PROTOCOL TITLE:

Pilot Study Evaluating the Elasticity and Shear Wave Modulus (Stiffness) of the Median Nerve in Patients with Mild to Moderate Idiopathic Carpal Tunnel Syndrome Receiving OMT and Conservative Therapy

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1		Updated CTS-6 form with corrections	No
2		After obtaining elastography software and training, study team added sonoelastography as a scheduled study event for all subjects to evaluate the elasticity and stiffness of the median nerve, the transverse carpal ligament, and the carpal tunnel	Yes
3	12/16/2023	Revised: • number of total # of visits from 8 to 6 • visit interval changed to every 3 weeks	Yes
4	1/10/2024	Revised: • Removed age cap for inclusion • Modified recruitment strategies • Allowance of remote consent and electronic documentation	
5	2/20/2024	Revised: Clarified exclusion criteria to include pregnancy and the criteria for uncontrolled hypothyroidism and diabetes mellitus; updated locations	No
6	4/08/2024	Revised Exclusion Criteria to exclude patients who have undergone OMT, Physical Therapy or Massage Therapy to the affected wrist(s) within the past 3 months.	Yes
7	8/20/2024	Revised Exclusion Criteria to expand time window for initial EMG from 3 months to 1 year.	Yes

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1.0 Study Summary

Study Title	**Pilot Study Evaluating the Elasticity and Shear Wave Modulus of the Median Nerve in Patients with Mild to Moderate Idiopathic Carpal Tunnel Syndrome Receiving OMT and Conservative Therapy**
Study Design	Randomized control trial with 3 arms of treatment
Primary Objectives	To evaluate and quantify changes in the elasticity and shear wave modulus (stiffness) of the median nerve in patients diagnosed with mild to moderate carpal tunnel syndrome following one of three pathways of treatment: • Patients receiving only OMT • Patients receiving only conservative therapy • Patients receiving both OMT & conservative therapy
Outcome measures	• Median nerve cross-sectional diameter (CSD) measurements taken by US and shear wave elastography (SWE) before and after the interventions for patients in the "OMT only" cohort & "OMT +conservative therapy" cohort (4x) • US & SWE (3x) in "Conservative therapy only" cohort • Quick DASH survey at each visit • CTS-6 tool completed by clinician at each visit • Full EMG done 1x at baseline & a limited EMG 1x at the end of study
Research Intervention(s)/ Investigational Agent(s)	Treatments: Three arms: 1. Patients in OMT cohort (3x) 2. Patients in conservative therapy (standard of care) only (2x) 3. Patients in OMT & conservative therapy (3x)
IND/IDE #	No IND/IDE will be utilized in this study.
Study Population	Patients with a diagnosis of unilateral or bilateral mild to moderate carpal tunnel syndrome based on clinical and recent EMG findings, ages 18 and above
Sample Size	36
Study Duration for individual subjects	Total of 6-7 visits over 8-10 weeks; Please see attached Schedule of Events
Study Specific Abbreviations/ Definitions	OMT- Osteopathic manipulative therapy US- ultrasound SWE- shear wave elastography CSD- cross-sectional diameter MN- median nerve DASH-Disabilities of the arm, shoulder, and hand survey CTS-6: Carpal Tunnel Syndrome EMG- electromyography

2.0 Objectives

To evaluate and quantify changes in the elasticity and shear wave modulus (stiffness) of the median nerve in patients diagnosed with mild to moderate carpal tunnel syndrome following one of three pathways of treatment:

- Patients receiving only OMT
- Patients receiving only conservative therapy
- Patients receiving both OMT & conservative therapy

3.0 Background

Carpal tunnel syndrome is the most common entrapment neuropathy in the human body and occurs at the level of the wrist.1-6 The diagnosis is typically made based on clinical signs and symptoms which may include nocturnal pain and numbness, weakness and/or atrophy of the thenar muscles, numbness or tingling in the median nerve distribution, loss of two-point discrimination, and positive provocative tests (ie. Phalen's and Tinel's). Most studies have suggested that the estimated prevalence is between 2-4% afflicting between 4-10 million patients in the United States.1-6 Other studies have estimated the incidence of carpal tunnel to be between 400,000 to 500,000 cases annually in the United States with economic costs in excess of $2 billion per year.7 Treatment is generally conservative and may include a combination of non-steroidal anti-inflammatory medications (NSAIDs), orthoses, and activity modifications along with adjunctive nonoperative treatments such as therapeutic ultrasound, extracorporeal shockwave therapy, corticosteroid injections, and platelet-rich plasma injections.8 Previous work by Yamanaka et al has shown that the mechanism of action of the corticosteroids is apparently mediated by their antifibrotic more than their anti-inflammatory and antiedematous properties.9The most effective combination of therapy, including musculoskeletal manipulation, remains unknown.10 Carpal tunnel release is reserved for refractory cases or those patients presenting with axonal loss on electromyography (EMG) and nerve conduction velocity (NCV) studies.

Osteopathic physicians have long relied on their palpatory skills as a qualitative diagnostic tool in detecting disease processes in their patients. Palpation is limited to the evaluation of superficial structures and lacks objectivity.11 Osteopathic physicians evaluate their patients by performing an osteopathic structural exam during which they detect clinical manifestations of somatic dysfunction. Somatic dysfunction is broadly defined as the impaired or altered function of the body which can involve myofascial, arthrodial, osseous, vascular, lymphatic, and neural structures. The clinical findings of somatic dysfunction are defined in the osteopathic literature by ***T***issue texture changes, ***A***symmetry, ***R***estricted range of motion, and ***T***enderness –otherwise mneumonically referred to as **TART**. Tissue texture changes may manifest themselves as edema, fibrosis, atrophy, rigidity, or hypertonicity of the soft tissues upon clinical examination.12-13 Osteopathic physicians make a diagnosis of somatic dysfunction based on palpation and intersegmental motion testing. Following a diagnosis of somatic dysfunction, an osteopathic physician may then choose to treat the area of concern with a wide variety of osteopathic manipulative techniques. Following an osteopathic manipulative treatment, the osteopathic structural exam is repeated to assess for and document post-treatment changes in the initial findings as well as to plan for further treatment and follow up. Osteopathic manipulative treatment (OMT) has been recognized as an additional

conservative management option for carpal tunnel syndrome (CTS), although limited research exists to objectively validate its ability to effect post-treatment changes in the median nerve or the surrounding soft tissues.14-15

The past few decades have seen an explosion in the rapid development of novel imaging modalities. From the development and clinical use of intravenous contrast in diagnostic ultrasound to the development of high-frequency linear array transducers which allow the depiction of anatomy in exquisite detail, ultrasound has been no such stranger to innovation during this time span. Sonoelastography is a modality which allows for the assessment of the mechanical properties (ie. Elasticity or stiffness) of soft tissue both qualitatively and quantitatively through a non-invasive imaging technique.16-17 Prior studies have demonstrated sonoelastography's ability to demonstrate higher shear wave velocities in the nerves of patients with a peripheral neuropathy as compared to a normal nerve.18-21 Specifically, sonoelastography has been shown to be effective in both diagnosing and distinguishing between mild and severe carpal tunnel disease.21

We hypothesize that OMT effects biomechanical changes in the transverse carpal ligament and soft tissue contents of the carpal tunnel in patients with carpal tunnel syndrome thus resulting in improvement of their symptomatology. We further hypothesize that sonoelastography will be useful in objectively detecting these effects as a change in the elasticity or stiffness of the transverse carpal ligamernt and the contents of the carpal tunnel in patients undergoing OMT. This is an area where grayscale (aka. B-scale) ultrasound and EMG have fallen short in the assessment of patients who have experienced subjective improvement in their symptoms post OMT.14

There are two forms of real-time sonoelastography which can be used to measure tissue stiffness: Strain and shear wave elastography. Both are non-invasive methods of imaging tissue stiffness or elasticity based on Young's Modulus.16 Strain elastography evaluates elasticity through compression, with the degree of displacement being larger in soft tissue than in hard tissue. Shear wave elastography evaluates the propagation of transverse-oriented shear waves, with the wave speed being faster in hard tissues as compared to softer tissues. With shear wave elastography, an acoustic radiation force is applied via the ultrasound probe which creates an "acoustic wind." This induces mechanical and shear waves in the affected tissue. This results in qualitative color coded elastograms and quantitative maps of elasticity (kPa) or shear wave velocity (cm/s). Shear wave elastography is relatively operator independent, reproducible, and quantitative.16 These portable ultrasound techniques result in "virtual palpation" which can be available at the point of care in both inpatient and outpatient settings.

As noted previously in the studies by Taljanovic et al and Sernick et al, there was a quantifiable difference in the stiffness of the median nerve in patients with carpal tunnel syndrome as compared to those without carpal tunnel syndrome.18-21To our knowledge, there are no known studies that have examined quantifiable objective measures which speak to the elasticity or stiffness of soft tissues pre and post OMT. If successful, this project could lay the groundwork for further research into the utility of sonoelastography as well as MR elastography in the diagnosis and post-treatment assessment of patients with somatic dysfunction.

4.0 Study Endpoints

Primary study endpoints:

Compare and contrast the following between three treatment modalities:

- US and shear wave elastography (SWE) before and after treatments
- Quick DASH survey at each visit
- CTS-6 tool completed by clinician each visit
- Full EMG done 1x at baseline & Limited EMG 1x at the end of the study

Please see attached Schedule of Events/ Cohort visit flowchart for visit activity specifics.

Secondary study endpoints:

- Concomitant medications, medical comorbidities, concurrent use of splint
- OMT techniques documented and categorized
- Types, dosages, and frequency of medications injected into carpal tunnel
- Types, dosages, and frequency of oral NSAIDS and opioids used to treat CTS symptoms
- Conservative therapy including OMT will include resolution of night symptoms or complete resolution of all symptoms

Demographic characteristics:

- Age
- Sex
- Race
- Ethnicity

5.0 Study Intervention/Investigational Agent

- Cohort 1, OMT only and Cohort 2, OMT + conservative therapy: will be utilizing standard of care osteopathic manipulation techniques as treatment
- Cohort 3 will be only utilizing standard of care conservative therapies (medications/splinting)

6.0 Procedures Involved

1. Following a full review and approval from the IRB, patients will be identified who have a definitive diagnosis of mild to moderate carpal tunnel syndrome (CTS).

2. Each potential subject will undergo an EMG to exclude findings related to severe carpal tunnel syndrome (ie. axonal loss) prior to being deemed eligible to enroll in the study.

3. Research personnel will then obtain informed consent from each eligible study participant.

4. The patients will be randomized to one of three groups via a simple randomization tool such as https://ctrandomization.cancer.gov/.

5. A total of 36 patients will be enrolled in this study consisting of three arms:
    - 12 patients will undergo OMT only
    - 12 patients will undergo conservative therapy
    - 12 patients will undergo a combination of conservative therapy and OMT

6. The individuals performing the ultrasound scans, EMG's, and collecting the symptom data will be blinded to the group assignment and whether the subject is pre-or post-treatment to minimize bias.

7. Three osteopathic primary care physicians will treat each of the patients in the experimental group. They will treat each patient with a minimum of three direct techniques focused on the carpal tunnel.

8. OMT therapy will include: the interosseous membrane technique, the flexor retinaculum soft tissue technique, and the radiocarpal somatic dysfunction technique (See the uploaded document).

9. The osteopathic physicians will also evaluate and treat the cervical spine, with particular attention to the C5-7 levels, all the way to the wrist and hand as they see fit based on the findings of their osteopathic structural exam.

10. All findings of the osteopathic structural exams and the subsequent respective treatments will be specifically documented in the patient's electronic medical record.

11. The greyscale US and shear wave elastography studies will be performed by two osteopathic fellowship trained musculoskeletal radiologists with a combined 25 years of experience in performing musculoskeletal ultrasound. The US and shear-wave elastography studies will be performed at baseline, 3 to 7 days after the initial intervention as well as the interventions at the 3-week and 6-week visits.

12. All patients will be asked to fill out the Quick DASH survey at each clinical visit, prior to receiving treatment.

13. A clinician will fill out the CTS-6 Evaluation Tool at each clinical visit, prior to performing treatment.

14. A limited EMG of the wrist will be performed no more than 3-14 days following the 6-week treatment visit. The EMG's will be performed by Kettering Health Dayton senior neurology residents with appropriate attending oversight. We expect the patients' EMG results to be categorized as mild, moderate or severe CTS.

15. For the purposes of this study, conservative therapy will be defined as including the use of splints, NSAIDs, opioids, and therapeutic injection of the carpal tunnel with steroids. Physical therapy will be excluded from the conservative therapy regimen so as not to act as a confounding therapy to the OMT outcomes.

16. All results will be entered into a database along with basic demographic information including age (age above age 89 will be categorized as >89), race, medical comorbidities; concurrent use of splint or other conservative therapies.

    Please see attached Schedule of Events/ Cohort visit flowchart for visit specific activity.

7.0 Data and Specimen Banking

Surveys:
The instruments as above (CTS-6 and Quick DASH) are needed to provide objective data on the severity, type of dysfunction, and overall functional capacity. These are standard treatment evaluations used by physicians. All efforts will be made to use study numbers but original (source) questionnaires may contain patient names or identifiers. However, the scores will then be transferred to a de-identified database (by using a linking key) that can be statistically analyzed.

All results will be entered into a database that will be accessed by study personnel only. A linking system will be utilized so only de-identified information will be sent to a statistician for analysis.

All results will be entered into a database along with basic demographic information including age (age above age 89 will be categorized as >89), race, medical comorbidities; concurrent use of splint or other conservative therapies.

Additional Variables to be collected:
•Complete OMT therapy schedule (including number of visits, time post initial evaluation)
•OMT techniques documented and categorized types, dosages, and frequency of medications injected into the carpal tunnel
•Types, dosages, and frequency of oral NSAIDs and opioids prescribed to treat the symptoms of CTS

8.0 Sharing of Results with Subjects

Study results will not be shared with study participants.

9.0 Study Timelines

Note – these are estimated time lines

Study enrollment following IRB approval: Study enrollment begins January 1, 2024 and will continue through November 1, 2024

Data Collection following IRB approval: Data collection will continue through December 31, 2024

Data analysis/write-up: January 1, 2025- March 31, 2025

Subject visit specific timeline: Please see attached Schedule of Events/ Cohort visit flowchart.

10.0 Inclusion and Exclusion Criteria*

Screening for Eligibility*:*
Patients from the Kettering Health facilities, Dayton Center for Neurological Disorders (DCND), OMT practices, Orthopedic Hand Clinic, as well as Orthopedics of Southwest Ohio offices may be screened for carpal tunnel syndrome and whether they meet study specific inclusion criteria.

Inclusion Criteria

- Men and women with a diagnosis of unilateral or bilateral mild to moderate carpal tunnel syndrome based on recent clinical finding and EMG within 1 year
- ages 18 and older
- any sex, race, and ethnic group

Exclusion Criteria:

- History of undergoing recent (prior 3 months/current) physical therapy, OMT or massage therapy for treatment of carpal tunnel syndrome
- No steroid injections in wrist in the last 3 months prior to enrollment
- History of wrist trauma or surgery
- Hypothyroidism (uncontrolled - defined as TSH >4.5 mIU/L in the last 12 months)
- Severe CTS
- Systemic disease or condition including but not limited to uncontrolled diabetes mellitus (defined as HgbA1c >6.5% in the last 12 months),

thyroid disorders, rheumatoid disorders, Paget's bone disease, gout, myxedema, multiple myeloma, acromegaly, hepatic disease, dialysis patients, or other diseases or conditions in which peripheral neuropathies are common
- Secondary cause of CTS such as a ganglion cyst, mass, or an accessory muscle shown by US or MRI of the affected wrist
- Bifid median nerve as shown by US or MRI of the affected wrist
- Pregnancy (self-reported)

11.0 Vulnerable Populations

No vulnerable populations such as pregnant women, minors, or prisoners will be included.

12.0 Local Number of Subjects

Up to 36 records meeting the inclusion/exclusion criteria will be included in the data collection.

13.0 Recruitment Methods

The target patient population are patients who have been diagnosed with mild to moderate carpal tunnel syndrome and will receive either traditional conservative therapy only, traditional conservative therapy + OMT, or OMT only. Within the past year, approximately 600 patients were seen by Orthopedics of Southwest Ohio alone for carpal tunnel syndrome, with 200 of these patients meeting criteria for immediate surgery and 400 meeting criteria for conservative therapy.

This orthopedic office is very active in research and actively recruits patients to open clinical trials. Additionally, referrals can also be made from primary care practices throughout the network (Internal Medicine and Family Practice) and neurology. As the sub investigators for this project span many disciplines, we have the capacity to reach a wide variety of patients in our community hospital network.

Recruitment materials will be available at other outpatient offices as approved by the practice. This includes, but not limited to: OMT offices, Orthopedic Hand Clinic, DCND, OASWO, and KH Primary Care. This also includes website presence.

Deep 6 AI screening tool will be utilized by the Kettering Health team to identify patients that have carpal tunnel and a recent EMG.

Screening the EMG schedule at DCND and EMG & Rehabilitation Physicians may also be performed.

Kettering Health Primary Care is also referring potential patients.

14.0 Withdrawal of Subjects

Patients may voluntarily withdrawal at any time without loss of benefit. Treating physicians will also have the option of withdrawing patients who are not benefiting from the prescribed therapy and require additional treatment options, who are not following their prescribed treatments or do not show up for scheduled visits, or any other reason they deem to be necessary in their clinical opinion. However, information that has already been collected and input into the database will be used up until the point the patient decides to leave the study.

15.0 Risks to Subjects

The treatments described are all considered standard of care. There are no new additional risks beyond those normally associated with each treatment modality. Each participant will be evaluated by the treating physician who may remove the patient from the study if they deem the participant needs additional treatment not allowed or included in this study.

As data is being collected, despite all efforts to safeguard the patients' personal information, there is always a possibility of a breach of patient confidentiality.

16.0 Potential Benefits to Subjects

Patients may not receive any direct benefits from the study. They are receiving standard of care treatment and therefore should receive the same benefit as receiving prescribed treatment for Carpal Tunnel Syndrome.

17.0 Data Management and Confidentiality

Data Analysis:

- Data will be evaluated for assumptions (e.g., normality, homogeneity of variances, etc.), checked for outliers, and assessed for systematic bias to ensure valid analysis. Transformations will be applied, as necessary. Significance will be evaluated at $\alpha<0.05$. Analyses will be conducted using SAS® v9.4.
- Descriptive statistics will be performed to describe and summarize the data. Median nerve mechanical properties (elasticity/stiffness) will be measured with shear wave elastography. The association between type of treatment and median nerve mechanical properties will be compared using analysis of variance (ANOVA), followed by multiple Bonferroni comparisons to compare difference in these parameters based on severity of properties.

Data security:

- All results will be entered into a database that will be accessed by study personnel only. A subject key will be utilized so only de-identified information will be sent to a statistician for analysis.
- All study personnel will be trained in HIPAA guidelines and the ethical conduct of research.

- Upon completion of data collection and analysis, all electronic data will be permanently deleted and saved as a blank document.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

All patients will be monitored by the treating physician. The treating physician may, for any reason , remove the patient from the study and receive additional treatment. Additionally, the research personnel will enter data and will inform the treating personnel if trends or concerning findings within specific groups are noticed.

19.0 Provisions to Protect the Privacy Interests of Subjects

Due to the possible risk of breaching confidentiality, the provisions discussed in section 17.0 will be followed.

20.0 Compensation to Subjects

If a patient agrees to take part in this research study, Kettering Health will mail them a check after completing visits, following this payment schedule:

· Initial Baseline/Screening Visit (includes EMG and Imaging) - $50

· Treatment visits - $20 per visit

· Ultrasound imaging visits - $20 per visit

· Final EMG - $80

21.0 Economic Burden to Subjects

Because these are standard of care procedures and should be covered by insurance, there will not be any economic burden to a subject.

22.0 Consent Process

Only study personnel will obtain informed consent. Participants who met inclusion criteria will meet with a member of the study team to discuss the study. Patients will be given adequate time to review the consent and ask any questions. Patients who are interested in the study after being informed by their treating physician may be enrolled over the phone and will sign consent prior to beginning therapy.

The informed consent discussion may be performed remotely via telephone, with the participant receiving an electronic copy of the informed consent prior to the discussion.

Patients will need to be enrolled into the study prior to discharge from the index surgery so they can be entered into conservative therapy and given proper instructions, baseline questionnaires completed, and all pain medication usage captured.

23.0 Process to Document Consent in Writing

- Patients who are seen in the or clinic who met inclusion criteria will meet with a member of the study team to discuss the study. Patients will be given adequate time to review the consent and ask any questions.

- Patients who are interested in the study after being informed by their treating physician will sign consent or they may be enrolled over the phone and will sign consent prior to beginning therapy.

- Patients will need to be enrolled into the study prior to discharge from the index surgery so they can be entered into the type of conservative therapy and the proper instructions can be given, baseline questionnaires can be completed and all pain medication usage will be captured

- Signatures for the informed consent may be obtained electronically via DocuSign.

22.0 Setting

Orthopedic Associates of Southwest Ohio clinics, Yankee Office Building (where OMT treatment visits will take place), DCND where limited EMG's will be performed, and Kettering Health Washington Township Radiology Department.

23.0 Resources Available

- Kettering Health is committed to innovation and research as evidenced by their Research Institute that is available to support experienced researchers and guide novice learners through the entire life cycle of a research project.

- All residents, faculty, and staff members have access to medical library services through the Office of Research Integrity, the Institutional Review Board (IRB) for Kettering Health ensure oversight of research projects.

- The Academic Research Specialist provides additional support and instruction ensuring projects are reasonable, feasible, and impactful. The other integral aspect of the Research Institute is a fully staffed and centralized clinical trial management capacity.

- Office of Orthopedics of Southwest Ohio research study coordinator

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