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Widespread pressure pain hypersensitivity in elderly subjects with unilateral thumb carpometacarpal osteoarthritis

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Abstract
Background Widespread pressure hypersensitivity is one of the signs that characterize central pain sensitization in subjects with knee and hip osteoarthritis (OA). The purpose of this study was to evaluate whether widespread pressure pain hyperalgesia is a feature of individuals with unilateral symptomatic thumb carpometacarpal (CMC) OA.
Methods A total of 16 patients with unilateral symptomatic thumb CMC OA and 16 healthy sex- and age-matched controls were recruited. Pressure pain thresholds (PPTs) were assessed bilaterally over the first CMC joint; the C5–C6 zygapophyseal joint; the median, ulnar, and radial nerves; and tibialis anterior muscle. Grip and key strength, intensity of pain, and function QuickDASH were also measured.
Results The analyses showed that patients with thumb CMC OA present bilaterally decreased PPTs over the first CMC joint, the C5–C6 zygapophyseal joint, and the tibialis anterior, median, ulnar and radial nerve as compared to controls (all, $P<0.01$). Patients with thumb CMC OA also exhibited a bilateral reduction in pinch and grip strength than controls ($P<0.05$). A significant correlation was found between PPT over the radial nerve and QuickDASH ($r=0.546$, $P=0.029$).
Conclusion This study revealed bilateral widespread pressure pain hypersensitivity in individuals with unilateral symptomatic thumb CMC OA, suggesting that central pain processing mechanisms might be a feature of this pain population. These results should be taken into consideration when addressing future treatment approaches.

Introduction

Thumb carpometacarpal (CMC) osteoarthritis (OA) affects several subjects after the age of 50, mostly postmenopausal women [3]. In thumb CMC OA, pain and function limitation can lead to a high degree of hand disability [48]. Factors

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characterizing OA are damage of the articular cartilage, changes in subchondral and marginal bone, synovial joint inflammation, and capsular thickening [27]. However, discrepancy between the presence of these anatomical findings and subjective symptoms is a feature of OA [10]. In fact, OA-related pain is a complex integration of sensory and cognitive processes involving abnormal cellular mechanisms at peripheral and central levels of the nervous system [10, 11]. The inflammatory modulators present in joint deterioration can be responsible of peripheral nociception [10, 45].

Increased synaptic transmission in nociceptive neurons of the dorsal horn can be sustained by stimuli originated in low level nociceptors and non-nociceptive afferent nerve fibers [10]. A continuous sensory input in the OA-damaged joint may change patterns of neurochemical secretion and neural reorganization leading to sensitization of the central nervous system [10, 34, 45].

One of the main features of central sensitization is widespread pressure pain hypersensitivity [8, 26, 45]. Several studies reported the presence of this feature in different pain disorders, including fibromyalgia [9], temporomandibular disorders [15], whiplash [7, 8, 38], headache [16], low back pain [30], lateral epicondylalgia [13], and carpal tunnel syndrome [14]. The importance of sensitization as an underlying mechanism for pain has also recently gained interest in OA. In fact, several studies showed that individuals with painful knee OA displayed pressure hypersensitivity in distant pain-free areas [2, 4, 23, 29, 46]. In addition, hyperalgesia over remote areas was found to be significantly associated with pain intensity, disability, and quality of life [2, 4, 23, 29].

The presence of widespread pressure pain hypersensitivity and the absence of correlation between symptoms and radiological findings suggest that central sensitization mechanisms may play an important role in OA-related pain [2, 10, 27]. The principal aim of the present study was to investigate the presence of widespread pressure pain sensitivity over deep tissues in subjects with a unilateral OA in a little joint, thumb CMC OA because, to the best of the authors' knowledge, no previous studies conducted this assessment. We hypothesized that individuals with unilateral symptomatic thumb CMC OA will exhibit widespread reduced pressure pain thresholds when compared to healthy controls. In addition, we analyzed whether pressure pain hyperalgesia was related to measures of pain intensity, functioning, and strength in thumb CMC OA subjects.

Materials and Methods

Participants

Consecutive individuals diagnosed with symptomatic and radiological thumb CMC OA by a medical doctor were screened for eligibility criteria at our institute. Patients underwent subjective and physical examination conducted by a therapist with 10-year experience in musculoskeletal pain disorders. Participants were included if they reported a history of repetitive use of their dominant hand (i.e., ex-factory worker) and exhibited a stage III–IV thumb CMC OA in the dominant hand confirmed radiographically according to Eaton–Littler–Burton classification [12, 24]. In addition, patients had also to report pain at the thumb as their main symptom. The combination of radiological and clinical findings has been recommended for making a more accurate diagnosis of thumb CMC OA [47]. Exclusion criteria were as follows: previous treatment intervention with surgery in the hand or the forearm; corticosteroid injection or any physical therapy intervention within 6 months before the study; multiple pain diagnoses of the upper extremity, e.g., carpal tunnel syndrome, de Quervain's tenosynovitis, shoulder pathology, and cervical radiculopathy; evidence of systemic illness (rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus); fibromyalgia syndrome; complex regional pain syndrome; any degenerative or non-degenerative neurological conditions where pain perception can be altered; presence of any symptom in the non-dominant hand; evidence of radiographic alterations at the first CMC joint in the non-dominant hand; presence of a score greater than 6 points in the Beck Depression Inventory (BDI-II); or presence of a score >30 points on the State Trait Anxiety Inventory (STAI).

Healthy controls without a history of upper extremity or neck pain, fractures or neurologic disorders, any systemic disease, or diagnosis compatible with pain symptoms were also recruited. Ethical approval of the study was received by the institutional local board review. Informed consent was obtained from all participants and all procedures were conducted according to the Declaration of Helsinki.

Self-Reported Measures

A 11-point Numerical Pain Rating Scale (NPRS: 0, no pain; 10, maximum pain) [25] was used to assess three separate pain status: (a) level of pain while executing a key pinch between the thumb and the index finger during daily life activities, (b) average level of pain over the last 24 hours, and (c) average level of pain over the last week.

The QuickDASH questionnaire was used to measure upper extremity function [5]. It consists of 11 items providing a total score ranging from 0 to 100. Eight items include questions about the ability of the patient to perform certain daily activities, whereas the remaining three items are related to upper limb symptoms [19, 31].

Pressure Pain Threshold Assessment

Pressure pain threshold (PPT) is defined as the minimal amount of force required for the sense of pressure to change into pain [18, 32]. A mechanical pressure algometer (Pain Diagnosis and

Treatment Inc., Great Neck, NY) was used in this study. The device consists of a round rubber disk (1 cm^2) attached to a pressure gauge. The gauge displays values in kilogram per square centimeter. Pressure was applied at a rate of approximately 1 $kg/cm^2/s$ with the algometer placed perpendicular to the point. Participants were instructed to inform when the sensation first changed from pressure to pain. PPTs were tested three times over each point, then converted to kilopascal, and the mean of the three values was used for the analysis. At least 1-min resting period was allowed between measurements. This procedure showed a high intra-class correlation coefficient [ICC 0.91 (95 % CI 0.82–0.97)] [6].

Strength Measurements

Grip strength measurements were obtained with a grip dynamometer (Baseline, NY, USA), which has a precision of ±3 % [33, 37]. The grip dynamometer has five settings representing grip spans; however, position 2 was used during this study because it has been shown to be the most reliable to report maximal grip strength for both clinical and research purposes [17]. The pinch strength was measured with a mechanical pinch gauge (Baseline, NY, USA). The reliability of this procedure to measure pinch strength has shown to be 0.93 [35].

Sample Size Determination

The sample size and power calculations were performed with the ENE 3.0 software (GlaxoSmithKline©, Universidad Autónoma, Barcelona) [40]. The determinations were based on detecting a difference of 20 % on PPT over each point between groups [32]; an alpha level of 0.05 and a desired power of 80 % were used. This calculation generated a sample size of 16 individuals per group. This sample size calculation has been used in previous studies conducted in other pain disorders [13–16].

Study Protocol

The study protocol was the same for patients and healthy controls. All examinations were performed in a quiet and draught-free laboratory. Participants were asked not to take analgesics, muscle relaxants, or anti-inflammatory drugs 24 h before the examination. Participants rested in a comfortable sitting position with the examined arm relaxed over a table. They were allowed to familiarize with PPT assessment for some minutes over their dominant biceps brachii muscle.

PPT were bilaterally assessed over the first CMC joint; the median, ulnar, and radial nerves; articular pillar of C5–C6 zygapophyseal joint; and tibialis anterior muscle. The order of assessment was randomized on each subject. All the points were identified by manual palpation and marked by the assessor with a pencil in order to be consistent between repetitive trials. The tested points were detected as follows: the articular rhyme of the first CMC joint inside the anatomic snuffbox, the articular pillar of C5–C6 was located 1.5–2 cm laterally from the C5 spinous process, the tibialis anterior muscle was assessed over the proximal third of the muscle belly, the median nerve was identified in the cubital fossa adjacent to the tendon of the biceps brachii, the ulnar nerve in the groove between the medial epicondyle and the olecranon, and the radial nerve through the lateral inter-muscular septum between the media and lateral heads of triceps to enter the mid to lower one third of the humerus. The first CMC joint was selected because it is the symptomatic area in thumb CMC OA [39–44]; the articular pillar of C5–C6 joint and the tibialis anterior muscle were used to evaluate non-neural distant pain-free sites [13–16, 36, 38], whereas peripheral nerves were used to investigate neural distant pain-free sites [13–16, 36, 38].

For strength measurements, subjects were seated with shoulders in a neutral rotation and elbow flexed at 90°. The forearm and the wrist were maintained in a neutral rotation and the wrist was also in mild extension (maximum of 30°). To get maximal grip strength, the second setting is recommended for both clinical and research purposes. Subjects were tested using one hand configuration: index, middle, ring, and little finger. The lateral pinch (key pinch) involved the thumb pulp and the lateral side of the second phalanx of the index finger. The thumb was positioned with a mild flexion of the interphalangeal joint, whereas the fingers not involved in the pinch were also in semi-flexion. Grip and key strength measurements were expressed in kilograms. The instrument was calibrated after each subject measurements and the mean of three successive measurements was used. The same procedure has been used in previous studies [39–44].

Finally, patients were asked to rate their pain intensity on the NPRS and to fulfill the QuickDASH regarding their upper limb function.

Statistical Analysis

Data were analyzed with SPSS statistical package (20.0 version). Results are expressed as mean±standard deviation or 95 % confidence interval. The Kolmogorov–Smirnov test was used to analyze the normal distribution of the variables ($P>0.05$). Quantitative data without a normal distribution (pain intensity) were analyzed with nonparametric tests, whereas data with a normal distribution (PPT, strength, QuickDASH) were analyzed with parametric tests. A two-way analysis of variance (ANOVA) was used to evaluate differences in PPT over each point and strength measures with side (affected/non-affected in patients or dominant/non-dominant in controls) as the within-subjects factor and group (patients, or controls) as the between-subjects factor. Separate ANOVAs were conducted with each outcome as the dependent variable. The Spearman rho (r_s) was used to determine associations of the intensity of pain with PPT, strength measures, and QuickDASH, and the

Table 1 Differences in pressure pain thresholds (PPT) over first carpometacarpal (CMC) joint, C5–C6 zygapophyseal joint, and tibialis anterior muscle between patients with thumb carpometacarpal osteoarthritis and healthy controls

	First CMC joint*	C5–C6 zygapophyseal joint*	Tibialis anterior*
Patients with thumb carpometacarpal osteoarthritis (CMC OA)			
Symptomatic side	272.0±90.0 (95 % CI 223.5–319.4)	270.0±91.0 (95 % CI 221.5–319.4)	290.8±96.9 (95 % CI 239.3–342.2)
Non-symptomatic side	316.5±93.0 (95 % CI 267.0–365.9)	274.9±84.1 (95 % CI 230.4–319.4)	304.6±93.9 (95 % CI 255.2–355.1)
Healthy controls			
Dominant side	432.2±118.7 (95 % CI 368.9–495.5)	359.0±80.1 (95 % CI 316.5–401.5)	506.4±121.6 (95 % CI 442.1–571.6)
Non-dominant side	413.4±121.6 (95 % CI 349.1–477.7)	326.4±84.1 (95 % CI 280.9–370.9)	480.7±106.8 (95 % CI 424.3–538.0)

Values (kilopascal) are expressed as mean (95 % confidence interval)

*$P<0.001$ (significant differences between groups, two-way ANOVA test)

Pearson product–moment (r) was used for analyzing the associations between PPT, strength, and QuickDASH. All statistical analyses were conducted at a 95 % confidence level and a $P<0.05$ was considered statistically significant.

Results

Demographic and Clinical Data of Participants

Between September 2012 and December 2012, a total of 16 subjects (15 females, 1 male, aged: 74–90 years old) presenting with unilateral symptomatic thumb CMC OA satisfied all the eligibility criteria and agreed to participate. All the patients displayed unilateral CMC OA in their right (dominant) hand. Sixteen age- and sex-matched healthy controls (15 females, 1 male, aged 70–88) were also included. Within the patient group, the mean intensity of pain while executing a key pinch was 3.2 (95 % CI 1.4–4.9), mean pain intensity over the previous 24 h was 2.8 (95 % CI 1.3–4.3), and mean pain level experienced the previous week was 2.7 (95 % CI 1.2–4.2). The mean score for QuickDASH was 65.2 (95 % CI 59.6–70.9). No significant correlations between age, pain intensity, and QuickDASH were found ($P>0.186$).

Pressure Pain Sensitivity over the First CMC Joint

The two-way ANOVA revealed significant differences between groups ($F=23.262$, $P<0.001$), but not between sides ($F=0.242$, $P=0.624$) for PPT over the first CMC joint. No significant group × side interaction was found ($F=1.409$, $P=0.240$). Patients with thumb CMC OA showed bilateral lowered PPTs when compared to healthy controls. Table 1 shows mean and 95 % CI for both sides on each group.

Pressure Pain Sensitivity over Non-symptomatic Sites

Table 1 summarizes PPT values over the C5–C6 zygapophyseal joint and the tibialis anterior muscle. The two-way ANOVA revealed significant differences between groups ($F=10.722$, $P=0.002$), but not between sides ($F=0.456$, $P=0.502$) for PPT over C5–C6 joint. No significant group × side interaction was either found ($F=0.772$, $P=0.383$). Similarly, significant differences between groups ($F=55.240$, $P<0.001$), but not between

Table 2 Differences in pressure pain thresholds (PPT) over median, ulnar, and radial nerves between patients with thumb carpometacarpal osteoarthritis and healthy controls

	Median nerve*	Ulnar nerve*, #	Radial nerve*
Patients with thumb carpometacarpal osteoarthritis (CMC OA)			
Symptomatic side	252.2±109.8 (95 % CI 193.8–310.5)	329.3±85.1 (95 % CI 283.8–374.8)	295.7±91.0 (95 % CI 247.2–344.2)
Non-symptomatic side	238.3±68.2 (95 % CI 201.8–274.9)	255.2±117.7 (95 % CI 192.9–318.5)	318.5±132.5 (95 % CI 247.2–388.7)
Healthy controls			
Dominant side	399.6±85.1 (95 % CI 354.1–445.0)	423.3±119.7 (95 % CI 359.0–486.6)	441.1±92.0 (95 % CI 392.6–490.5)
Non-dominant side	391.6±99.9 (95 % CI 338.2–445.0)	381.8±112.7 (95 % CI 321.4–441.1)	468.8±114.7 (95 % CI 407.5–530.1)

Values (kilopascal) are expressed as mean±standard deviation (95 % CI)

*$P<0.001$ (significant differences between groups, two-way ANOVA test)

$P=0.039$ (significant differences between sides, two-way ANOVA test)

sides (F=0.050, P=0.824), were found for PPT over the tibialis anterior muscle, without group× side interaction (F=0.581, P=0.449). Patients with thumb CMC OA exhibited bilateral lower PPTs over distant non-symptomatic non-neural points than controls.

Pressure Pain Sensitivity over Peripheral Nerve Trunks

Table 2 summarizes PPT level over peripheral nerve trunks. The ANOVA revealed significant differences between groups and sides for PPT over the ulnar nerve (group: F=15.989, P<0.001; side: F=4.437, P=0.039) and significant differences between groups, but not between sides, for PPT over the median (group: F=42.466, P<0.001; side: F=0.226, P=0.636) and radial (group: F=29.543, P<0.001; side: F=0.845, P=0.362) nerves. No group × side interactions were found (median: F=0.016, P=0.899; ulnar: F=0.343, P=0.560; radial: F=0.008, P=0.928). Patients showed bilateral lowered PPTs over the median, radial, and ulnar nerves as compared with controls. In addition, PPT over the dominant arm was lower for the ulnar nerve in both groups (P<0.05).

Strength Measures

Table 3 shows the scores for key and grip strength. The two-way ANOVA revealed significant differences between groups, but not between sides, for key strength (group: F=21.896, P<0.001; side: F=2.054, P=0.157) and grip strength (group: F=8.770, P=0.04; side: F=0.875, P=0.353). No significant group×side interactions were found (key strength: F=0.228, P=0.635; grip strength: F=0.002, P=0.969). Patients exhibited bilateral reduced pinch and grip strength when compared to healthy controls.

Correlations of Clinical Features with PPT and Hand Strength in Patients with Thumb CMC OA

PPT over the radial nerve was found to be positively and significantly correlated with QuickDASH (r=0.546, P=0.029). No other significant correlation between PPT and upper limb function was found (−0.182<r<0.448; all, P>0.082). No significant associations between key strength (r=−0.11, P=0.686) or grip strength (r=−0.022, P=0.936) and upper extremity function were observed.

The intensity of hand pain was not associated with either PPT (−0.218<r_s<0.238; all, P>0.375) or strength (−0.249<r_s<−0.162; all, P>0.353). Finally, no significant correlation between PPT and strength measurements was either observed (−0.263<r<0.268; all, P>0.315).

Discussion

This study demonstrated that patients with unilateral symptomatic thumb CMC OA demonstrated a widespread hypersensitivity to mechanical pressure stimuli. When compared to healthy subjects, patients showed bilateral decreases of PPTs over symptomatic (first CMC joint) and distant pain-free areas (C5–C6 zygapophyseal joint, peripheral nerve trunks of the upper extremity, and tibialis anterior muscle). Altered sensory responses over sites distant from the pain area could be related to central sensitization mechanisms in this population [7, 8, 26, 38, 45]. However, widespread mechanical pain hyperalgesia was not directly associated with pain, function, or strength outcomes.

Central Sensitization in Patients with Thumb CMC OA

The presence of bilateral pressure hypersensitivity over the first CMC joint in patients with unilateral symptomatic thumb CMC OA argues for the hypothesis that peripheral sensitization mechanisms are involved in the pathogenesis of OA-related pain as previously suggested [10, 27, 45]. The presence of widespread pressure pain hypersensitivity over neural and non-neural remote sites suggests the presence of central sensitization mechanisms in CMC OA-related pain [7, 8, 26, 38, 45]. Our results agree with previous studies reporting the presence of central mechanisms in patients with OA of the knee [2, 4, 23, 29, 46] and hip OA [22, 28]; however, the presence of widespread pressure hyperalgesia is a novel information in individuals with thumb CMC OA. Nevertheless, widespread pressure pain hyperalgesia is not the only sign that characterize central sensitization since additional signs have been also reported in OA-related pain. For instance, Arendt-Nielsen et al. [2] found

Table 3 Differences in key and grip strength between patients with thumb carpometacarpal osteoarthritis and healthy controls

	Key strength*	Grip strength*
Patients with thumb carpometacarpal osteoarthritis (CMC OA)		
Symptomatic side	3.4±1.3 (95 % CI 2.7–4.1)	11.1±5.0 (95 % CI 8.5–13.8)
Non-symptomatic side	3.1±1.1 (95 % CI 2.5–3.7)	9.7±4.2 (95 % CI 7.5–11.9)
Healthy controls		
Dominant side	5.0±1.3 (95 % CI 4.3–5.7)	15.9±8.0 (95 % CI 11.7–20.2)
Non-dominant side	4.4±1.2 (95 % CI 3.8–5.0)	14.4±7.7 (95 % CI 10.3–18.5)

Values (kilogram) are expressed as mean±standard deviation (95 % CI)

*P<0.05 (significant differences between groups, two-way ANOVA test)

that individuals with severe painful knee OA also exhibited enhanced temporal summation of pain and impaired diffuse noxious inhibitory control. A brain imaging study revealed greater activation in the brain stem in patients with hip OA when compared to healthy people [22]. These other manifestations of central sensitization mechanisms should be investigated in future studies also in individuals with symptomatic thumb CMC OA.

Our study provides evidence for the hypothesis that the presence of central sensitization is a common feature of localized pain syndromes of the upper extremity since widespread pressure pain hyperalgesia has been also previously reported for lateral epicondylalgia [13] and carpal tunnel syndrome [14]. It would be interesting to determine if common nociceptive pathways are involved in different syndromes. Nevertheless, the individuals included in our study were recruited from an old population and a similar study should also be conducted in younger subjects to evaluate if these findings are similar for all subjects with thumb CMC OA. In fact, discrepancies on pressure pain sensitivity can be related to age-related changes in anatomical, physiological, and biomechanical structures of peripheral pathways involved in pain processing [20, 49].

Peripheral Sensitization in Patients with Thumb CMC OA

It is suggested that the peripheral noxious input to the central nervous system may play an important role in initiating or maintaining central sensitization in OA [1, 21, 28] and in upper extremity-localized pain disorders [13, 15]. However, we did not find a significant association between pressure pain hyperalgesia over the injured area and pain intensity suggesting that the role of peripheral sensitization might be less relevant in thumb CMC OA than in other pain disorders. A significant correlation was found between PPT over the radial nerve and upper limb function, but this result was too isolated to be considered as a manifestation of underlying pathological mechanisms. Our results are in contrast with previous findings reported in patients with knee OA where pain intensity and function were related to pressure hyperalgesia [2, 4, 23, 29, 46]. At the moment, it is not known if nociceptive barrage from joints such as the hip or the knee induces more sensitization than other joints such as the thumb CMC. Future studies are now needed to determine the relationship between peripheral and central mechanisms in individuals with thumb CMC OA.

Clinical Implications

Current results have potential implications for the management of individuals with thumb CMC OA. Clinicians should take into account the presence of central sensitization and widespread pressure pain hypersensitivity in this pain population by not limiting their intervention to the injured area. For instance, recent evidence showed that upper limb manual treatments were effective for improving pressure sensitivity over the injured area, even though they were not specifically directed to the first CMC joint [39–44]. Therefore, treatments applied to patients with thumb CMC OA should be targeted to address sensitization mechanisms. However, the effect of interventions on widespread pressure pain hyperalgesia is not currently known. Therefore, future research investigating the effects of conservative treatments should focus on the effects on both peripheral and central sensitization mechanisms. Additionally, it would be interesting to evaluate whether surgery is effective for decreasing this widespread pressure pain hypersensitivity, also to have a better insight into the role of the peripheral input in the maintenance of central sensitization in this disorder [3, 21, 28].

Limitations

Finally, although the results of the current study are relevant for a better understanding of pain mechanisms in thumb CMC OA, some limitations should be considered. First, it is known that pressure pain sensitivity can be influenced by depression or anxiety; however, this was unlikely to occur in our study because we excluded individuals with depression (i.e., >6 points in the BDI-II) and/or anxiety symptoms (i.e., >30 in the STAI). Second, it would be interesting to investigate other somatosensory tests, e.g., thermal thresholds or stimulus–response functions, to confirm the presence of central sensitization in individuals with symptomatic thumb CMC OA. Finally, our sample cannot represent general patient population since they were old people recruited from ex-workers on factories. Population-based studies with greater sample size are needed to permit a more generalized interpretation of these results.

Conclusions

The current study found widespread pressure pain hypersensitivity over the first CMC joint, C5–C6 zygapophyseal joint, tibialis anterior muscle, and peripheral nerves of the upper extremity in individuals with unilateral symptomatic thumb CMC OA, suggesting that central sensitization might be an underlying pain mechanism in this population. Widespread pressure pain hyperalgesia was not directly associated with pain, function, or strength outcomes. Future studies should be conducted to confirm these results and to establish whether other features of central sensitization are also present in subjects with thumb CMC OA.

Conflict of Interest No conflict of interest has been declared by the author(s).

Statement of Human and Animal Rights Ethical approval of the study was received by the institutional local board review (Department of Physical Therapy, Residenza Sanitaria Assistenziale "A. Maritano", Sangano, Italy). All procedures were conducted according to the Declaration of Helsinki of 1975, as revised in 2000 (5).

Statement of Informed Consent Informed consent was obtained from all participants and all procedures were conducted according to the Declaration of Helsinki

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