objective: Thumb carpometacarpal osteoarthritis (CMC1 OA) is a prevalent and debilitating condition that lacks effective treatments. Understanding the multidimensional pain experience across CMC1 OA disease stages is crucial to improving treatment outcomes. This study examined how radiographic CMC1 OA severity is associated with physical, psychological, and somatosensory function.

Method: Thirty-one women with early-stage (Eaton-Littler 1–2) or end-stage (Eaton-Littler 3–4) radiographic CMC1 OA completed validated questionnaires to assess pain, disability, and psychological function. Additionally, experimental pain was measured in each participant using quantitative sensory testing (QST) (mechanical, pressure, vibratory, thermal) at seven body sites (thenar, hypothenar, brachioradialis bi-laterally; quadriceps on affected side). Cohort differences (early-vs. end-stage) across all variables were analyzed using a multivariable modeling approach that included fixed effects and interactions; notably, age was controlled as a confounder.

Results: End-stage CMC1 OA participants had higher scores in the pain ($p = 0.01$) and function ($p = 0.02$) portions of the AUSCAN assessment, self-reported disability of the DASH questionnaire ($p = 0.04$), and painDETECT scores ($p = 0.03$), indicating greater pain and disability compared to early-stage participants. Additionally, end-stage CMC1 OA participants demonstrated reduced vibratory detection and heat pain thresholds at multiple body sites (p's < 0.05), with significant interactions observed across the mechanical and cold stimuli.

Conclusion: Findings revealed women with end-stage CMC1 OA exhibited increased neuropathic pain characteristics and somatosensory loss compared to those with early-stage CMC1 OA. These results underscore the importance of addressing both peripheral and centralized pain mechanisms and the need for multimodal approaches in the treatment of CMC1 OA.

1. Introduction

Carpometacarpal osteoarthritis (CMC1 OA) is a debilitating condition that affects the thumb joint, causing pain and reduced functionality [1]. It is estimated that CMC1 OA affects 40–80% of women over 80 years old, and its prevalence is expected to rise with the aging population [2,3]. The impact of CMC1 OA extends beyond physical limitations, as it can also lead to higher psychological distress and reduced quality of life [4,5]. Despite the significant burden of this condition, effective treatments, and consensus on how to select an optimal treatment are lacking. Identifying OA-related pain and self-reported physical and psychological differences in people at different stages of CMC1 OA could help tailor interventions and improve treatment outcomes.

Several studies have investigated the effects of OA on somatic senses, including quantifying changes in pain sensitivity through standardized quantitative sensory testing (QST) [6–13], and assessing psychological factors that contribute to higher physical disability and postoperative recovery [14,15]. However, most of these studies have focused on hand OA (HOA), examined pain across multiple joints in the hand, or examined specific treatment outcomes [12,16,17]. Some studies indicate individuals with HOA may exhibit signs of peripheral and central sensitization [9,18]. Peripheral sensitization is the heightened sensitivity

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of nerve endings in response to tissue damage or inflammation, while central sensitization is an amplification of pain signals in the central nervous system [11,19]. However, pain sensitivity in individuals with HOA is not necessarily associated with the overall extent of structural or inflammatory severity experienced by those individuals [9,18]. Moreover, studies that have specifically examined individuals with unilateral CMC1 OA indicate these individuals experience bilateral pressure hyperalgesia [20] and when compared to healthy individuals experience significantly lower pressure pain thresholds at the CMC1 joint [6]. These studies suggest that centralized pain may be a feature in CMC1 OA and highlight the significance of understanding OA at the thumb given its greater impact on hand disability compared to OA at other hand joints [21].

A multimodal approach to treatment, including a complete QST assessment and an understanding of the self-perceived physical disability and psychological impact of CMC1 OA pain on patients, can lay the foundation for more effective treatments [22]. Studies have extensively explored the effects of thermal and mechanical stimuli in the context of OA, particularly in larger joints, such as knee OA. However, there is a critical gap in the existing data when it comes to understanding somatosensory changes associated with radiographic CMC1 OA. For example, previous studies [22–24] have posited that different types of OA pain may exist, ranging from nociceptive pain arising from joint damage to peripheral and central pain arising from a lesion of the somatosensory system. This has led to knee OA studies demonstrating the presence of peripheral and central sensitization, and how these changes in pain sensitivity are associated with greater pain severity and disability [25–29]. However, the transformation of pain or whether these peripheral pain characteristics arise during the development or progression of OA remains unanswered, particularly in the context of CMC1 OA. Similarly, multiple psychological factors have been associated with poor physical function in knee OA, thereby contributing to prolonged disability and further pain [15,29]. The knowledge gained from these knee OA studies has led to the development of rehabilitation treatments. Equivalent advances in knowledge are currently lacking in the CMC1 OA literature and may be a contributing factor in explaining why certain individuals undergoing rehabilitation eventually opt for surgery [30] or experience suboptimal outcomes following surgery for CMC1 OA. Addressing these gaps in knowledge is crucial to improve quality of care and outcomes for individuals with CMC1 OA.

This study aimed to assess and compare the physical, psychological, and somatosensory profiles of women based on their CMC1 OA severity. Participants were grouped as either early-stage or end-stage CMC1 OA using radiographs. Based on literature at other joints, we hypothesized that women with end-stage CMC1 OA would have higher self-perceived disability and experience greater loss of somatosensory function, primarily at sites near the CMC1 joint, compared to women with early-stage CMC1 OA.

2. Methods

2.1. Participants

Sixteen participants clinically diagnosed with either unilateral or bilateral CMC1 OA and fifteen participants who self-reported being free of hand pain were recruited for this IRB-approved study (University of Florida, IRB#201900693). All participants were female between 40 and 90 years of age and were recruited from central Florida. Demographic data were collected for all participants. Radiographic evidence of CMC1 OA was assessed for all participants by a board-certified orthopaedic surgeon using the Eaton-Littler scale [31] and posterior-anterior, lateral, and/or oblique radiographs of the CMC1 joint. Early-stage CMC1 OA was defined as participants with either Stage I or II on the Eaton-Littler scale (i.e., subtle widening to slight joint space narrowing, osteophytes or loose bodies <2 mm). End-stage CMC1 OA was defined as participants with either Stage III or IV (i.e., advanced space narrowing or arthritic changes at CMC1 joint, osteophytes >2 mm). Groupings were dichotomized due to the small sample size and narrow hypothesized research focus. Exclusion criteria included concomitant musculoskeletal pathologies in the hand or wrist (e.g., trigger finger, carpal tunnel), rheumatoid arthritis, and/or neuropathy. All participants provided written, informed consent.

2.2. Self-perceived pain, physical disability and psychological assessments

Pain characteristics, physical disability, and psychological function were assessed across all participants. Instructions for each questionnaire were read from a script for consistency. Participants also completed health and pain history forms to control for any pre-existing or current health conditions aside from CMC1 OA.

Australian Canadian Osteoarthritis Hand Index (AUSCAN) was used to assess health status and health outcomes in OA of the hand [32]. Participants were asked to complete 15 questions targeting their pain, stiffness, and physical function using a 11-point numerical rating scale. Scores were averaged, with a higher score indicating worse self-reported outcomes.

The ***Disabilities of the Arm, Shoulder, and Hand*** (DASH) is a 30-item questionnaire that assessed the participant's ability to perform upper extremity activities [33]. Participants could rate their difficulty and interference with daily life using a 5-point Likert scale. Higher scores indicate worse self-reported outcomes.

Number of Pain Sites was gathered based on self-reported body sites where a participant often experienced pain over the past 3 months. The average sum of all areas reported was calculated for comparisons.

PainDETECT is a nine-item screening questionnaire used to identify neuropathic components in persons with CMC1 OA [34]. Higher scores indicate a higher likelihood of neuropathic pain.

Patient-Reported Outcomes Measurement Information System Anxiety and Depression questionnaire included 28 items related to depression and 29 items related to anxiety [35]. Participants used a 5-point Likert scale to rate how often they experienced an emotion during the last 7-days. Scores were averaged with a higher score indicating higher severity of distress.

Perceives Stress Scale is used to assess how different situations affect feelings and perceived stress during the last month [36]. Scores were summed with scores ranging from 0 to 13 considered low stress, 14–26 considered moderate stress, and 27–40 considered high stress.

Brief Pain Inventory assessed severity and impact of pain on daily activities through a self-reported questionnaire [37]. It includes 11 different numeric rating scale questions for which higher scores indicate worse pain and higher disability.

The ***Montreal Cognitive Assessment*** is a rapid screening instrument to assess mild cognitive dysfunction [38]. A score of 26 or higher indicates the absence of cognitive dysfunction [39]. Scores were adjusted for education level and averaged, with a lower score indicating higher cognitive impairment.

Coping Strategies Questionnaire-Revised is a 27-item questionnaire used to measure the use of six different domains for coping with pain [40]. Using a 7-point scale, participants rated the frequency with which they engage in either passive or active coping. Scores for each domain were summed with a higher score indicating a preference for a coping mechanism.

Positive and Negative Affect Schedule included a set of 20 words associated with positive and negative affect [41]. Using a 5-point Likert scale, participants ranked how they generally felt. Higher scores on positive affect indicate positive feelings, such as enthusiasm, versus higher scores on negative affect indicate negative feelings, such as distress.

Satisfaction with Life Scale uses a 5-item scale designed to assess cognitive judgments of one's life satisfaction [42]. Participants use a 7-point scale to indicate their agreement with each of 5 items. Scores were averaged with higher scores indicating more feelings of satisfaction.

2.3. Experimental pain

A standardized QST protocol [43,44] was used to measure experimental pain and included four modalities (mechanical, pressure, vibratory, thermal) applied to 7 different body sites. Body sites included the thenar, hypothenar, and brachioradialis on the affected (or dominant if participant was asymptomatic) and contralateral sides as well as the quadriceps on the affected (or dominant) side (Fig. 1). If bilateral CMC1 pain was reported, the affected side was chosen based on the most self-reported CMC1 pain. If no CMC1 pain or prior diagnosis of CMC1 OA was reported prior to data collection, the dominant side was chosen; dominance was defined as the hand used for writing [45]. The thenar eminence, where the first CMC1 joint is located, was selected as the symptomatic area, whereas the hypothenar was evaluated as the asymptomatic region of the hand. The brachioradialis was chosen as a neural distant and pain-free site. Similar to previous studies, these sites were also inclusive of the median, ulnar, and radial nerve dermatomes [6]. Bilateral measurements allowed us to examine the extent and characteristics of pain on both sides. For testing, body sites were randomized for each participant and instructions were standardized. All testing was completed by trained research staff.

Mechanical Detection Thresholds were calculated using a series of von Frey filaments (Stoelting, Wood Dale, Illinois, USA), which are calibrated to known forces. The filaments were applied in an up-and-down pattern (i.e., increasing and decreasing pressure). Participants were instructed to indicate whether they could feel the sensation while having their eyes closed. The geometric mean was calculated for each site.

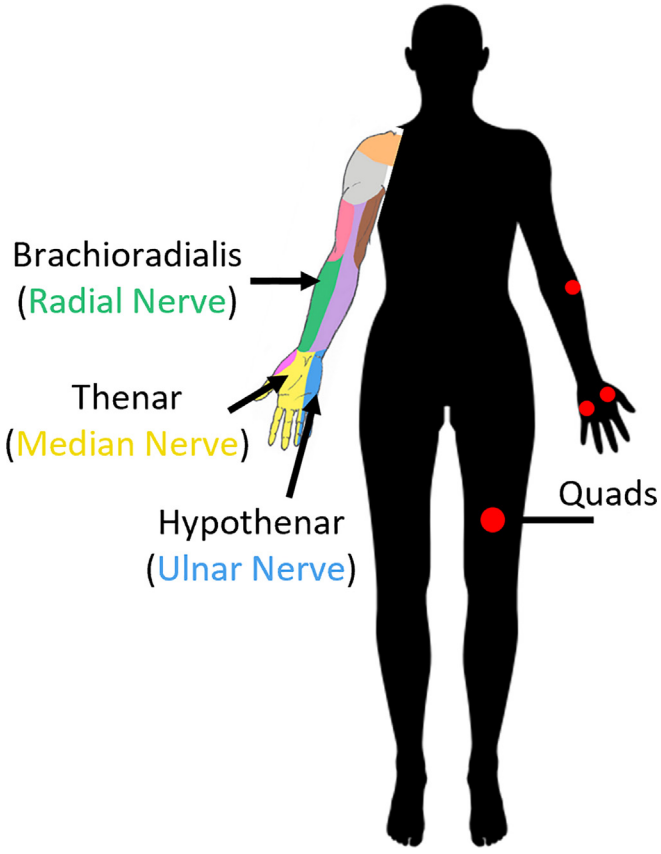

Fig. 1. Representation of selected body sites for QST assessment. Upper extremity sites were performed in both arms and were selected to include three dermatomes. Red dots indicate testing sites on the affected or dominant side. Dermatomes are shown on the contralateral arm. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article).

Pressure Pain Thresholds were evaluated using a calibrated handheld algometer (AlgoMed, Medoc) applied at a constant rate of 30 kPa/s. The participants were instructed to stop the procedure as soon as the sensation "first became painful." An average pressure pain threshold was determined for each site.

Vibratory Detection Threshold (VDT) was assessed using a handheld VSA-3000 circular probe of the Medoc system. Participants were instructed to indicate as soon as they felt vibratory sensations. Three trials were performed beginning at 0 μm and an increasing intensity rate of 0.5 μm/s. The mean value across the three trials was calculated for each site.

Thermal stimuli were applied using a computer-controlled Medoc PATHWAY Pain & Sensory Analyzer for 13 participants and using a thermal cutaneous stimulator (TCS, QST.Lab) for 18 participants. The protocol for both machines was matched with baseline temperatures at 32 °C and a ramp rate of 0.5 °C/s. For the ***Warmth Detection Threshold*** and ***Cool Detection Threshold*** (CDT), participants were instructed to indicate when they "first felt the neutral temperature turn warm" or "cool," respectively. For ***Heat Pain Threshold*** (HPT) and ***Cold Pain Threshold*** (CPT), participants were instructed to indicate when the warm or cold temperature "first became painful." Temperature thresholds were set between 0 °C and 50 °C for safety.

2.4. Statistical methods

All data analyses were performed in SPSS v.28 (IBM, Armonk, NY). Variable distribution were checked for skewness, kurtosis, and normality using the Kolmogorov-Smirnov test. Variables with non-normal distributions (i.e., VDTs and pressure pain thresholds) were log-transformed. To enable analyses of cohort interactions, all QST variables underwent z-transformation. Specifically, the mean and standard deviation of the early-stage CMC1 OA participants were calculated and used as the control to standardize the QST variables across all participants.

To analyze data from the self-reported pain, physical disability, and psychological function questionnaires, two statistical models were employed. First, a univariate model was used to compare participants with early- and end-stage CMC1 OA. Second, a multivariable model incorporating age and employing multiple linear regression was used. For both models, t-tests were used to compare continuous variables, while chi-square analyses were used to compare nominal variables. One-tailed tests were conducted for functional and pain questionnaires, focusing on the directional significance (i.e., end-stage participants performing worse than early-stage participants). Two-tailed tests were explored significance in both directions for cognitive assessment, coping, and psychological questionnaires.

For the QST variables, the mean difference between cohorts (Δ) and 95% confidence intervals (95%CI) were calculated. To account for known variations in age [44], somatosensory perception across different body sites [46], and correlations among the repeated observations, linear mixed models were employed. In essence, the models considered fixed effects such as the stage of disease severity (either early- or end-stage), body site, and age, with certain models incorporating interactions among these factors. Body site was designated as the repeated effect, while participant variability was accounted for as random effects. Across all analyses, Sidak correction was applied in pair-wise comparisons to prevent Type I errors. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Demographics

Sixteen women were classified as end-stage CMC1 OA and fifteen women as early-stage CMC1 OA (Table 1). Age differences were observed between cohorts, with women with end-stage CMC1 OA being significantly older than those with early-stage CMC1 OA (Δ: 8.2 years; 95%CI: 0.2–16.2 years; $p = 0.04$). No differences were observed across body mass index, race, education, or income level.

Table 1
Demographic variables.

Characteristics	Early CMC1 OA (n = 16)	End-stage CMC1 OA (n = 15)	*p*	Δ [95%CI] *χ^2
[a]OA Diagnosis, *n (%)*				
Unilateral CMC1 OA	1 (6.3)	5 (33.3)	–	–
Bilateral CMC1 OA	4 (25.0)	6 (40.0)	–	–
Age (years), *mean ± SD*	59.9 ± 11.2	68.1 ± 10.4	**0.044**	8.2 [0.2–16.2]
BMI, *mean ± SD*	26.8 ± 4.9	26.6 ± 4.6	0.865	−0.3 [-3.8-3.2]
Race, *n (%)*			0.293	2.5*
Caucasian	12 (75.0)	14 (93.3)		
African American	2 (12.5)	1 (6.7)		
Asian	2 (12.5)	0 (0)		
Education Level, *n (%)*			0.145	−0.4 [0.3 to −0.9]
High school degree or lower	2 (12.5)	5 (33.3)		
2- or 4-year college degree	8 (50.0)	7 (46.7)		
Graduate Degree	6 (37.5)	3 (20.0)		
Income Level, *n (%)*			0.076	−0.6 [0.3 to −1.2]
<$40k annually	1 (6.3)	5 (33.3)		
$40k – $80k annually	6 (37.5)	4 (26.7)		
>$80k annually	7 (43.7)	6 (40.0)		
Preferred not to answer	2 (12.5)	0 (0)		

Bold indicates statistically significant p-values.
[a] OA Diagnosis reported for participants recruited from the clinician's office before any data collection. OA = osteoarthritis; SD = standard deviation; BMI = body-mass index; Δ = mean difference; CI = confidence interval; χ^2 = chi square.

Early- and end-stage classifications were based on radiographs, and do not correspond to the recruitment groups of those with and without diagnosed CMC1 OA. Additionally, out of the 16 women initially recruited with a diagnosis of CMC1 OA, 10 were diagnosed with bilateral CMC1 OA and the remaining 6 had unilateral CMC1 OA. For the 16 women initially recruited as having no hand pain, radiographs were only taken for their dominant hand. This means the presence of bilateral CMC1 OA in this group was not assessed, even though these individuals were identified as having radiographic CMC1 OA in their dominant hand.

3.2. Clinical characteristics

Women with end-stage CMC1 OA had higher self-reported pain and physical disability compared to women with early-stage CMC1 OA (Table 2). Specifically, significant differences in the univariate model were observed in the pain (Δ: 2.0; 95%CI: 0.3–3.7; p = 0.01) and function (Δ: 2.1; 95%CI: 0.2–4.0; p = 0.02) portions of the AUSCAN and the self-reported disability of the DASH (Δ: 7.0; 95%CI: −2.0-27.0; p = 0.04). Scores in the painDETECT were also higher in women with end-stage

Table 2
Self-perceived physical disability and psychological variables across groups. Mean ± standard deviation.

Characteristics *(score range)*	Early CMC1 OA (n = 16)	End-stage CMC1 OA (n = 15)	*Univariate p-value*	*Multivariable p-value*	Δ [95%CI]
One-tailed t-test					
AUSCAN					
Pain *(0–20)*	1.3 ± 2.0	3.3 ± 2.6	**0.022**	**0.011**	2.0 [0.3–3.7]
Stiffness *(0–4)*	1.6 ± 2.3	2.0 ± 2.0	0.642	0.317	0.4 [0.9 to −1.2]
Function *(0–10)*	1.6 ± 2.2	3.7 ± 2.8	0.052	**0.015**	2.1 [0.2–4.0]
DASH Disability, mean ± SD *(0 – 100)*	15.3 ± 16.4	27.8 ± 22.2	0.099	**0.044**	7.0 [-2.0 – 27.0]
Num. of Pain Sites, mean ± SD	2.4 ± 1.8	2.6 ± 1.7	0.758	0.399	0.6 [-1.1-1.5]
painDETECT, mean ± SD *(0 – 38)*	4.7 ± 4.1	8.2 ± 5.3	**0.025**	**0.029**	2.8 [-0.1-7.1]
PROMIS, mean ± SD					
Anxiety [1–5]	1.8 ± 0.8	2.0 ± 0.8	0.169	0.177	0.3 [-0.3-0.8]
Depression [1–5]	1.5 ± 0.6	1.5 ± 0.6	0.746	0.452	−0.2 [-0.4-0.5]
Perceived Stress Scale, mean ± SD *(0 – 40)*	6.9 ± 4.5	8.1 ± 5.5	0.967	0.273	0.4 [-0.4-0.8]
BPI Pain Severity *(0 – 10)*	2.4 ± 2.0	3.1 ± 2.1	0.280	0.178	0.7 [-0.8 – 2.2]
BPI Pain Interference *(0 – 10)*	1.4 ± 1.4	2.7 ± 2.4	0.083	0.089	0.7 [-0.2-2.8]
Two-tailed t-test					
MoCA, mean ± SD *(0 – 30)*	27.7 ± 1.4	27.1 ± 2.5	0.751	0.402	0.7 [-2.1-0.9]
Coping Strategies Questionnaire, mean ± SD					
Distraction *(0 – 30)*	11.5 ± 8.0	14.5 ± 10.0	0.359	0.302	0.6 [-0.6-2.0]
Catastrophizing *(0 – 36)*	4.2 ± 4.2	4.2 ± 4.2	0.795	0.823	0.3 [-6-0.5]
Ignoring *(0 – 30)*	11.5 ± 8.0	12.0 ± 7.5	0.827	0.858	0.6 [-1.0-1.2]
Distancing *(0 – 24)*	2.8 ± 4.0	5.2 ± 6.0	0.216	0.236	0.5 [-0.4-1.5]
Coping *(0 – 24)*	15.6 ± 6.8	14.8 ± 6.8	0.488	0.765	0.6 [-1.5-1.1]
Praying *(0 – 18)*	5.4 ± 5.4	5.1 ± 5.7	0.510	0.806	0.7 [-1.5-1.2]
Satisfaction w/ Life Scale, mean ± SD *(0 – 35)*	35.0 ± 9.1	32.3 ± 9.1	0.490	0.348	0.5 [-1.4-0.5]
PANAS-Positive Affect, mean ± SD [10–50]	35.2 ± 5.9	35.5 ± 7.4	0.898	0.909	2.4 [-4.7-5.3]
PANAS-Negative Affect, mean ± SD [10–50]	15.0 ± 4.4	15.7 ± 5.2	0.422	0.701	1.7 [-2.9-4.2]

Notes: OA = osteoarthritis; SD = standard deviation; AUSCAN=Australian Canadian Osteoarthritis Hand Index; DASH=The Disabilities of the Arm, Shoulder, and Hand; PROMIS=Patient-Reported Outcomes Measurement Information System; BPI=Brief Pain Inventory; MOCA = Montreal Cognitive Assessment; PANAS=Positive and Negative Affect Schedule; Δ = mean difference; CI = confidence interval. In multivariable models, age was a covariate. Bold indicates statistically significant p-values.

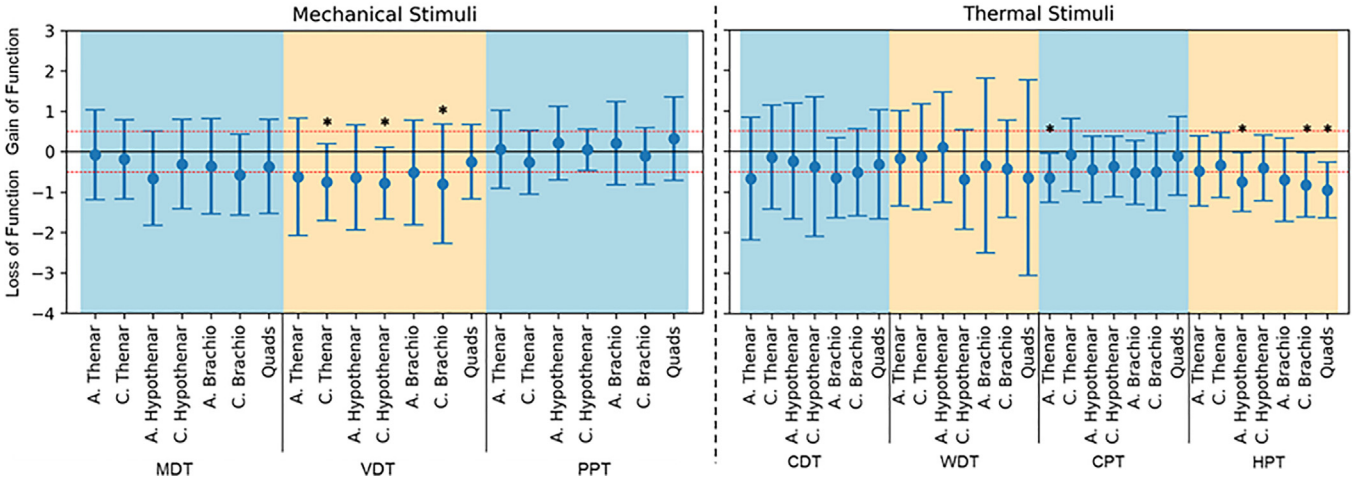

Fig. 2. Standardized QST, mechanical stimuli (left) and thermal stimuli (right) scores for women with end-stage CMC1 OA. Values are presented as Z-scores using women with early-stage CMC1 OA as the control (Z-score = 0). Error bars represent standard deviation. "*" denotes significant differences ($p < 0.05$) found during the preliminary t-tests. *Notes: A=affected or dominant side; C=contralateral side.*

CMC1 OA (Δ: 2.8; 95%CI: −0.1-7.1; p = 0.03). No significant differences were observed in any of the other questionnaires (all p's > 0.05). Although significant differences were noted in the AUSCAN pain and painDETECT questionnaire outcomes in the multivariable regression, the incorporation of age as a covariate, considering the small sample size, may have compromised overall model performance.

3.3. Somatosensory response to mechanical stimuli

Varied somatosensory function was observed across early- and end-stage CMC1 OA. Specifically, there were significant cohort differences in vibratory detection thresholds (Fig. 2) where women with end-stage CMC1 OA had lower VDTs at the contralateral thenar ($F_{(15,14)} = 0.006$, p = 0.02), hypothenar ($F_{(15,14)} = 0.002$, p = 0.01), and brachioradialis ($F_{(15,14)} = 3.5$, p = 0.05) body sites in comparison to women with early-stage CMC1 OA. The linear mixed model also showed significant body site ($F_{(6,27.5)} = 3.6$, p = 0.01) and age ($F_{(1,27.7)} = 6.2$, p = 0.02) differences for VDTs and age differences for the mechanical detection thresholds ($F_{(1,26.9)} = 4.6$, p = 0.04). Cohort and site interactions were also found during the mechanical detection thresholds ($F_{(6,26.4)} = 2.8$, p = 0.03) and pressure pain thresholds ($F_{(6,24.7)} = 5.5$, $p < 0.001$) (Table 3). Specifically examining these interactions, women with end-stage CMC1 OA had higher mechanical detection thresholds, higher VDTs, and lower pressure pain threshold, with exception of the contralateral thenar site (Fig. 3A).

There were significant age interactions across all three mechanical stimuli. We found site and age interactions during the vibratory detection threshold ($F_{(6,27.6)} = 3.9$, p = 0.01) and three-way interactions (i.e., cohort, site, and age) for the mechanical detection thresholds ($F_{(6,26.5)} = 3.1$, p = 0.02) and pressure pain thresholds ($F_{(6,24.7)} = 5.4$, p = 0.001). Women with end-stage CMC1 OA had lower pressure pain thresholds (Fig. 3B) and higher VDTs with age in comparison to early-stage CMC1 OA. Means of the mechanical stimuli and site interaction plots of the vibratory and mechanical thresholds are provided in the supplementary material.

Table 3
Linear mixed effect model analyses of the three mechanical stimuli, disease cohorts, and seven test site interactions with age as a covariate.

Variable		Multiple Interactions	
		$F_{(df)}$	p-value
MDT	Cohort	$0.197_{(1,26.9)}$	0.660
	Site	$0.670_{(6,26.4)}$	0.675
	Cohort*Site	$2.848_{(6,26.4)}$	**0.028**
	Age	$4.626_{(1,26.9)}$	**0.041**
	Cohort*Age	$0.154_{(1,26.9)}$	0.698
	Site*Age	$0.622_{(6,26.5)}$	0.711
	Cohort*Site*Age	$3.093_{(6,26.5)}$	**0.020**
VDT	Cohort	$0.029_{(1,27.9)}$	0.866
	Site	$3.564_{(6,27.5)}$	**0.010**
	Cohort*Site	$0.624_{(6,27.9)}$	0.710
	Age	$6.230_{(1,27.7)}$	**0.019**
	Cohort*Age	$0.227_{(1,26.8)}$	0.638
	Site*Age	$3.908_{(6,27.6)}$	**0.006**
PPT	Cohort	$1.723_{(1,25.7)}$	0.201
	Site	$2.417_{(6,24.7)}$	0.056
	Cohort*Site	$5.549_{(6,24.7)}$	**<0.001**
	Age	$0.796_{(1,25.7)}$	0.380
	Cohort*Age	$1.728_{(1,25.7)}$	0.200
	Site*Age	$2.306_{(6,24.7)}$	0.066
	Cohort*Site*Age	$5.360_{(6,24.7)}$	**0.001**

Notes: MDT = mechanical detection threshold; VDT = vibratory detection threshold; PPT = pressure pain threshold; F = effect size; df = degrees of freedom.

3.4. Somatosensory response to thermal stimuli

Women with end-stage CMC1 OA started to experience a loss of function during thermal stimuli. There were significant cohort differences in the cold and heat pain thresholds (Fig. 2). Women with end-stage CMC1 OA had lower CPTs at the affected thenar ($F_{(15,14)} = 2.3$, p = 0.05) and lower HPTs at the affected hypothenar ($F_{(15,14)} = 3.1$, p = 0.03), contralateral brachioradialis ($F_{(15,14)} = 1.0$, p = 0.03), and quadriceps ($F_{(15,14)} = 2.3$, p = 0.007) test sites in comparison to women with early-stage CMC1 OA. The linear mixed model showed significant differences for the cold stimuli (Table 4). Specifically, we saw site differences in cold pain thresholds ($F_{(6,23.4)} = 4.0$, p = 0.007) and cold pain ratings ($F_{(6,24.7)} = 3.3$, p = 0.02), and age differences in cool detection thresholds ($F_{(1,23.8)} = 5.2$, p = 0.03). Cohort and site interactions were also found in cool detection thresholds ($F_{(6,23.7)} = 5.6$, p = 0.007) and cold pain thresholds ($F_{(6,23.9)} = 3.9$, p = 0.001). Apart from the CDTs, the CPTs and cold pain ratings only had two-way interactions. Women with end-stage CMC1 OA had lower CDTs, lower CPTs, and higher cold pain ratings except for the contralateral thenar site. For the warm and heat stimuli, there were no significant interactions; thus, only main effects were analyzed. We only found cohort differences during the heat pain thresholds ($F_{(1,25.1)} = 6.6$, p = 0.02). Women with end-stage CMC1 OA had higher warm detection thresholds, with exception of the affected hypothenar site, higher HPTs, and higher heat pain ratings (Fig. 4A).

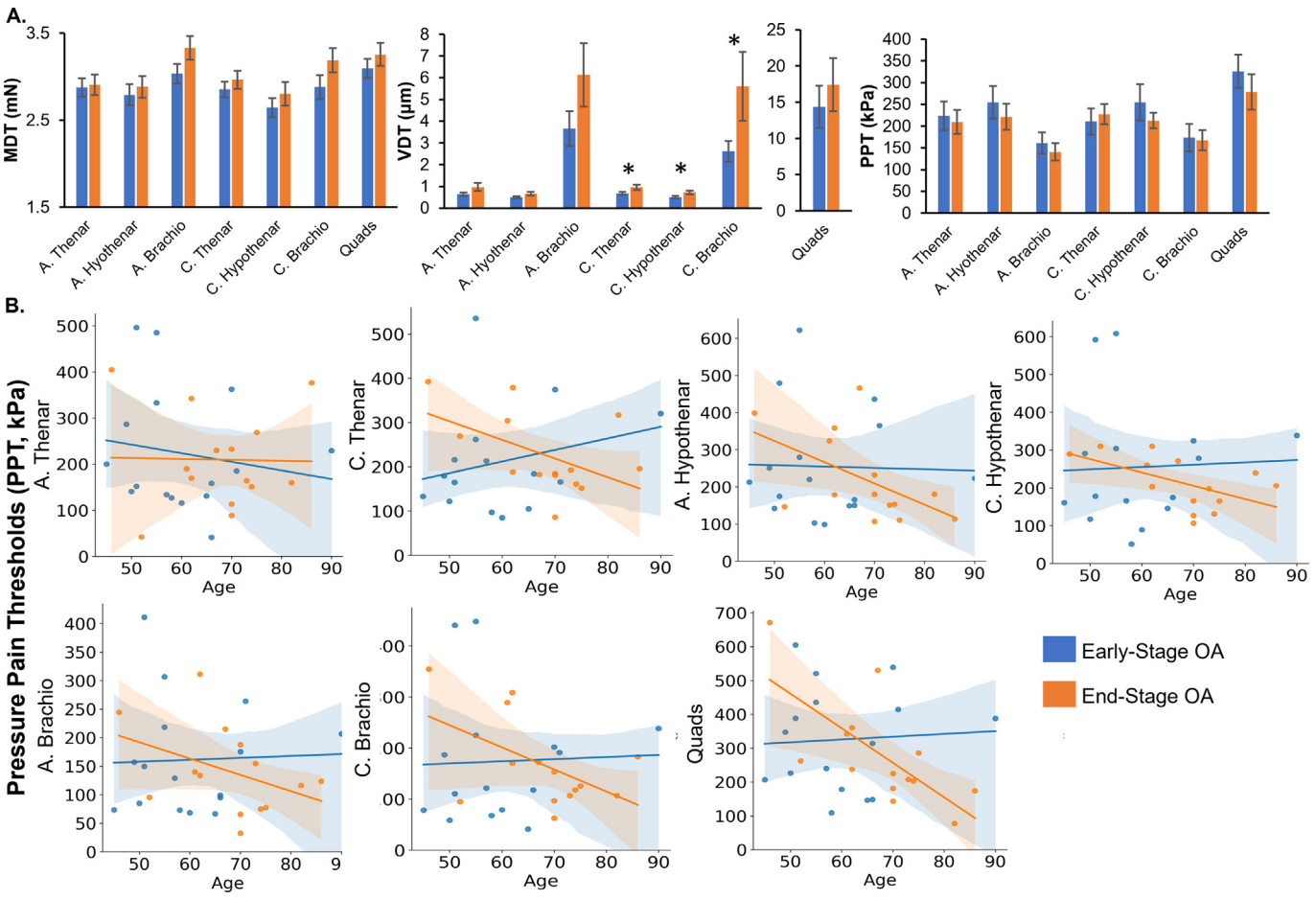

Fig. 3. **A.** Disease severity and testing sites interactions for all mechanical stimuli. Significant differences ($p < 0.05$) between cohorts by testing site is denoted by an '*'. **B.** Age and testing sites interactions grouped by disease severity for pressure pain threshold. Shaded regions represent the 95% confidence intervals.

There were significant age interactions during the cold stimuli. Site and age interactions were observed for the cold pain thresholds ($F(6,23.5) = 3.5$, $p = 0.01$) and cold pain ratings ($F(6,24.8) = 2.8$, $p = 0.03$) and three-way interactions (i.e., cohort, site, and age) were found during the cool detection thresholds ($F(6,23.8) = 5.0$, $p = 0.002$). The CPTs increased with age bilaterally at the thenar and hypothenar test sites in women with end-stage CMC1 OA but decreased with age at the affected thenar and contralateral hypothenar for women with early-stage CMC1 OA (Fig. 4B). For the CDTs, women with early-stage CMC1 OA had lower CDTs at the contralateral brachioradialis site while women end-

Table 4
Linear mixed effect model analyses of the six thermal stimuli, disease cohorts, and seven test site interactions with age as a covariate.

Variable		Multiple Interactions		Variable		Multiple Interactions	
		$F_{(df)}$	p			$F_{(df)}$	p
CDT	Cohort	$0.023_{(1,23.8)}$	0.880	WDT	Cohort	$0.768_{(1,25.0)}$	0.389
	Site	$1.434_{(6,23.7)}$	0.243		Site	$0.807_{(6,26.6)}$	0.574
	Cohort*Site	$5.550_{(6,23.7)}$	**0.001**				
	Age	$5.158_{(1,23.8)}$	**0.032**		Age	$0.123_{(1,24.7)}$	0.729
	Cohort*Age	$0.027_{(1,23.8)}$	0.871				
	Site*Age	$1.094_{(6,23.8)}$	0.394				
	Cohort*Site*Age	$4.951_{(6,23.8)}$	**0.002**				
CPT	Cohort	$1.697_{(1,24.3)}$	0.205	HPT	Cohort	$6.621_{(1,25.1)}$	**0.016**
	Site	$4.001_{(6,23.4)}$	**0.007**		Site	$1.316_{(6,26.8)}$	0.284
	Cohort*Site	$3.900_{(6,23.9)}$	**0.007**				
	Age	$0.079_{(1,24.0)}$	0.781		Age	$0.182_{(1,\ 25.0)}$	0.674
	Cohort*Age	$2.323_{(1,24.1)}$	0.140				
	Site*Age	$3.495_{(6,23.5)}$	**0.013**				
CPR	Cohort	$0.179_{(1,24.6)}$	0.676	HPR	Cohort	$1.462_{(1,25.4)}$	0.238
	Site	$3.253_{(6,24.7)}$	**0.017**		Site	$1.814_{(6,26.8)}$	0.134
	Cohort*Site	$2.234_{(6,25.1)}$	0.073				
	Age	$2.192_{(1,25.1)}$	0.151		Age	$2.473_{(1,25.0)}$	0.128
	Cohort*Age	$0.155_{(1,24.3)}$	0.697				
	Site*Age	$2.765_{(6,24.8)}$	**0.034**				

Notes: CDT = cool detection threshold; WDT = warm detection threshold; CPT = cool pain threshold; CPR = cool pain rating; HPT = heat pain threshold; HPR = heat pain rating; F = effect size; df = degrees of freedom.

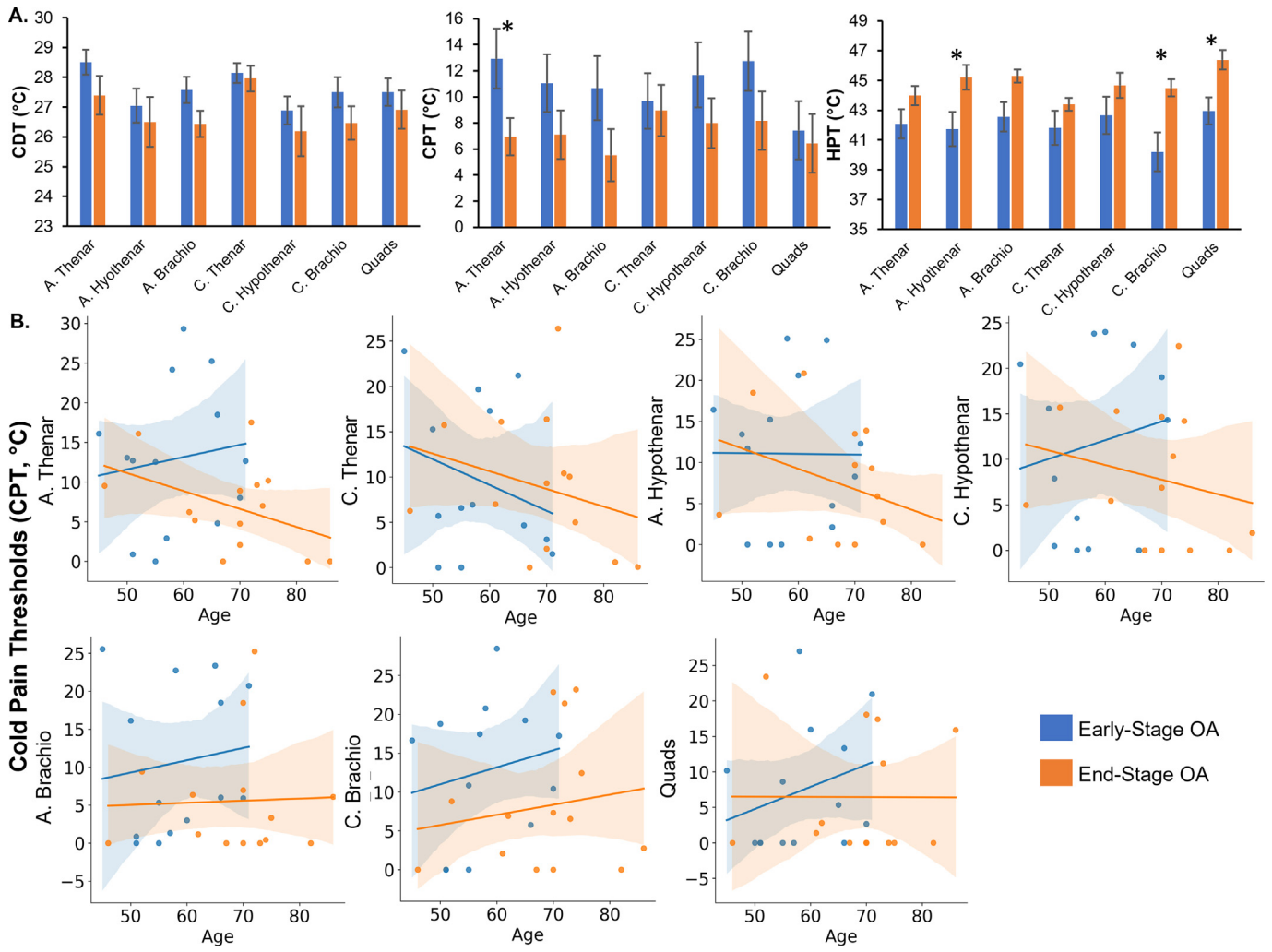

Fig. 4. **A.** Disease severity and testing sites interactions. Significant differences ($p < 0.05$) between cohorts by testing site is denoted by an '*'. **B.** Age and testing sites interactions grouped by disease severity for CPT. Shaded region represents the 95% confidence intervals.

stage CMC1 OA displayed the opposite. Similarly, women with end-stage CMC1 OA had greater cold pain rating pain scores at the affected thenar and hypothenar with age but women with early-stage CMC1 OA had similar or lower rating with age. Means and site interaction plots of the thermal stimuli are provided in the supplementary material.

4. Discussion

This study investigated the clinical characteristics and somatosensory responses to mechanical and thermal stimuli in women with early-versus end-stage CMC1 OA. Women with end-stage CMC1 OA had worse self-reported pain, physical and somatosensory function, and disability. Specifically, women with end-stage CMC1 OA were less sensitive to detecting vibration, cold, and heat pain stimuli. In agreement with prior research, the subtle differences between cohorts at the thenar site and increased sensitivity over close and distant anatomical sites likely underscore the presence of peripheral and central sensitization in end-stage OA [6,20]. Therefore, interventions that address both peripheral and central sensitization may be beneficial in improving pain and physical function in individuals with CMC1 OA.

Our study also highlights the complex interplay between aging, pain perception, and somatosensory function in women with CMC1 OA. Except for the heat stimuli, our results revealed significant interactions between age and all other assessments, indicating worse detection and pain thresholds across body sites for both early-stage and end-stage CMC1 OA cohorts. Notably, our findings suggest that women with end-stage CMC1 OA experienced less sensitivity, indicating a more severe sensory deficit in this population. Age-related decline in somatosensation is a common occurrence [47] and distinguishing between changes attributed to aging versus those related to OA may be essential.

Moreover, our findings underscore the importance of addressing both symptomatic and radiographic severity in the treatment of CMC1 OA. Despite initially recruiting 16 thumb pain-free participants, subsequent x-ray imaging revealed that the thumbs of these individuals spanned all four stages of the Eaton-Littler classification. This observation resonates with prior research highlighting the lack of correlation between symptom severity and radiographic evidence [31]. However, unlike previous studies [48,49], when participants were separated into cohorts by radiographic severity of OA (not self-reported pain), we found significant physical disability differences between women with early- and end-stage CMC1 OA. This discord with previous literature may stem from our comparatively smaller sample size and significant age difference between the early- and end-stage CMC1 OA cohorts. However, in our study, the DASH questionnaire demonstrated that women with end-stage CMC1 OA had a clinically important [50] and statistically worse functional score in comparison to women with early-stage CMC1 OA. Women with end-stage CMC1 OA also had significantly higher painDETECT scores, indicating that they experienced more neuropathic pain characteristics. Interestingly, both cohorts showed similar coping strategies, endorsing coping self-statements and distraction strategies. Given that prior research has

demonstrated that psychological questionnaires may provide a more accurate indication of a patient's pain experience compared to radiographic evidence [4], these findings provide valuable information for healthcare professionals to incorporate into pain management interventions. Yet, it is crucial to recognize that the disease is multifactorial and thus, treatment must be multimodal.

Lastly, we found small but significant differences in somatic senses in women with early- and end-stage CMC1 OA, which could be indicative of disease progression. For example, women with end-stage CMC1 OA had an overall loss of sensation during both mechanical and thermal stimuli. However, despite the importance of performing a complete QST assessment, the limited number of studies that have performed QST prior to any treatment focus only on pressure pain thresholds [6,20]. By incorporating diverse modalities and analyzing sensitization patterns across patients at different stages of disease progression, we can gain insights on specific sensory fibers that might be impacted in the early stages of the disease. Sensory fiber information could offer crucial guidance for developing targeted pain treatments, such as neurorehabilitation.

This study has several limitations that should be considered. The prevalence of multi-joint OA in this cohort, particularly the presence of bilateral CMC1 OA, limited our ability to use the contralateral arm as the control, and thus no comparisons within participants were performed. Our exclusion criteria also did not exclude participants with pain in body regions other than the hand/arm, which commonly included shoulder, neck, back, and/or hip pain [51]. Even though the number of pain sites reported by the participants were similar across cohorts, the results still highlight the presence of multi-joint OA and/or comorbidities associated with osteoarthritic pain. As such, the pain results may be compounded by other factors aside from CMC1 OA. Many of our results were also not significantly different, possibly because of our sample size. However, it is worth noting that the DASH questionnaire results were both statistically and clinically significant, indicating that our QST assessments may also have important clinical implications.

Even with our small sample size, our study demonstrates that there are peripheral sensitization differences as CMC1 OA severity worsens. We also observed that women with end-stage CMC1 OA experienced more neuropathic pain characteristics. Thus, future longitudinal studies should examine whether a possible shift from nociceptive to neuropathic pain occurs as CMC1 OA disease severity worsens, or whether these are reflective of distinct OA disease phenotypes. Above all, it is imperative to implement a comprehensive, multi-modal evaluation of CMC1 OA, such as that presented herein, to establish a baseline for the testing and development of new treatments that effectively slow disease progression and improve outcomes.

Author contributions

Tamara Ordonez Diaz (tordonezdiaz@ufl.edu): conception and design, analysis, and interpretation of the data, drafting of the article, final approval of the article, collection of data. **Thomas W. Wright** (wrightw@ortho.ufl.edu): interpretation of the data, final approval of the article. **Terrie Vasilopoulos** (TVasilopoulos@anest.ufl.edu) statistical analysis, final approval of the article. **Yenisel Cruz-Almeida** (cryeni@ufl.edu): conception and design, analysis and interpretation, critical revision of the article for important intellectual content, final approval of the article, statistical expertise. **Jennifer A. Nichols** (jnichols@bme.ufl.edu): conception and design, interpretation of the data, critical revision of the article for important intellectual content, final approval of the article, obtaining of funding.

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Ethics approval of research on humans

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ocarto.2024.100515.

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