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NEUROPATHIC PAIN IN AN ELDERLY POPULATION OF AN URBAN AREA OF IRAN WITH A SPECIAL FOCUS ON CARPAL TUNNEL SYNDROME: EPIDEMIOLOGICAL ASPECTS, CLINICAL CHARACTERISTICS, AND NON-SURGICAL THERAPY

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Neuropathic Pain in an Elderly Population of an Urban Area of Iran with a Special Focus on Carpal Tunnel Syndrome: Epidemiological Aspects, Clinical Characteristics, and Non-Surgical Therapy

Thesis for Doctoral Degree (PhD)

By

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The thesis will be defended in public at Karolinska Institutet, Karolinska University Hospital Huddinge, NVS Department, NEO building, Room DNA, Thursday Feb 17, 2022, at 1 pm

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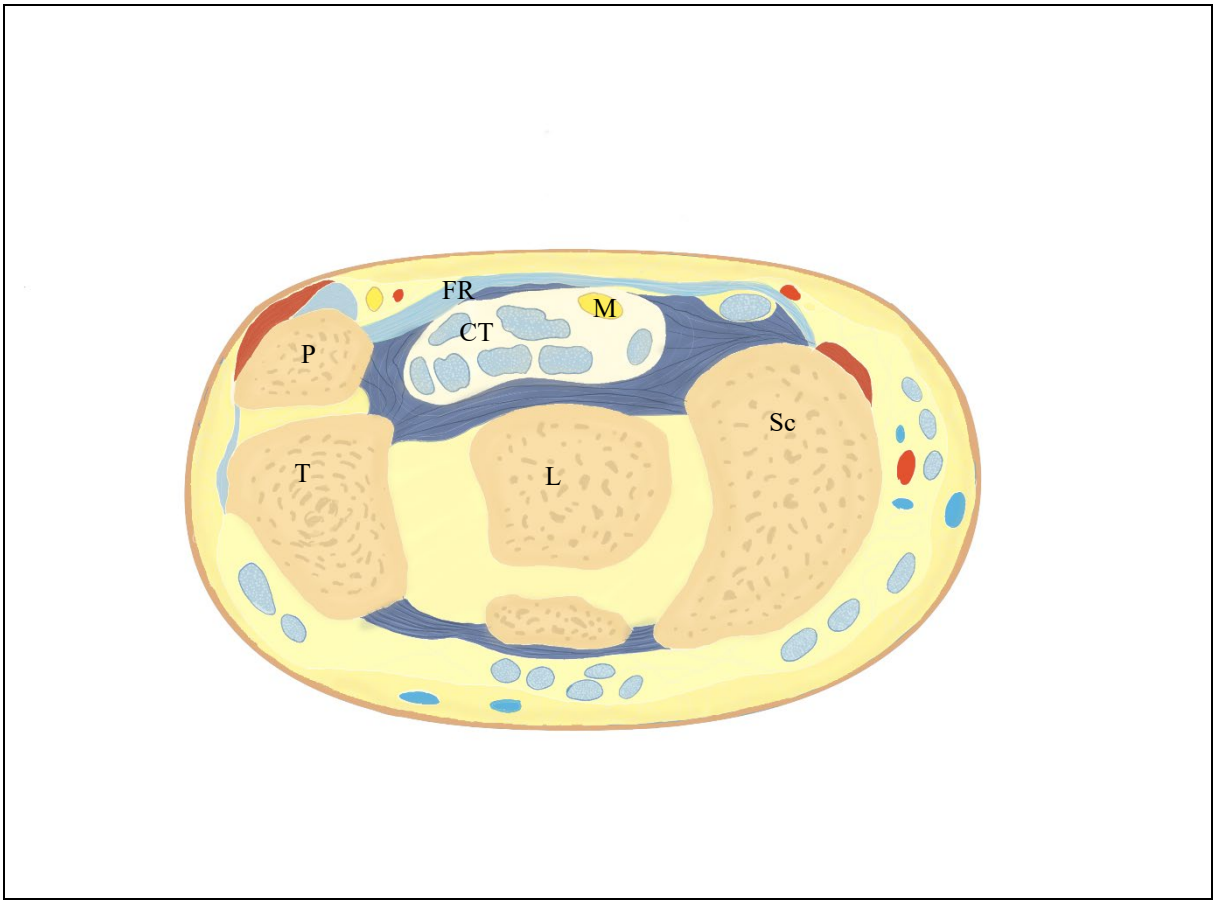
To my parents, who have sacrificed everything for me; to my beautiful wife, who has accompanied and supported me in more than twenty years of education and learning; and to my lovely daughter, who has tolerated and understood me during long periods of loneliness.

POPULAR SCIENCE SUMMARY OF THE THESIS

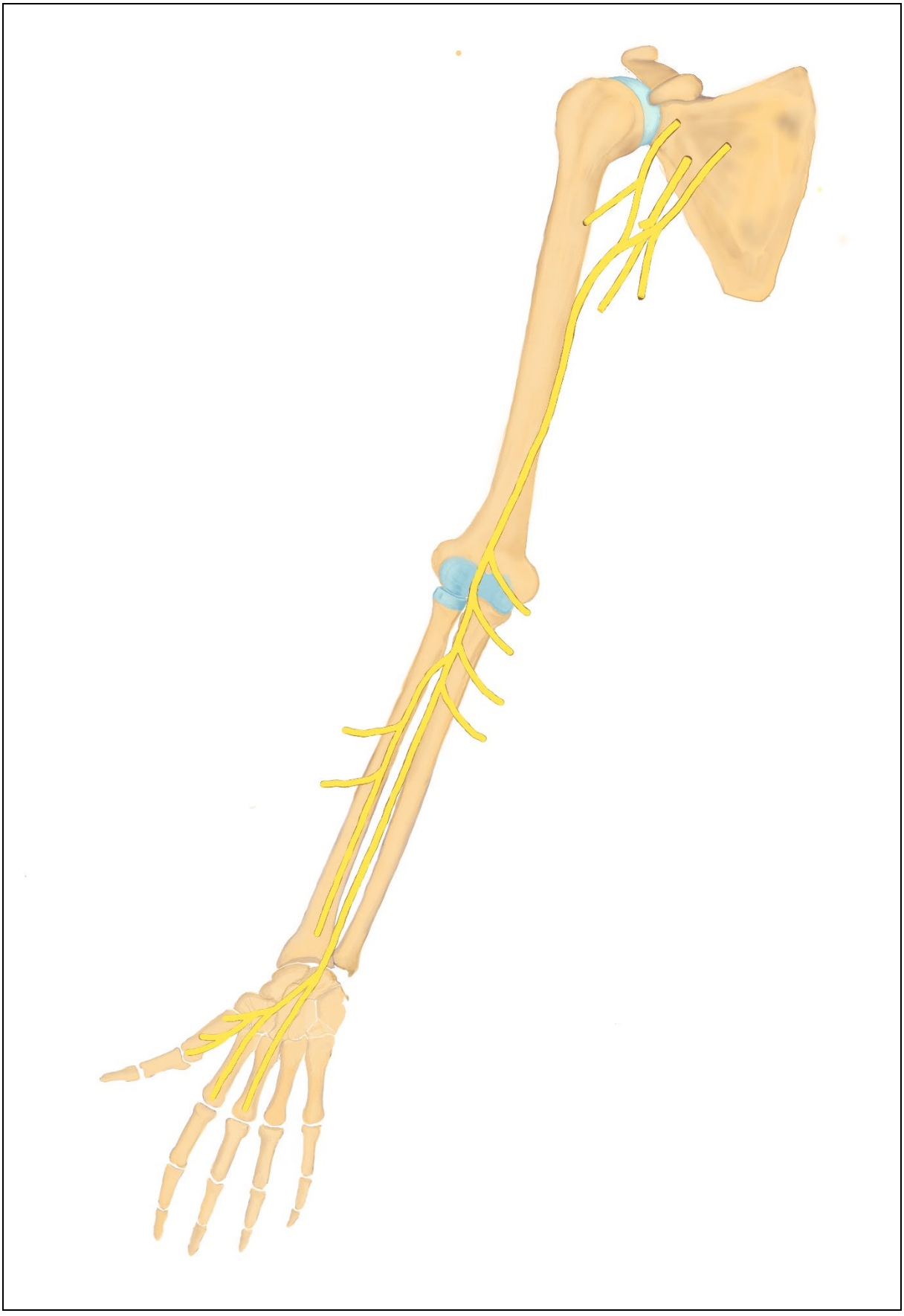
I am sure almost all of you have senile family members. One of the most common complaints by older adults is pain. Hand pain is one of the most common variants, and we think it is a normal part of aging. Our mothers or grandmothers complain about this problem more than others. It may be due to musculoskeletal problems or degenerative joint disease-causing nociceptive pain, or neurological derangement causing neuropathic pain sometimes due to nerve entrapment at the wrist. Pain is common in the elderly, in this study a frequency of 70%, and it is not a normal part of aging. It can be detected and managed properly. Neuropathic pain can be central or peripheral and can be a very disabling entity of pain with another cause than nociceptive pain. Peripheral neuropathy is quite common and in some cases the origin is from large nerves coming from the neck to the hand that sometimes become entrapped at a tunnel in the wrist. You can see a schematic drawing of the carpal tunnel in the wrist (Image 1) and the median nerve (image 2) below. Our nerves act like computer wires, transmitting signals from the peripheral environment to the body processing center, the brain. From there, action orders are transmitted back to the limbs and other organs, to move or react to a stimulus. These wires sometimes become compromised through trauma or compression and their functions impaired. One of these problems can occur at the wrist and the nerve sheet, just like it can happen with wires, and the function may be compromised or lost. Thus, the patient perceives light sense, tingling, or dysesthesia at their fingertips, or pain at their wrist. It is important to detect these problems in early stages to prevent muscles wasting, and hand function impairment in the patient. Carpal tunnel syndrome (CTS) may occur when the median nerve of the wrist is compromised and is usually suspected and diagnosed by its clinical presentations in an experienced physician’s hands.

Image 1: Schematic carpal tunnel and median nerve



Abbreviations: CT: Carpal Tunnel, FR: Flexor Retinaculum, L: Lunate bone, M: Median nerve, P: Pisiform bone, Sc: Scaphoid bone, T: Triquetrum bone

Image 2: Median nerve from the neck to the fingers



However, some para-clinical tools are necessary to confirm the diagnosis. I am sure that everybody sees or hears about the ultrasonography (US) that is used for monitoring babies before the birthdate in a mom's belly. That variant is completely noninvasive and pain free. The same machine, with a specific software, can detect and visualize other parts of the body like the anatomy of the wrist. In this study, we not only found high pain prevalence among elderly people in our society, but we also examined and found that US is a reliable tool for detecting a pathological condition of the wrist --- median nerve entrapment, carpal tunnel syndrome (CTS) --- with high accuracy and precision. In the accompanying images, you can see how easily a nerve disease could be diagnosed by US.

With high resolution US we can detect small objects in a tissue and targeting the spread of injected pharmacological compounds at the right site without damaging vital adjacent structures such as nerves and vessels. In this study, we investigated the effects of injections of different pharmacological medications in the carpal tunnel at different target sites with a very fine needle near the entrapped nerve of the carpal tunnel and found positive benefits which can improve the pain of the afflicted patients without a risky, invasive surgery.

ABSTRACT

Background: People are getting older, and aging problems and disorders are increasing fast. Knowing the rates, causes, symptomatology, treatment, relief, and prognosis of associated disorders can help and facilitate the elderly, their families, primary health care providers, and health policymakers. Chronic pain in the elderly is a common complaint and its prevalence differs in society and depends on many factors, including type, severity, and localization but also comorbidities, socio-economic factors, and genetics. Pain is in two main categories, nociceptive and neuropathic. Nociceptive pain usually occurs after end-organ damage or derangement such as musculoskeletal problems, osteoarthritis, or trauma. Neuropathic pain arises from central or peripheral nervous system injuries. One of the most common types of peripheral neuropathic pain is hand pain caused by the carpal tunnel syndrome (CTS). Hand pain and CTS are common among the elderly, especially in women. The etiology usually remains uncertain until the late stages of the disorder, when intrinsic hand muscles become weak or atrophy, when it is too late to manage the CTS adequately. Thus, it is important to be aware of its clinical symptoms, signs, and provocation maneuvers, but also to have a noninvasive diagnostic tool when CTS is suspected. Also, it is important to have a solution for mild and moderate types of CTS to prevent surgery in older adults, especially in those with frailer constitutions.

Objectives: We evaluated the prevalence of pain, with special focus on neuropathic pain and CTS, in a large population-based study in Tehran, the capital of Iran. We chose CTS as being the most common symptom of focal neuropathy and evaluated the median nerve by noninvasive, high-resolution ultrasonography. We investigated and diagnosed CTS and determined its severity. Following the results of our diagnostic study, we performed interventional treatment studies on patients diagnosed with CTS. To find the optimum steroid dose site, we examined three different doses of steroid in a mixture injected in the tunnel near the affected nerve medianus with an adhesion removal technique called hydro dissection. Finally, we compared different methods of injection in our last study to examine a hypothesis about nonsurgical flexor retinaculum release.

Methods and material: More than 5,000 patients were investigated randomly by a multistage cluster sample. Participants were then interviewed using a sociodemographic checklist, a standard pain questionnaire, and general health through GHQ-28. In the 2nd study, demographics were noted along with the clinical presentation of CTS, and the median nerve anatomy was assessed by ultrasound and electrodiagnostic tests. The median nerve cross-sectional area (CSA) at the tunnel inlet and four different areas over the median nerve were

measured and analyzed. In the 3rd paper with an intervention, we designed a prospective three group, randomized, double-blind trial to evaluate 40, 80, and 0 mg triamcinolone in a mixture of 3 mL containing 1 cc of lidocaine 2%. Outcome measures included the Boston Carpal Tunnel Questionnaire, VAS (visual analog scale), median nerve conduction criteria, and the ultrasound median CSA. All data were recorded at the baseline, 14 days, 1 month, and 6 months after the injection. In the 4th study, the design was similar to the 3rd one, though we had only two groups and the injecting mixture was 40 mg of triamcinolone and 1 cc of lidocaine 2%. The location of the injection was different with one group injected in the flexor retinaculum and the other near the nerve. All data were recorded as in the 3rd study but only at baseline, and 6 weeks after injection.

Results: We found a 13.7% prevalence of chronic neuropathic pain and 30% of chronic nociceptive pain, overall chronic of 31.7% and overall acute of 39.1% which, in combination, add up to 70.8%. The major comorbidities were osteoporosis, diabetes, disability, and stroke. In the 2nd study with 203 CTS and 103 control subjects, CSA at the tunnel inlet with a threshold of 8.5 mm^2 had a sensitivity and specificity of 96.9% and 93.6% respectively. In the 3rd study with 161 patients, we did not find any statistically significant differences between groups, i.e., all groups with a steroid dose had similar results. In the last study with 50 eligible subjects randomized into two groups, there was a significant improvement in Boston scores (p-value 0.023), VAS (p-value 0.026), and ultrasonographic measure (p-value 0.004), in favor of intra-flexor retinaculum steroid injection compared to near the nerve.

Conclusions: Neuropathic pain prevalence is relatively high; 13.7% among Iranian elderly people, and the overall pain is very high around 70 %. It should be addressed by health policymakers, primary care physicians, and caregivers. High-resolution ultrasonography is a noninvasive diagnostic tool with about 95% sensitivity and specificity in detecting CTS in the elderly and should be introduced as a screening tool by primary physicians engaged in elderly care. The use of plain lidocaine was beneficial in managing CTS in elderly patients, and we did not find any superiority for the steroids. Finally, in case of no contraindication for steroids, we prefer the intra-flexor retinaculum injection. Larger studies should be performed in future studies in this field to confirm our results.

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CONTENTS

LIST OF ABBREVIATIONS

ANOVA	Analysis of variance
BCTQ	Boston Carpal Tunnel Questionnaire
BMI	Body Mass Index
CTS	Carpal Tunnel Syndrome
CSA	Cross Sectional Area
Ca	Capitate
DML	Distal Motor Latency
EDX	Electrodiagnostic studies
EMG	Electromyography
FR	Flexor Retinaculum
LU	Lunate
MN	Median Nerve
NCV	Nerve Conduction Velocity
NCS	Nerve Conduction Studies
NP	Neuropathic Pain
Ra	Radius
ROC	Receiver Operating Characteristic
SNAP	Sensory Nerve Action Potential
Sc	Scaphoid
SD	Standard Deviation
US	Ultrasound
UA	Ulnar Artery
VAS	Visual Analog Scale

1. INTRODUCTION

Pain is an unpleasant emotional or sensation incidence with potential or actual tissue damage .(1) The elderly has a higher risk of experiencing pain but are less likely to receive proper pain management.(2) Senility per se predisposes older adults to repetitive and multiple traumas as the physical cause of pain. Other sources of pain are mood fluctuation and psychological stressors, which are more frequent in the elderly. Coexisting medical conditions, poly pharmacy, and frailty make the pain picture complicated in this age group.(2) Physical labor put significant stress on bone, joints, muscle, and nerves. As a result, degenerative joint disorders, discopathies, neuropathies, vascular insufficiencies, and muscular weakness appear; the leading belief is that they are the sources of pain and its prevalence in the elderly. There are two major types of pain, the nociceptive and the neuropathic pain with different causes. There is central neuropathic pain and peripheral neuropathic pain i.e. neuropathies. Neuropathies due to sensory nerve damage may present with pain or numbness and coping skills with pain in the elderly lead to decreased pain frequency. Older people may be over- or under-sensitive to pain perception, and this complicates diagnosis and management of pain in this group.(2) A false belief in the general population and even among some physicians and practitioners is that pain is a natural part of aging. Others are not aware of specific features of pain presentation in the elderly, and first-line practitioners have no insight about neuropathy, neuropathic pain, and its management. Therefore, it is important to evaluate the prevalence of neuropathic pain and one of its common etiologies, carpal tunnel syndrome or CTS.

Acute vs. chronic pain:

Usually, a physical assault is what leads to acute pain. It is sometimes associated with hyperactivity of the sympathetic nervous system, and muscle spasms. Acute pain is generally self-limiting and lasts no longer than six weeks, though, in contrast, chronic pain is not always only a symptom but may be associated or a part of a disease, outlasting the reasonable period of tissue healing time. Psychological problems may initiate or be associated with this type of pain, whose period may be unpredictably long.(2)

Structural changes, called synaptogenesis, may occur in dorsal horn cells or in the brain in chronic pain. Typically, a harsh stimulus, such as tissue injury, activates nociceptors in the peripheral organs. These receptors generate an impulse which is transmitted by peripheral

nerves to the dorsal horn of the spinal cord, continuing to the superior nervous system's organ, the brainstem, and the cerebral cortex, leading to it being precepted as pain. (2)

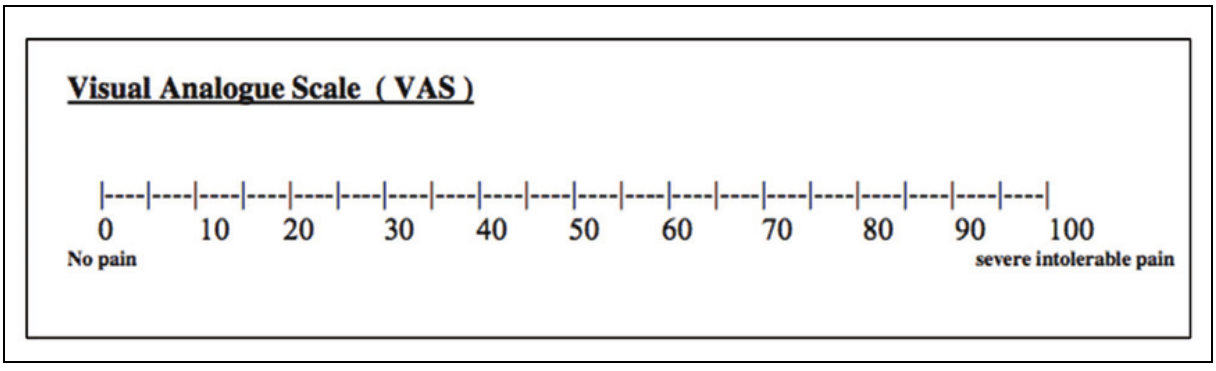
Peripheral hyperalgesia means hyperactivation of peripheral nociceptors by small molecules called pain mediators released by different damaged tissue cells or inflammatory cells attracted to the assault. Central hyperalgesia or central sensitization occurs when glial cells excessively secrete mediators that activate cortical neuronal cells. Anxiety, mood changes, and personality also affect pain perception via synapse modulation in the central nervous system. After a while, or due to genetic factors, an aberrant relation such as synapse hyperactivity or extra synapse formation activates the cortical pain perception area. There is also the possibility that some inhibitory neuronal activity malfunction may appear.(2)

This process, called synaptogenesis, is usually the main cause of persistent pain, even in the absence of end-organ tissue damage. It is also the real dilemma in pain management. Acute pain management focuses on nociceptive signal interrupting, whereas its chronic counterpart needs a multidisciplinary approach such as physio-psychosocial approach.(3)

Assessment of neuropathic pain:

Comprehensive and precise pain assessment is the cornerstone of accurate pain management. The first step is history taking and physical examination. A good pain assessment tool should have numeric scores or other measurable scales. It should be administered easily; understandable by patients; and have reasonable specificity, sensitivity, and reproducibility. The visual analog scale (VAS) is one of the most frequently used pain assessment tools. It has a 100-mm ruler (Image 3) where 0 means no pain and 100 the worst pain. Usually, a patient marks a number in between. (4)

Image 3: Visual analog scale



The other logical pain measurement scale is the assessment of functional impairment due to pain, such as the functional independent measurement (Image 4).(5)

Image 4: Functional independent measurement (FIM)

Category	Task Type	#	Task
Motor	Self-care	1	Eating
		2	Grooming
		3	Bathing
		4	Upper body dressing
		5	Lower body dressing
		6	Toileting
	Sphincter control	7	Bladder management
		8	Bowel management
	Transfers	9	Bed to chair transfer
		10	Toilet transfer
		11	Tub/shower transfer
	Locomotion	12	Walk/wheelchair
		13	Stairs
Cognitive	Communication	14	Comprehension
		15	Expression
	Social cognition	16	Social interaction
		17	Problem solving
		18	Memory

Depression and anxiety have a significant role in pain perception and become chronic, so it is important to measure these variables when quantifying pain. However, it depends on the elderly's beliefs in pain, and how they report their experience. (5)

Therefore, pain assessment in the elderly needs more accurate and reliable means, exemplified by specific questionnaires and paraclinical tests. Moreover, healthcare

professionals should have knowledge and awareness of pain assessment tools to act proactively in determining the elderly's level of pain.(4,5)

In addition, paraclinical tests can help in pain evaluation, especially in determining etiology. Conventional radiography can detect bony defects and degeneration, and more advanced magnetic resonance imaging can show nervous system tissue. Positron emission tomography can evaluate the functional brain magnetic resonance imaging, and Electrodiagnosis (EDX) (Image 5) including electromyography (EMG) (Image 6) and nerve conduction studies (NCS) (Image 7) can evaluate the peripheral nervous system function. (6,7)

Image 5: Electrodiagnosis machine

Image 6: Electromyography: needle insertion and waveform

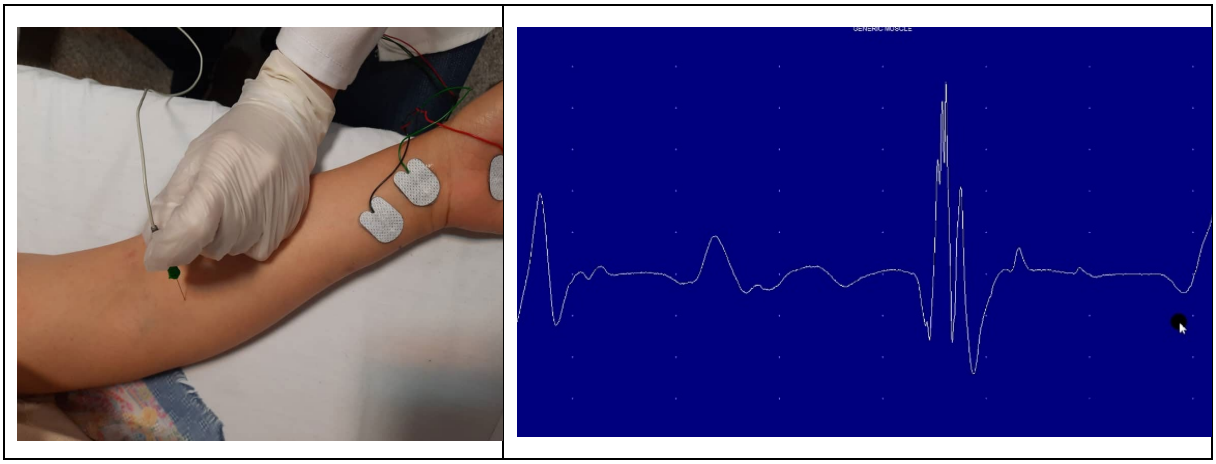
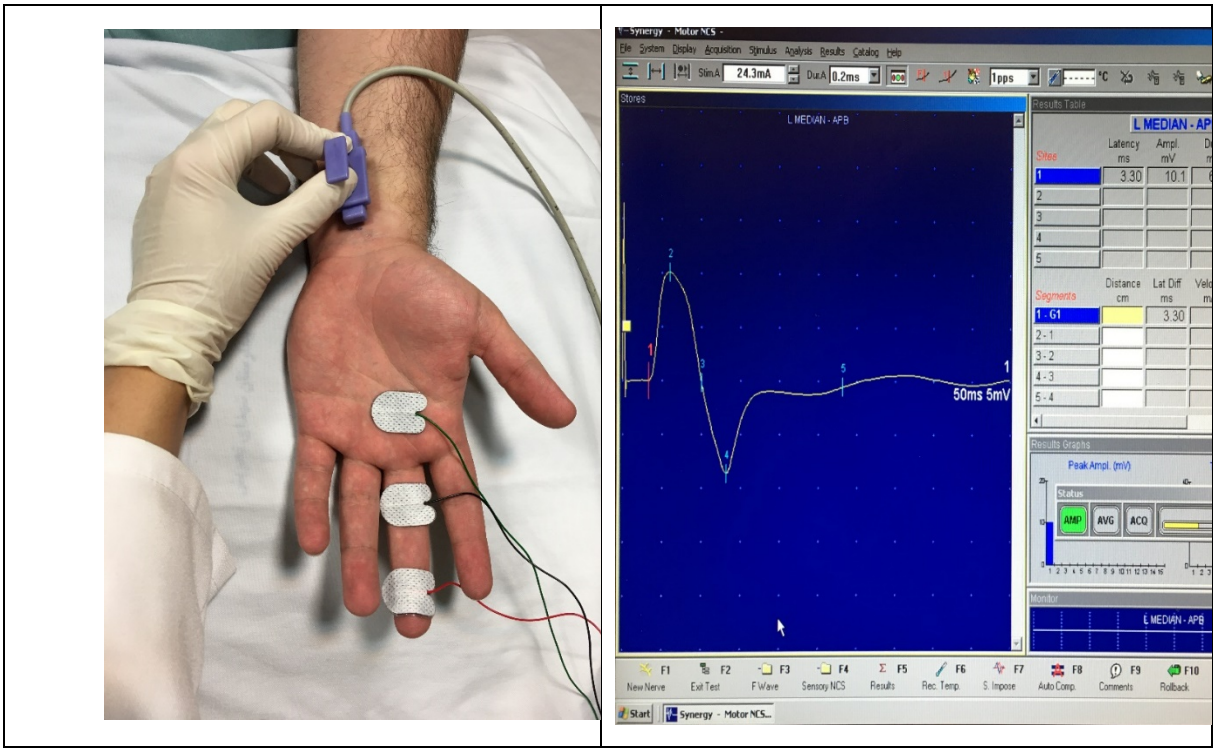


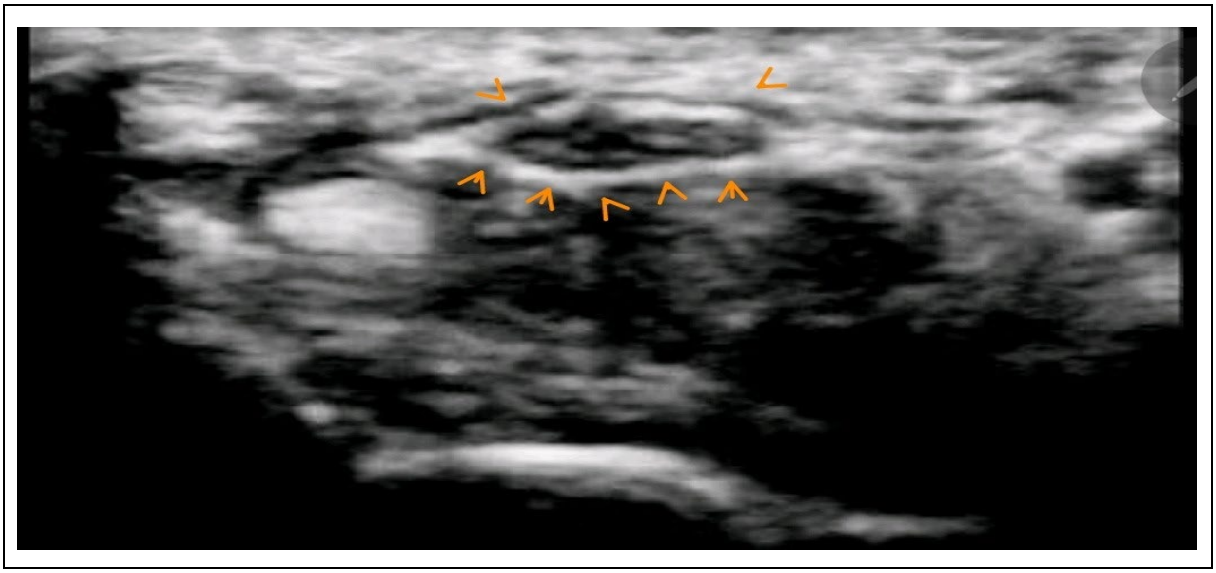
Image 7: Nerve conduction studies: electrode placement and waveform



Ultrasonography (Image 8) is a noninvasive, low-cost method that helps visualize musculoskeletal system and peripheral nerves and detect entrapments (Image 9).(8)

Image 8: Ultrasonography machine

Image 9: Ultrasonography sample image of carpal tunnel



Arrows showing the enlarged median nerve usually seen in carpal tunnel syndrome.

2. LITERATURE REVIEW

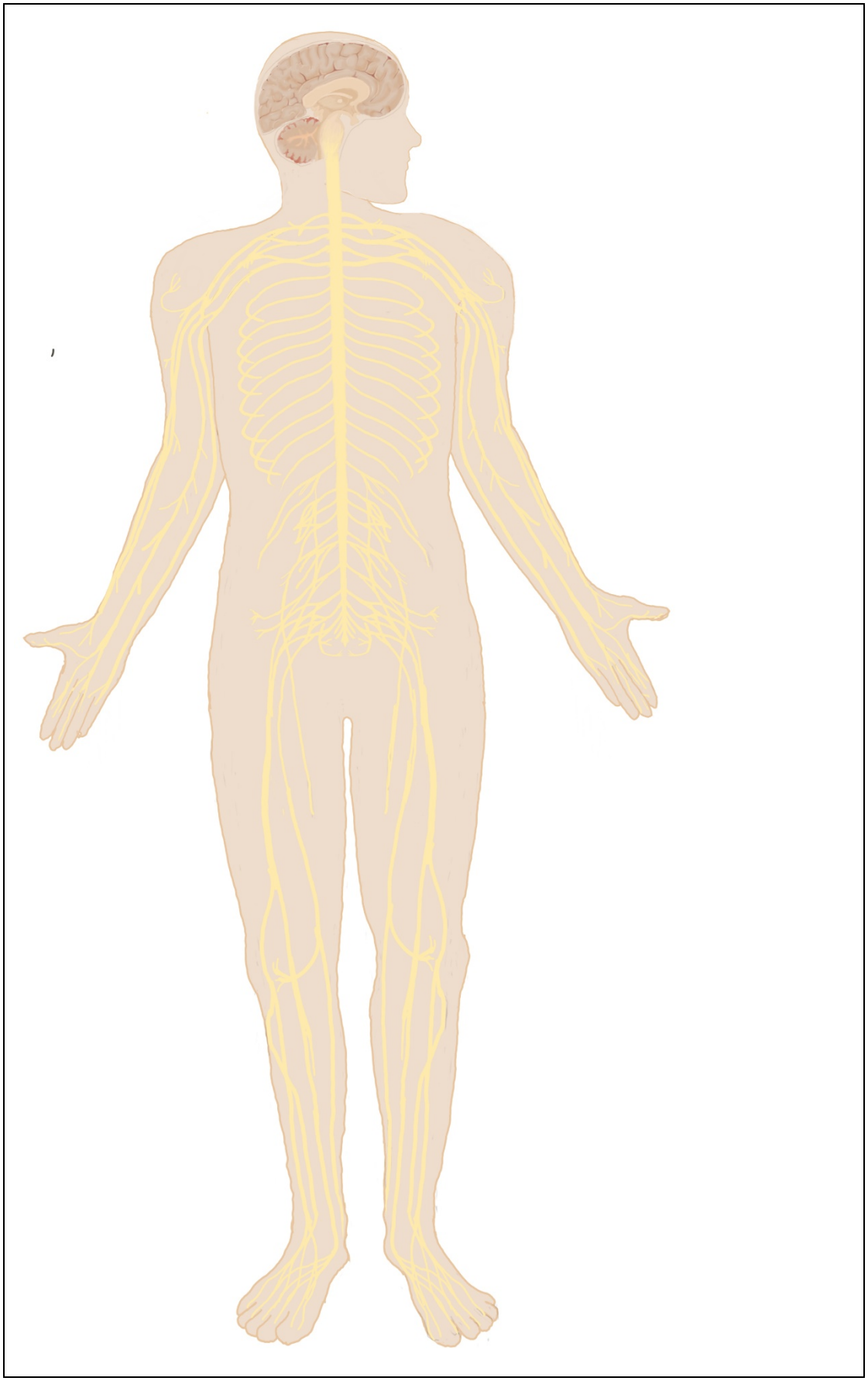
i. The nervous system

The nervous system has two main parts: central and peripheral. The central nervous system (CNS) includes the spinal cord and brain (Image10), and the peripheral part includes nerve branches which link the spinal cord to the end organs. Its functions are divided into sensory and motor functions. The sensory part receives external stimuli and sends it to the brain. The brain processes signals and sends proper functional tasks to the peripheral muscles. In addition, the nervous system also controls the vital organs by its autonomic parts. The smallest part of the nervous system is a nerve cell called the neuron. Each neuron has a thin and long part called an axon, a nucleus, which is the central part, and a small, tiny part referred to as dendrites. Each nerve has a few axons, including sensory and motor axons. The sensory part transmits peripheral information to the brain and is the mediator for any perception, including pain, in the mind. After processing the afferent stimulus, the brain sends motor orders to the limbs and controls voluntary body functions. Involuntary vital body activities, such as lung and heart activities, are controlled by the third part of the nervous system, the autonomic nervous system.(9,10)

The nervous system function depends on electrical signals, which are transmitted in the nerve cells, and chemical materials, which connect nerves to each other. Other than the nerve cells in the nervous system, a network of supportive cells is important for normal neuron function and maintenance. These supportive cells are called glial cells in the central parts and Shawn cells in the periphery. Shawn cells produce myelin that covers medium and large nerve fibers and are vital for transmitting signals rapidly for motor orders and transmitting sensory stimulus such as touch, but pain fibers are usually small, unmyelinated fibers. CNS connects to the peripheral nervous system (PNS) by the anterior horn cell for the motor orders and posterior gray matter of the spinal cord (Image 11), which is the interface of sensory nerves. These two branches are nerve roots from the spinal cord and come out from spinal foramens across the spine, from the neck to the sacral area. They connect and make cervical plexus for the upper limbs and lumbo-sacral plexus for the lower limbs. Median, ulnar, and radial nerves are the final branches of the upper extremity, with PNS and sciatic being the major nerves of the lower limbs.(10)

Image 10: Central nervous system (Brain and Spinal Cord)

Image 11: Peripheral nervous system (All nerves excluding brain and spinal cord)



ii. Nervous system and aging

Nervous systems and aging have a bidirectional relationship. Aging, by itself, has a degenerative effect on the nervous system, leading to a decreased number and function of nerve cells, leading to atrophy in the CNS and malfunction in the PNS. On the other hand, analysis of the nervous system and its reactions can modify the aging process. (11) Neurodegenerative disorders of the brain, such as dementia and Parkinson's disease that present in the second half of a person's lifespan are some of the most prominent examples of the effects of aging on the nervous system. A relatively similar process can occur in the PNS, which leads to neuronal or Shawn cell damage, called neuropathy or peripheral neuropathy.(11)Aging affects the PNS by changing the nerve cells' physiology, supporting the cells' malfunction, and delaying injury repair. Old neurons transfer messages more slowly because of damaged or thinner myelin sheets. With aging, the cytoskeleton proteins of axons diminish so axonal loss is more prevalent. Also, trophic chemical malfunction in the aged nervous system is more prevalent, so the neuron scan atrophy. Repetitive labor during one's lifespan leads to anatomical changes in the limbs and spine structure, such as bony spoor formation, adhesion of nerve roots, or peripheral nerves in some tunnels, such as the carpal tunnel, leading to neuropathic pain. Weakness and autonomic imbalance such as hypertension are the result of motor nerve and autonomic system malfunctions.(9,11,12)

iii. Peripheral nerve damage

Peripheral neuropathy refers to any damage to the nerves outside of the spine. It is a common neurological problem, and its prevalence is reported to be 2.4% in the general population, with more than 8% in people older than 55 years. (13) Peripheral nerve injuries can be classified in different ways, for example, based on the mechanisms of injury, severity of damage, etc. The mildest nerve injury is a block in the membrane of the nerve cells. It is entirely reversible, and most people have experienced it as a transient paresthesia in situations like relatively prolonged inactivity and putting prolonged pressure on a nerve. If this pressure does not relieve on time, it may affect the complete nerve function and cause paralysis because of a complete nerve block. In long-term situations, such as compartment syndromes or entrapment syndromes, myelin integrity may be damaged, and, finally, axonal damage and loss, leading to pain, weakness, and functional loss. Sharp, penetrating assaults can cut the nerves, and axonal injury is the dominant pathophysiology.(14) Clinical evaluation, history

taking, and electrodiagnostic studies together help classify peripheral neuropathies in a more organized and approachable way. With this approach, peripheral neuropathies can be classified, based on the distribution and severity of the disease, into subgroups such as mononeuropathy, mononeuropathy multiplex, and polyneuropathy. The first subgroup is damage of a single nerve at a focal point due to pressure or trauma, and the most frequent form in this category is CTS. Mononeuropathy multiplex and polyneuropathy are usually present because of systemic or hereditary disorders. Carpal tunnel syndrome is the focal entrapment of the median nerve at the wrist(15,16).

iv. Nociceptive vs. neuropathic pain:

The International Association of the Study of Pain defines pain as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[1] Physical causes usually lead to tissue damage and pain, but psychological etiologies cause pain without tissue damage.(1) These two etiologies overlap and are usually found simultaneously, especially in chronic pain. They can potentiate each other and create a vicious cycle, thus complicating the chronic pain picture and treatment. Nociceptive pain (Image 12) arises from end organ, nonneural tissue damage that activates pain receptors. Bruising, soreness, stab wounds, sprain, and strain of muscles and tendons are samples of nociceptive pain generators. Nociceptive neurons are specific neurons which have receptor functionality at one side, continuing as a long neuronal tissue or part of a neuronal cell called axon, which transfers the stimulus to the cell body; at another site the axon attaches to other neurons in the spinal cord. Spinothalamic and then thalamocortical pathways transfer signals to the cortex. If the neuronal tissue is damaged after peripheral receptors, or centrally in the spinal cord or brain, it usually induces discomfort and pain, or neuropathic pain (Image 13).(1)Examples of neuropathic pain are stroke, traumatic brain injury, headache, dysesthesia, and paresthesia due to multiple sclerosis, numbness due to diabetic neuropathy, herpes zoster pain, hand pain due to the entrapment of the median nerve at the carpal tunnel and sciatica.(3)

Image 12: Pain receptors and nociceptive pain (pain originated from end organs)

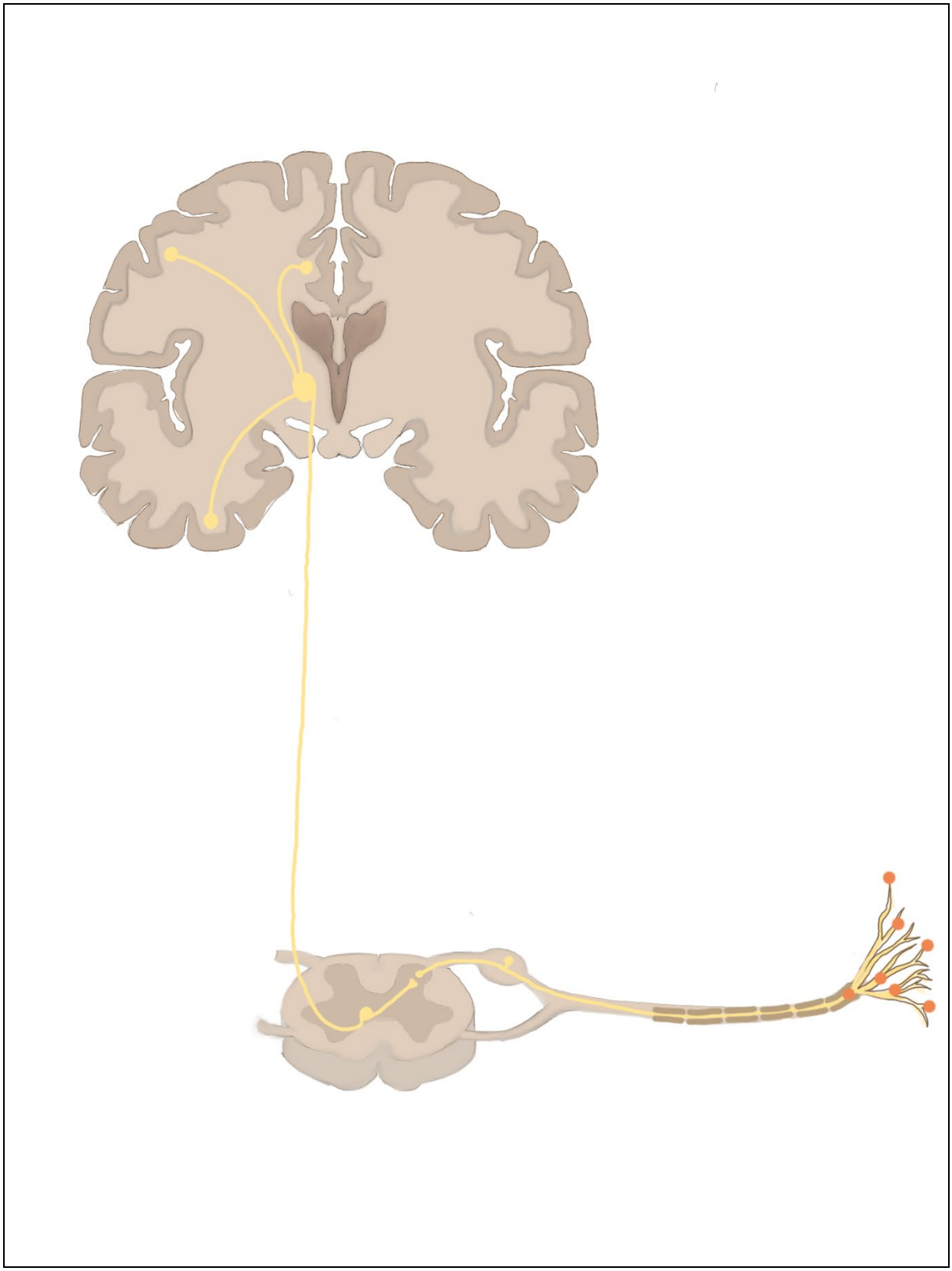
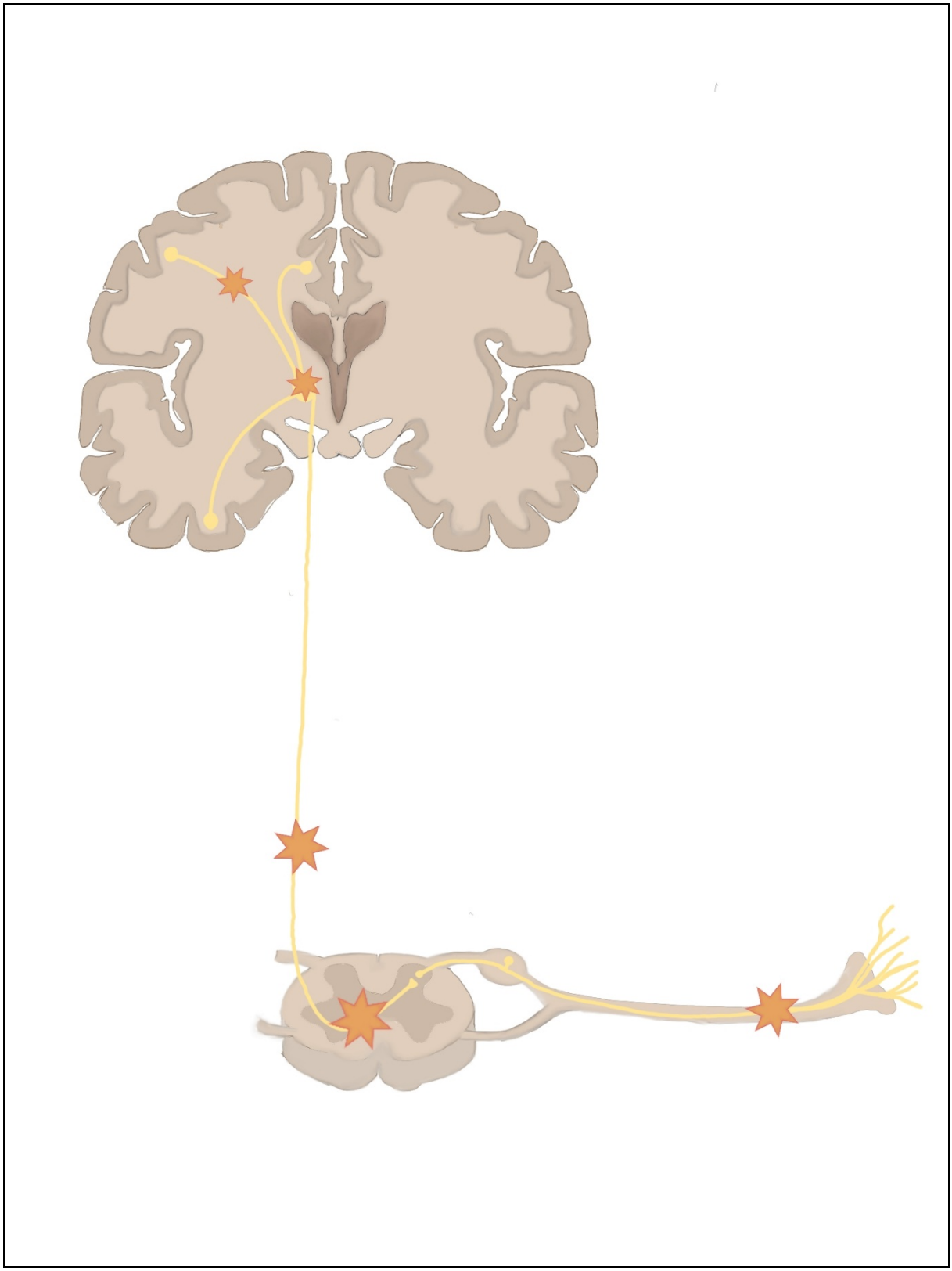


Image 13: Neuropathic pain (Pain arising from the nervous system not from the end organs)



v. Peripheral neuropathy (PNP) and the elderly

We can classify PNP by type of deficit, underlying pathology, time course and/or the pattern of nerve involvement, type of deficit, or nature of the underlying pathology. Different patterns of nerve involvement are mononeuropathy, radiculopathy, symmetrical PNP, multiple mononeuropathy (mononeuritis multiplex) and polyradiculoneuropathy. (14) Major nerve trunk involvement is mononeuropathy. Involvement of single or several nerve roots is radiculopathy. In polyneuropathy, terminal branches of several nerves affected are usually symmetrical and more severe in the legs than in the arms. (14,17)

Chronicity can be acute (full progression in less than one month, Guillain–Barré syndrome), sub-acute (reaching maximal deficit in 1–2 months), or chronic (the process taking more than 2 months to develop). Neuropathic damage could be sensory (e.g., diabetic distal symmetrical polyneuropathy), pure motor (e.g., acute motor axonal neuropathy), mixed sensory and motor (e.g. Charcot–Marie–Tooth disease), and autonomic. Based on pathology, it could be demyelinating, axonal, or mixed. PNP may involve small nerve fibers, large nerve fibers, or both. Large fibers are responsible for motor function, vibration, and position senses. Small fibers transmit pain and paresthesia. The most common type of neuropathy in the elderly is small fiber neuropathy, affecting mainly the lower limbs. Conventional nerve tests can only detect large fiber involvement. Neuropathies arising from inflammation or compression tend to recover completely because of the Schwann cells' ability to proliferate and remyelinate the affected nerve if the patient is treated precisely and on time.(14,16,17)

With aging, genetic mutations and even gene presentations will affect the myelination of the peripheral nerves and may cause axonal degeneration. Medical disorders such as diabetes mellitus and thyroid dysfunction have significant effects on the integrity and function of the nervous system. (18)

Some cancers and cancer management chemotherapy and radiotherapy affect the susceptible nerve tissue.(19) Multimorbidity and polypharmacy put older people at a significant risk of peripheral neuropathy. Environmental factors such as chemical toxins, mechanical overload, and repetitive work tasks make the elderly more vulnerable to peripheral neuropathy.(20)

Evaluation: History taking should investigate symptoms, time course, and possible causes. It is important to determine sensory, motor, or mixed neuropathy. Symptoms showing the

sensory nerves are involved are usually numbness, paresthesia, a burning sensation, glove and socks wearing sensation, and sometimes imbalance. Weakness, wasting, and ambulation difficulty are motor neuropathy symptoms. Sometimes, dexterity functions such as key turning, buttoning, and unbuttoning may become impaired. Cramps and spasms are other symptoms of PNP. We have also autonomic neuropathy. Symptoms differ based on the involvement of vital organs. Cardiac involvement symptoms are heart rate variability and dizziness on standing due to orthostatic hypotension. Gastro-intestinal involvement symptoms are constipation or diarrhea, vomiting, and nausea. Genito-urinary involvement may result in incontinency and sexual dysfunction. Family history, recent infections, drug or alcohol intake, diet, toxicity, work, and diabetes should be probed for possible causation. Autonomic symptoms can be very disabling.(17,21,22)

Clinical examination: Patient examination usually starts with growth motor function such as ambulation, toe and heel walking, and balance tests, then manual muscle tests, and skin inspection for trophic changes or ulcers. Light touch, vibration, pinprick, and joint position for sensory examination should be done. Distal tendon reflexes usually are impaired. Fundoscopic examination may be abnormal in diabetes and in chronic inflammatory demyelinating polyneuropathy.(4,13)

Investigations: We can order a long list of Para-clinics, but in a good clinical examination the final diagnosis can be reached by a few tests. General laboratory tests and electrodiagnosis are the first examinations and should be done in the first few steps.(13,23)

General laboratory tests: Thyroid function tests, complete blood count and differentiation, renal and liver function tests, and urine analysis should be performed on all patients with PNP. Inflammatory serologic tests such as erythrocyte sedimentation rate and C reactive protein, fasting blood glucose, serum B12 level, serum vitamin E level, and serum proteins are other necessary tests. Lyme serology, chest X-rays, and viral serology such as hepatitis and HIV tests may be ordered if all above tests become negative. Cerebrospinal fluid proteins are usually elevated in the Guillain–Barré syndrome, and the white blood cell is increased in HIV infection and Lyme disease.(4,13,19,20,23)

Recent advancements in magnetic resonance imaging (MRI) have made it the method of choice in assessing the human anatomy. For example, an MRI can show the structure of the median nerve at the wrist, its integrity, compression sites, and swelling. MRIs can also show the consequences of peripheral nerve damage such as muscle atrophy. Although it has good sensitivity and specificity in detecting peripheral nerve damage, MRI is expensive and

is not as available as other diagnostic methods for detecting damage to the peripheral nerves.(24–26) Quantitative sensory testing, autonomic function studies, nerve biopsy, and molecular genetics are some of the targeted investigations. Electrodiagnostic Studies (EDX) and ultrasonography will be discussed after CTS. (16,27)

vi. Entrapment neuropathies

One of the most common nontraumatic focal nerve injuries is entrapment neuropathy. Some examples are entrapment of the nerves passing through the ulnar groove at the elbow, carpal tunnel, Guyon's canal at the wrist, femoral canal at the thigh, radial tunnel at the arm, and the proximal of the forearm.(28,29) The carpal tunnel is the most common site of nerve entrapment, presenting with sensory symptoms such as paresthesia, tingling, numbness, and motor signs, and motor symptoms such as weakness and sometimes impaired dexterity.Repetitive movement and cumulative minor trauma during hand works, such as typing, lead to functional and structural changes in the median nerve at the wrist canal and cause signs and symptoms such as pain, weakness, and dysesthesia. Repetitive minor traumas lead to summation of minor injuries, prevent on time and proper healing, and put the elderly at more risk. The prevalence of CTS after 50 years of age rises significantly.(7,30–32)

vii. Carpal Tunnel Syndrome (CTS)

Definition: The median nerve is one of the final branches of the brachial plexus. It runs from the arm to the hand, passing the carpal tunnel in the wrist. CTS occurs when this nerve is compressed, squeezed, or adheres at the tunnel. The carpal tunnel is a narrow passageway of finger flexor ligaments and median nerve. Its roof is a tight ligament that keep its contents functional and acts as a pulley. This ligament runs from the radial to the ulnar side of the carpal bone, side to side, and from the beginning of the first wrist bones' row to the end of second row. The floor of the tunnel forms by eight small bones in two rows. There are nine flexor tendons in the canal plus the median nerve. The median nerve is responsible for sensory feelings of the palmar side of radial side three, half fingers and the motor function of some small muscles of the hand. Swelling of the flexor tendons in inflammatory disorders narrows the tunnel and put significant pressure or shear injury on the median nerve. Such disorders include rheumatoid arthritis, adhesion of the tendons to the nerve, thickening and flattening of the flexor ligament, the pressure effect of some tumors, carpal cysts, or even fracture of the wrist bone. The symptoms are sensory findings such as numbness, tingling and

pain, or motor signs such as weakness. Pain produced by CTS may be presented just at the wrist or palm, or radiating proximal even to the arm.(30,31)

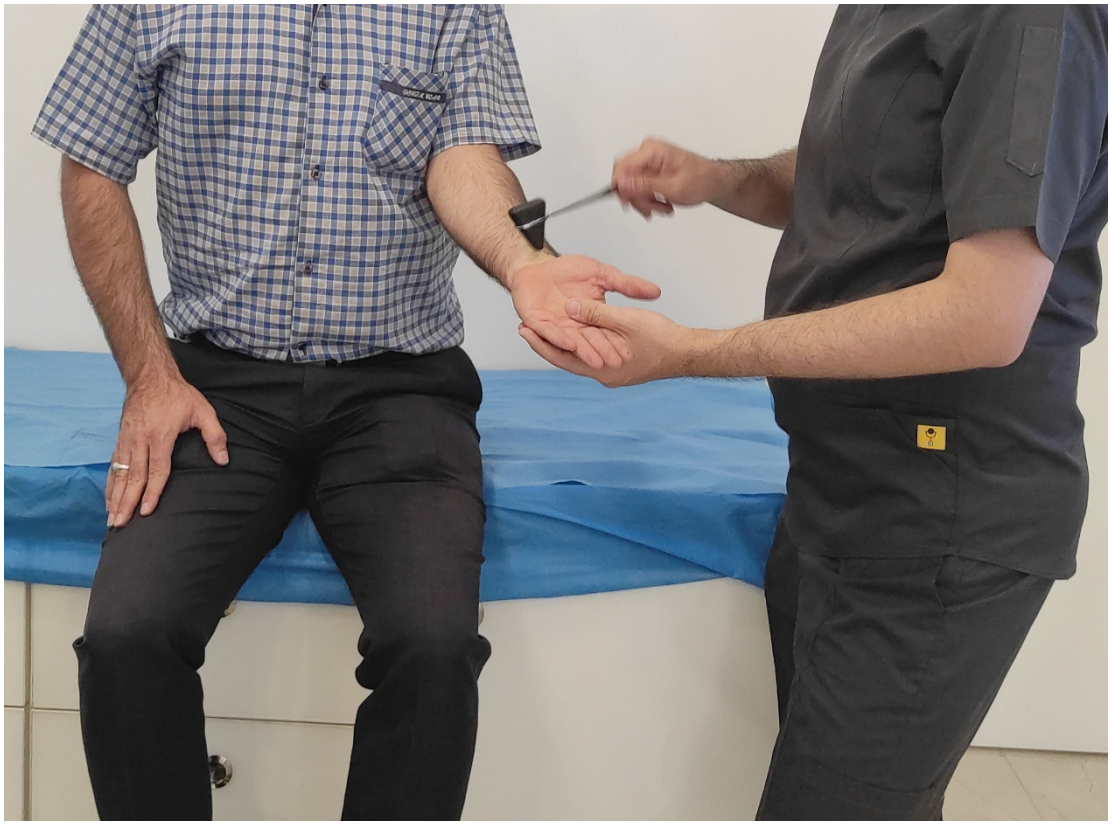
Symptoms: Tingling and numbness are the most frequent symptoms present, gradually localized to three radial side fingers on the palmar side. Symptoms usually start small and slowly. Heaviness, a swelling sensation, and useless feeling are other frequent signs.[39,43,75] These symptoms often present at night, sometimes awakening the patient and forcing them to shake the hand until partial improvement and resolution. Symptoms usually present first and more severe in the dominant hand. As the syndrome progresses, symptoms become worse and may lead to a degree of disability during the day, especially with talking on the phone, driving, kitchen activities, reading, and writing. If the syndrome is left untreated the muscles at the thenar area (base of the thumb) may disintegrate, and the distinction between hot and cold sensations by the fingers can become impossible.(7,30)

Etiology: There are different hypotheses regarding the etiology of CTS. Compression of the nerve in the tunnel due to an increase in pressure is one of the most accepted reasons. Injuries to the wrist, synovial cyst, or tumor in the tunnel, carpal bone fracture, enlarged vasa-nervurum, swelling, and inflammation of the tendons are some of these reasons. Fluid retention due to pregnancy or menopause can be one of the symptoms, too. The other hypothesis is the adhesion of the nerve to the surrounding structure, as evidenced by the flexor retinaculum and flexor tendons. This adhesion puts force on the nerve sheet and irritates the nerve.(33,34)

Risk factors: Gender is one of the most important factors and women are affected three times more than men. Metabolic and endocrine disorders, such as diabetes and thyroid dysfunction, are other risk factors. Environmental and workspace factors, such as repetitive working, heavy labor, vibrating tools, and data entry works, affect people more. Fine arts and music playing are the other endangering factors. CTS is more frequent in older adults.(33,35)

Diagnosis: To avoid permanent median nerve damage and disability, early diagnosis and treatment are crucial. A comprehensive physical examination of the upper extremity and neck is the first step in evaluation. Wrist appearance for swelling and tenderness, finger sensation, and provocation tests such as wrist compression and the Tinel test (Image 14) are helpful. In the Tinel test, the physician taps the wrist by an examination hammer and if a shock-like sensation appears, the result would be positive.(30)

Image 14: Tinel test



The Phalen test (Image 15) is another provocation test. In this test, the physician asks the patient to abduct the arms, flex the elbow, and put the back of wrist and hands together. If numbness or dysesthesia presents in one minute, the Phalen test would be positive for CTS. (30)

Image 15: Phalen test

It is important to examine the elbow and neck to rule out differential diagnosis. Endocrine disorders could be ruled out by routine lab tests. X-rays can evaluate the wrist for possible fracture and arthritis. Electrodiagnostic tests are one of the most sensitive laboratory tests for detecting any nerve electrophysiology malfunction and will help to confirm and grade the diagnosis of the CTS. This test has two parts: electromyography (EMG) and nerve conduction studies (NCS). With NCS, surface electrodes are attached to the specific area of the skin and on command of the stimulator, insert a shock-like stimulus to the nerve. The machine calculates the nerve-transmitting speed and can detect any abnormality. With electromyography, a sharp and thin needle inserts to a specific muscle and records muscle

activity. Nerve damage has a specific pattern in needle electromyography, which could be helpful in detecting malfunction.(36) Ultrasound imaging is another method to evaluate peripheral nerves. It can scan nerve anatomy and measure the circumference of the nerves, which is the most sensitive and specific index for detecting CTS at the carpal tunnel inlet.(32) MRI provide advanced magnetic field and technology and can show the anatomy of the median nerve in the wrist, and any tumors or cysts on the other space-occupying lesions.(26)

Treatment: Early treatment is essential to get satisfactory results. Diabetes or any other systemic underlying disorders should be addressed at the beginning.(37,38) Mild forms of CTS usually respond well to rest, including intermittent day work, breaks, and night splinting. Over-the-counter drugs such as nonsteroidal, anti-inflammatory medicine may work in early stages of the disease but are usually useless. Prescription medicines such as corticosteroids may be helpful orally if the underlying disease is rheumatoid arthritis, otherwise steroid injection in the tunnel adjacent to the nerve is the preferred method in mild to moderate CTS.(4,30)

Alternative medicine such as acupuncture may be beneficial in some individuals, but there is no scientific evidence for their effectiveness. However, corrective exercises and yoga are promising in reducing pain and increasing grip strength. Surgical release for CTS is one the most common surgeries in the US. In this procedure, the surgeon cuts the flexor retinaculum above the nerve to resolve high pressure in the tunnel. This type of surgery is usually done under local anesthesia and sedation and does not need an overnight stay at the hospital, except in patients with multiple complications and risk factors. It could be done by cutting the skin, although the ligament, traditional open surgery, or doing it by endoscopy, which needs smaller incisions and has a faster recovery time.(39) The symptoms may relieve immediately after surgery, but complete recovery may take several months. To prevent recurrence, daily work and lifestyle modification are necessary. Traditional or endoscopic surgery are invasive and have complications, especially in the elderly. Noninvasive or minimally invasive procedures, such as ultrasound guided injections, are preferred in the elderly with multiple problems and risk factors.(40)

viii. Electrodiagnosis studies:

Electrodiagnostic studies consist of nerve conduction studies and needle electromyography. These tests evaluate the function of nerves and muscles based on electrophysiology principles.(16,36)

Nerve conduction studies: NCS applies an electrical stimulation on a specific body part and detects the response on another part of the body innervated by the same nerve. It has two parts, motor and sensory responses: the motor response records the muscles action potentials on a muscle, and the sensory response "catches" the wave when the recorder is placed on the specific skin area. For example, in the evaluation of CTS the stimulator is placed on the median nerve pathway at elbow and wrist, the motor recorder is placed on the thenar muscles of hand, and the sensory recorder is placed on 2nd finger. Amplitude, duration, and velocity of these responses are used to diagnose different types of neuropathies. Types of neuropathies, such as distal, symmetrical, or compression neuropathies, could be diagnosed by NCS, including the pathology such as axonal degeneration or demyelination. Decreased nerve conduction velocity indicates possible demyelination, and decreased amplitude suggests axonal degeneration.(16,36)

Needle electromyography: Needle EMG is a part of EDX; it applies a fine needle attached to the machine by a cord inserted to specific muscles to record muscle action potential. It is useful in differentiating neuropathy from myopathies. Several muscles should be examined, and distal muscles have more findings in EMG. In neuropathies, axonal degeneration produces large and wide potentials, but demyelination cannot be distinguished by needles. Considering both EMG and NCS, diagnosis of neuropathy and its subtypes could be confirmed.(16,41,41)

ix. Ultrasonography:

Ultrasonography is another method for evaluating the human anatomy. With a special probe, an ultrasound wave is transmitting to a specific tissue and its echo is captured by the same probe. With special software, captured sound waves make the cross-sectional image of the tissue under the probe, and the topographic parameters of the tissue organs can be seen and measured.(42)

The most important part of an ultrasonogaphy machine, choosing the appropriate transducer, significantly affects the quality of the scan. Of the three types of transducers available, the linear probe is most commonly used in Musculoskeletal (MSK) ultrasonography examination. These are high-frequency transducers designed for scanning the superficial (up to 6 cm depth) tissues, such as wrist joint and forearm muscles, with high-resolution images. Curvilinear transducers use lower frequency ultrasonography waves with more penetration potential and wider beam emission to scan deeper tissues and larger fields (e.g. hip joint or spinal vertebrae). The hockey stick probe is a linear transducer with the same scanning characteristics but a smaller footprint, and it is used where

maneuvering over and around bony prominences or small areas are required (such as the ankle or small joints in the hand).(43–45)

Despite how easy it sounds, holding and handling the probe plays a major role in the quality of ultrasonography examination and ultrasonography-guided injections. The body of the transducer is held and fixed between the thumb and index finger, and the three fingers and ulnar side of the hand rest on the subject, providing proper support and stability for scanning maneuvers, to obtain a steady image of the target. This matter is even more highlighted in guided injections, as visualizing the needle trajectory or the proximate neurovascular components is important.(46,47)

The characteristic echogenicity (i.e. the shades of gray) is the key to distinguish different structures in an ultrasonography examination. Tendons with a hyperechoic outline (tendon sheath) wrapping the fibrillar hypoechoic pattern are well viewed in ultrasonography imaging. Changes in a normal pattern, echogenicity, thickness, or integrity of the tendon can indicate interstitial, complete or partial tears, tendinosis, or peritendinous effusion.(48) Muscular tissue is also seen as a hypoechoic mass with hyperechoic lines within (septum). With the optimum resolution and a probe placed exactly aligned with the muscle fibers' direction, the fibrillary pattern of fibers can also be detected.(46) Cartilage is also seen as a hypoechoic tissue, noting the water content of these two latter structures, they are far less echogenic than tendons. Although ultrasonography can help detect some cases of minor cortical fractures, this is not a modality of choice to evaluate bony tissue, as the bone reflects most of the US waves on its cortical rim, resulting in a very hyperechoic line and causing a posterior acoustic shadow effect.(47,48) Nerves are one of the most favorite structures for MSK sonologists. This method pictures the neural hyperechoic (containing fat) sheath and gives a fibrillar railway pattern of nerve fibers on the long axis and a honeycomb pattern in a short-axis view. The ability of ultrasonography to follow the nerve through its path, measuring its cross-section area, the integrity of the nerve sheath, and dynamic examination, provides the examiner with useful information about possible neural damage.(42,45) Ultrasonography is entirely noninvasive, comfortable, low cost, and relatively available. Nerve damage usually presents as thinning of the nerve and entrapments present as swelling of the nerve before the entrapment site. It is a reliable diagnostic method and a perfect guide for minimally invasive interventions. Diagnosis of CTS in the elderly can be done cost and time efficiently but we need to establish the diagnosis criteria and normal value in this population.

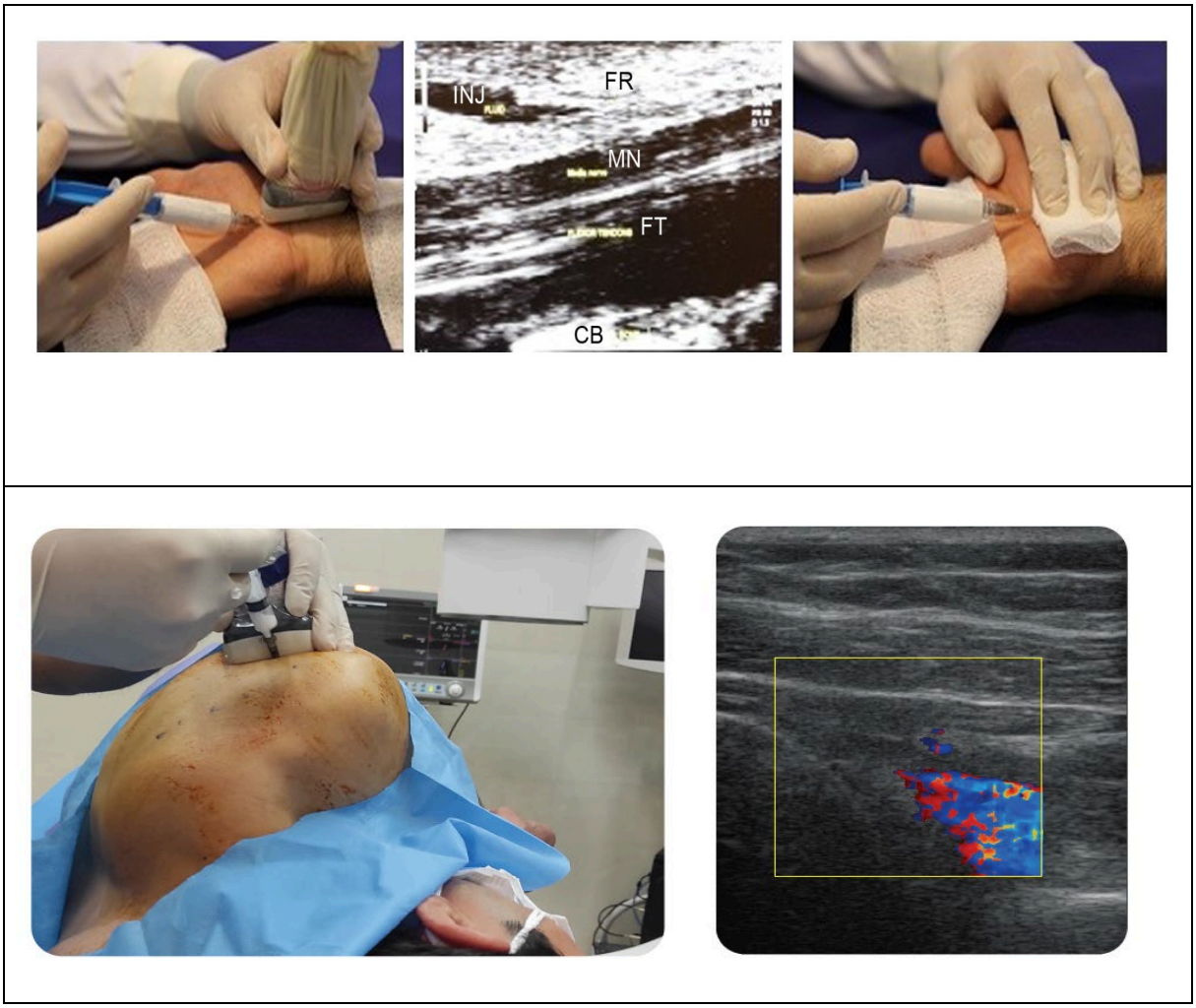
x. Management

Neuropathic pain management has several variables. The etiology of neuropathic pain is the most crucial parameter in the early stages of the disorder; other parameters are severity, localization, and chronicity. To prevent complications such as falls or pressure sores, neuropathies are usually managed comprehensively with physical modalities, mobility aids, orthotics in case of foot drops, coordination and balance exercises, and oral pain killers that affect central pain pathways such as Gabapentin or Pregabalin.(13,23)

Acute generalized peripheral neuropathies, such as the Guillain–Barré syndrome, need immediate attention, hospitalization, and medication such as with intravenous immunoglobulin. Multifocal neuropathies have a similar situation and need the same level of attention.(49,50) Focal neuropathies like CTS are categorized under non-urgent disorders.

We can manage mild CTS with oral medication and splints, moderate CTS with splint and steroid injections, and moderate to severe CTS with endoscopic or open surgery.(35,40) We can inject in the carpal tunnel with anatomical landmarks but using ultrasound we can apply different approaches more precisely without risk of nerve or artery penetration. The needle can be inserted either parallel or perpendicular to the transducer, called in-plane or out-of-plane respectively. In-plane insertion (Image 16) is used when visualizing the whole needle trajectory (as a hyperechoic line) is needed, and enough space is available to reach the target. The short-axis view of the needle inserted out-of-plane will be seen as a hyperechoic dot.(40)

Image 16: Long (upper image) and short (lower image) axis view of needle in ultrasound imaging



Steroids are the most common antiinflammatory injectable medications used in MSK condition; despite the wide variety of available, Methylprednisolone and triamcinolone are the injectatables of choice for most of the MSK interventions including CTS. Steroids have side effects and contraindications especially in older adults with comorbidities and having many madications, so determining optimum dose in this population is crucial.(51,52) On the other hand one its complications; atrophyzing effect coud be beneficial in the treatment of CTS.

3. Research aims

The overall aim: To determine the prevalence of neuropathic pain and its comorbidities among community-dwelling elderly adults in an urban population in Tehran, Iran. We focus on one of the common types of neuropathies, entrapment neuropathy at wrist (CTS): screening and accurate diagnosis, the best injection method, and steroid dose. Our main topic is divided into four sub-studies:

Substudy 1: To assess epidemiological aspects of neuropathic pain in community-dwelling elderly adults in Tehran, an urban area of Iran: prevalence, classification, comorbidities, and quality of life.

Substudy 2: To evaluate the sensitivity and specificity of ultrasonography in detecting CTS in the elderly.

Substudy 3: To compare the therapeutic outcome of variable steroid dose injections with hydrodissection in an elderly population with CTS.

Substudy 4: To compare the therapeutic outcome of steroid injection in the carpal tunnel versus in the flexor retinaculum.

4. Material and methods

Design: Different designs for different studies: pooled data for an epidemiology study, cross-sectional for accuracy study, prospective triple blind for determining the best steroid dose, and prospective double blind for the intra-flexor retinaculum injection.

Substudy 1: Epidemiological study: we had a data pool from a large population-based study, which we conducted in all 22 districts of Tehran, the capital of Iran. Trained personnel interviewed participants face to face at their houses to gather the required information.

Substudy 2: A cross-sectional study with prospective recruitment of elderly patients with hand pain referred to our University Hospital in Tehran, Iran. Based on the American Academy of Neurology's criteria for CTS, the diagnosis was established clinically.[21,22] Patients within the same age group without any musculoskeletal symptoms as the control group were examined to be sure not to include subclinical CTS. Subjects entered their groups consequently until desired sample size was attained.

Substudy 3: A prospective, randomized, triple-blind study of patients referred to our University Hospital, Tehran, Iran. Computerized randomization was used to place patients in three groups. A special label with a unique code was put on opaque syringes by a third person

and then injection materials were prepared immediately before injection without the injector knowing this process and material. All syringes contained 3 mL of injectate for the hydrodissection. All groups received 3 cc of injectate including had 1 cc of lidocaine 2% in all groups, 80 mg of triamcinolone (2 cc) for group I, 40 mg (1 cc) for group II, and zero for group III. We added 1 cc of normal saline and 2cc in group III to reach the total volume of 3 cc in all 3 groups.

Substudy 4: A prospective, double blind, parallel randomized trial on clinically diagnosed CTS patients older than 50 years, referred to our University Hospital, Tehran, Iran. After confirmation by EDX, a third party allocated them by simple randomization into two groups, applying a computer-generated random and gave each patient a unique code. Both groups received 40 mg of triamcinolone suspension and 1 cc of lidocaine (2 cc accumulated) in different target places. Patients in group I received the injection within the flexor retinaculum over the median nerve guided by ultrasonography. Those in group II received the suspension, injected between the flexor retinaculum and the median nerve guided by ultrasonography. Each patient in both groups was asked to use a wrist splint immediately thereafter for 6 weeks. They were also advised not to use any other therapy for the CTS. Patients and the analyzer remained blind to allocation information during the trial.

Sampling: Cluster sampling for the prevalence study, convenience for the accuracy study, and randomized for the clinical intervention.

Substudy 1: A multistage random cluster sampling method was used to select participants, as follows. At the beginning, our strata was all 22 city districts. Next, we chose 200 clusters randomly in each zone. Finally, using a systematic random sampling method we selected eight households in each cluster. We considered all household members as primary sampling units. For large populations, the cochran's formula(53) is usually used to calculate the sample size, so we did too. Using this formula, the sample size in each district was 1535 families. The total sample size was 34,116 households: 118,542 individuals from 22 districts and 368 neighborhoods. Among them, 5326 individuals were older than 60 years and were included in the study.

Substudy 2: Convenience sampling(54) for elderly patients recruited prospectively, with an absolute precision of 0.5 and an standard deviation (SD) of 1 for the median nerve inlet cross-sectional area (CSA), 95% confidence interval and considering 80% power, a sample size would be at least 63 patients in each group.

Substudy 3: Considering a total success rate of 70% for local steroid injections, based on a review by Jeremy Bland, with an absolute precision of 0.2, the final sample size was estimated to be at least 21 patients per group. The power and the significance level were set at 0.8 and 0.05 respectively. Jeremy Bland considered the last two responses from worth/no effect/slightly better/much better/cured, as equivalent to success after CTS treatment. 102 patients were randomly allocated to three intervention groups. Of these, 94 patients completed the entire study course and were analyzed.

Substudy 4: Considering all the parameters of the third study, with the power of 80% and significance level of 0.05, at least 21 patients were needed for this study in each group, and were allocated as in substudy 3 method. Of 92 individuals screened, 50 eligible participants were randomized into study groups, and all completed the study and were analyzed.

Instruments:

Appropriate checklists and questionnaires for all studies, EDX, and sonography for accuracy and clinical studies.

i. Sociodemographic checklist, General Health Questionnaire-28, neuropathic pain questionnaire for substudy I.
ii. Sociodemographic checklist, biophysical profile, CTS Boston questionnaire (BCTQ), VAS nerve conduction studies, ultrasonography for studies II, III, and IV.

Statistical analysis

Substudy 1: Descriptive statistics, independent t-test, chi-square test, and multiple regression.

Substudy 2: Descriptive statistics, receiver operating characteristics (ROC) for the cutoff point of median nerve CSA and dependability coefficient (Φ) was used for intra-rater reliability.

Substudy 3: Descriptive statistics were used to summarize the data, representing medians and ranges with nonparametric data, while the mean and standard deviation were employed using parametric data. Distribution of the data was tested using the Kolmogorov–Smirnov test.(55) An alpha <0.05 was considered significant. Repeated-measures analysis of variance (ANOVA)(56), followed by Tukey's post-hoc testing and its nonparametric equivalent, Friedman(57), were used to compare quantitative variables among the three treatment groups before the study intervention and at follow-up visits. To compare the demographic variables, a one-way ANOVA test was applied.

Substudy 4: Distribution of data was tested applying the Kolmogorov–Smirnov test. An α 0.05 was considered significant. Pre- and posttreatment comparisons applied the paired sample t-test(58). Baseline characteristics and primary outcome measures of the two groups were compared using an independent sample t-test, and the chi-square test(59) was used for categorical variables.

Ethical consideration

Substudy 1: A prevalence observational cross-sectional study. Each family was informed verbally about the aims of the project before asking any questions. If they consented, the interviewer started the questionnaire, otherwise the interviewer left that residence and knocking the next one which was assigned in advanced for this situation. In addition to fully complying with the Declaration of Helsinki(60), we got approval from the Ethics Committee of the Iran University of Medical Sciences.

Substudy 2: A non-invasive, non-interventional, cross-sectional study. We provided the informed consent orally and in print, to inform the volunteers of their rights and ensure their willingness to participate in the study. The sonography and NCS studies were non-invasive and harmless. The ethics committee of the University of Welfare and Rehabilitation approved the study. This study complies with all considerations stated in the Declaration of Helsinki.

Substudies 3 and 4: Interventional studies: mandatory registration of trials before enrolling the first patient. It is available online as: IRCT2014020416485N1. Our institutional ethics committee asked for written informed consent, voluntary participation of all subjects, discontinuation of the projects whenever requested, safety of wrist injections, and acceptance of any consequences after intervention, and we complied to the best of our knowledge and power. The safety of our study's medications, including lidocaine, triamcinolone, and normal saline, had been approved many years before our project, and we did not use any unknown medicine. We injected all participants under ultrasound guided by a highly trained physician, so the probability of nerve damage was rare. The main question was related to the lidocaine and normal saline group in substudy 3. Steroid effects were tested before, and the study group IV might have left untreated. Our response to this concern was that all groups would receive a wrist splint, which is a treatment, and if their outcome fell significantly below others after analyzing the data, we will offer them the best injectate. Our institutional ethics committee

approved this and our offer for a nominal fee to cover the travel expenses of participants. All tests for case and control groups were free of charge as well.

5. Results:

Substudy 1: Among 118,542 individuals, 5326 had inclusion criteria and were entered in the study. The mean age 68.92 ± 7.02 years (range: 60–90 years, SE: 0.096). Table 1 shows their demographics. Table 2 presents prevalence of pain by type and location. 70.8% of the patients had pain at the time of interview; of these 31.7% were chronic in at least one part of the body. 13.7% had chronic neuropathic pain and 30% chronic nociceptive pain. There were several comorbidities with chronic pain (neuropathic and nociceptive) including diabetes mellitus, osteoporosis, stroke, and disability (Table 3). Pain was severe enough in 86% of participants to make them seek a physician. Pain prevalence, both neuropathic and nociceptive, was significantly more in females than in males ($p < 0.001$). The relation was not significant between sociodemographic characteristics and pain (i.e., age, body mass index, marital status, occupation, and education).

Table 1: The demographic and social characteristicsof the participants.

Variable	Groups	Number	Percent
Education	Illiterate Elementary Guidance school High school Diploma Academic	1388 1134 808 397 727 827	26.1 21.3 15.2 7.5 13.7 16.4
Age	60-69 70-79 80-89 ≥ 90	3070 1785 453 18	57.6 33.5 8.5 0.3
Gender	Male Female	2529 2797	47.5 52.5
Marital Status	Single Married Divorced Widow	65 3811 83 1367	1.2 71.6 1.6 25.7
BMI	< 20 20-25 25-30 > 30	97 2263 2087 879	1.8 42.5 39.2 16.5
Occupation	Employed Housekeeper Retired Unemployed	595 1893 2685 153	11.2 35.5 50.4 2.9

Table 2: location of pain and the prevalance

Chronocity of Pain	Type of Pain	Painfull Location	Number	Percent%
Acute	Neuropathic	Hand Feet Radicular neck pain Radicular back pain Overall	437 519 261 420 879	8.2 9.8 4.9 7.9 16.5
	Nociceptive	Back Neck Shoulder Knee Overall	1171 522 694 1638 2040	22 9.8 13.1 30.8 38.3
	Overal		2082	39.1
Chronic	Neuropathic	Hand Feet Radicular neck pain Radicular back pain Overall	314 416 172 291 731	5.9 7.8 3.2 5.5 13.7
	Nociceptive	Back Neck Shoulder Knee Overall	727 304 471 1098 1598	13.6 5.7 8.8 20.6 30.0
	Overal		1688	31.7
Overall			3770	70.8

Table 3: Multiple regression analysis of comorbidities and chronic pain.

Model	B		Beta		t		P-value		R	
	Neu	Noc	Neu	Noc	Neu	Noc	Neu	Noc	Neu	Noc
(Constant)	0.263	0.263			7.782	7.576	< 0.001	< 0.001		
Osteoporosis	0.104	0.094	0.092	0.081	6.403	5.632	< 0.001	< 0.001		
Disability	- 0.070	- 0.071	- 0.060	- 0.062	- 4.101	- 4.571	< 0.001	< 0.001	0.161	0.160
Gender	0.051	0.069	0.060	0.079	4.198	5.510	< 0.001	< 0.001		
Diabetes mellitus	0.061	0.052	0.052	0.043	3.805	3.133	< 0.001	0.002		
Stroke	0.115	.093	0.032	0.029	2.317	1.932	0.021	0.047		

Neu: Neuropathic. Noc: Nociceptive

Substudy 2: Of the 723 elderly patients (>60 years) with upper limb pain, 380 had clinical characteristics of CTS. In these patients, 203 had EDX criteria of CTS; 113 without any hand complaints; 103 had NCS and EMG in normal range and were considered for ultrasound evaluation as the reference group. Table 4 presents the demographic data. We categorized CTS in three groups based on NCS results: mild, moderate, and severe. Table 5 summarizes the ultrasonography CSA of the median nerve. CSA threshold values of the median nerve were determined by ROC curves (Figure 1). The area under the curve was 0.58 (95% CI, 0.52–0.65) for the CSA at the pre-carpal level, 0.98 (95% CI, 0.97–0.99) for the tunnel inlet, 0.67 (95% CI, 0.61–0.72) for the mid canal, 0.68 (95% CI, 0.63–0.74) for the tunnel outlet, 0.54 (95% CI, 0.48–0.61) for the antecubital level, and 0.97 (95% CI, 0.96–0.99) for the inlet CSA/antecubital CSA ratio. For CTS detection, sensitivity of CSA at the tunnel inlet with a threshold of 8.5 mm^2 was 96.9% and specificity 93.6%. The inlet/antecubital CSA ratio was 99% sensitivity and 28% specificity. Intra-rater reliability, as described in the "Methods" section, gave the ϕ equal to 0.937.

Table 4: Subjects demographic data

Variable CTS Severity	Control group N=103	Mild N=109	Moderate N=65	Severe N=29	*P*-value
Age (years), mean ±SD	67.9±7.9	67.4±7.6	68±7.2	72.2±8.7	**0.356**
gender (n), female/male	64/39	75/34	49/16	24/5	**0.107**
Affected side (n), right/left	49/54	63/46	33/32	12/17	**0.315**
Weight (kg), mean ±SD	71.4±10	76.7±10	73.8±12.3	72.3±15.1	**0.015***
height (cm), mean ±SD	165.4±8.7	163±9.6	159.6±8.3	156±7.7	**<0.001***
BMI (kg/m^2), mean ±SD	**23.7±3.6**	**26±3.2**	**25.5±3.9**	**25.9±4.9**	**<0.001***

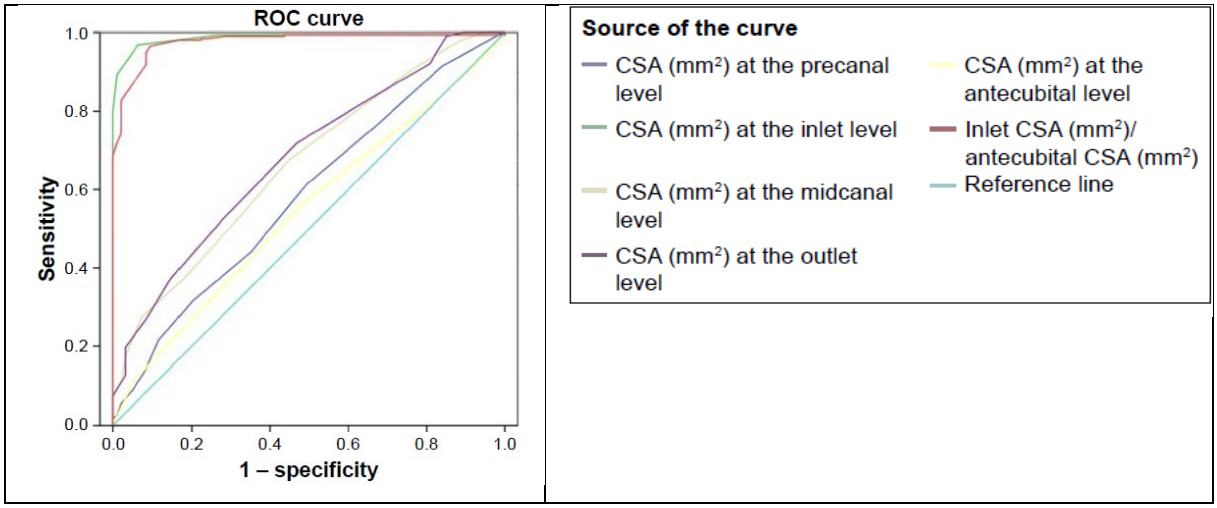
Note: *Statistically significant. BMI: body mass index; CTS: carpal tunnel syndrome.

Table 5: Different carpal tunnel levels median nerve CSA (mm^2) based on CTS severity.

Ultrasonographic measurements	Severe CTS	Moderate CTS	Mild CTS	Control group	*P*-value
Pre-canal CSA (mm^2), mean ±SD	14±2.8	12±2.8	11.2±2.1	10.8±2.3	<0.001
Inlet CSA (mm^2), mean ±SD	14.6±4.6	13.9±3.9	12.8±2.6	7±1	<0.001
Mid-canal CSA (mm^2), mean ±SD	14±3.6	12.8±3.4	11.7±2.2	10.3±2.2	<0.001
Outlet CSA (mm^2), mean ±SD	14.9±3.5	13.9±3	12.9±2.4	11.2±2.5	<0.001
Antecubital CSA (mm^2), mean ±SD	10.1±1	9.7±1.1	9.7±1.4	9.5±1.1	0.194
Flexor retinaculum thickness (mm), mean ±SD	2.20±0.31	2.25±0.49	2.22±0.5	2.19±0.54	0.886
Pre-canal CSA (mm^2)/outlet CSA (mm^2), mean ±SD	0.91±0.22	0.88±0.17	0.86±0.20	0.95±0.28	0.044
Pre-canal CSA (mm^2)/antecubital CSA(mm^2),mean ±SD	1.34±0.38	1.22±0.31	1.13±0.29	1.09±0.31	<0.001
Inlet CSA (mm^2)/outlet CSA (mm^2), mean ±SD	0.97±0.19	1±0.2	1±0.1	0.67±0.19	<0.001
Inlet CSA (mm^2)/antecubital CSA (mm^2), mean ±SD	1.44±0.42	1.43±0.45	1.33±0.3	0.74±0.14	<0.001

Abbreviations: CSA, cross-sectional area; CTS, carpal tunnel syndrome.

Figure 1: ROC curves- cross sectional area of median nerve at different levels



Substudy 3: We screened 161 patients for the study, and 59 did not have inclusion or had exclusion criteria or refused to participate in the study. The remaining 102 subjects were allocated randomly into three groups. Eight patients dropped out during the study (2 from

group I, 3 from group II and 3 from group 3), so the distribution of dropout patients was almost even among groups and 94 were analyzed (Fig.2). We followed them by phone and asked them to withdraw, but they refused to explain the reason. They also did not report any side effects or complications from injections. Table 6 presents the demographic data. Figure 2 is a flowchart of the study. We did not find any statistical differences between the groups. Table 7 summarizes the intervention outcomes at follow-up. Variables with a normal distribution (p-value 0.05) were marked. Although, we did not match the groups, we did not find any significant differences between-group variables at the beginning, except for the VAS measures between group I and III by post-hoc analysis. Table 8 presents the between-group outcome comparison. Almost all measures improved significantly in all three groups during the study, but we did not find any significant differences between the groups. Table 9 summarizes the Boston CTS Questionnaire subscales.

Figure 2: Study III flowchart.

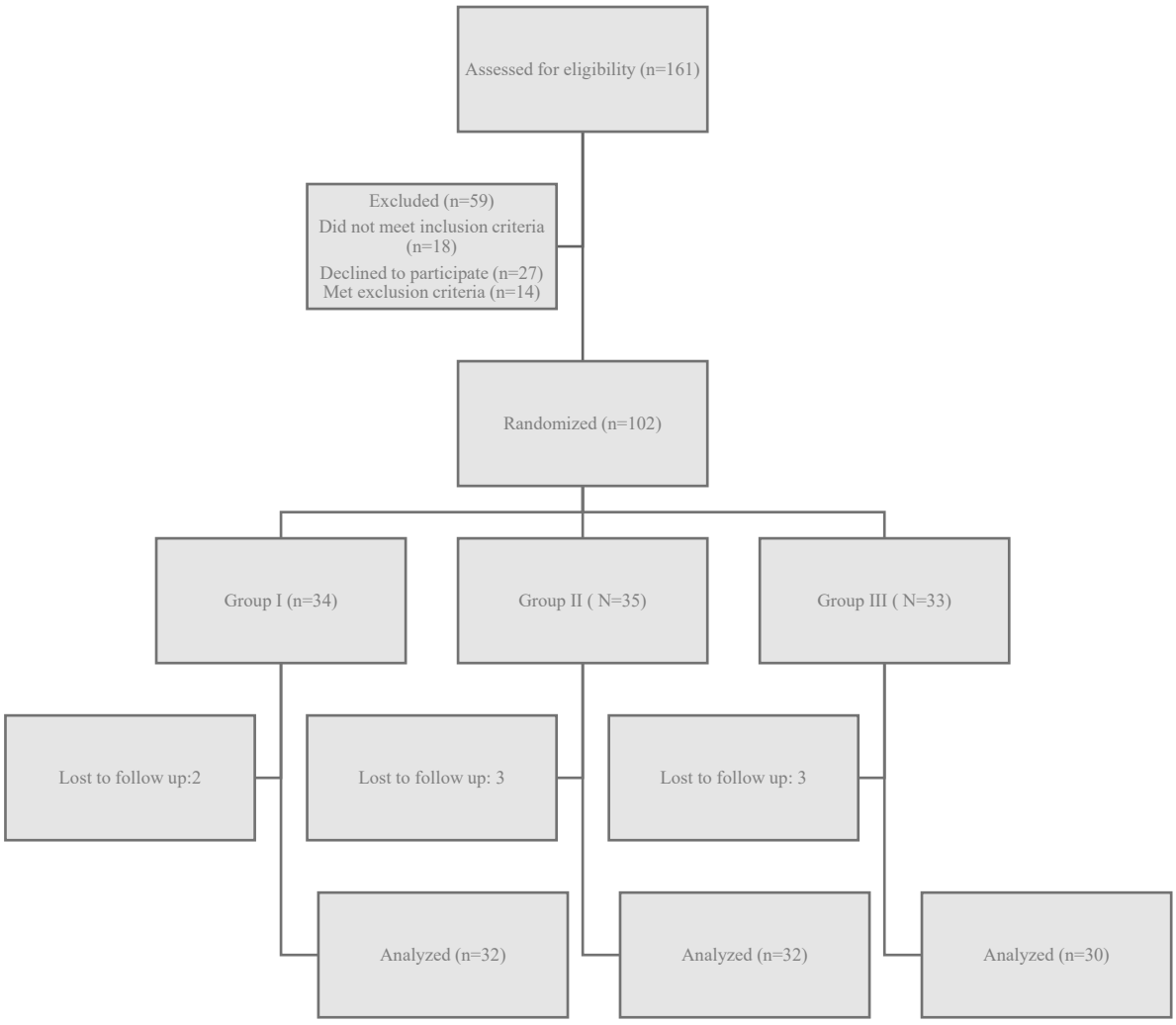


Table 6: **Subject's demographics**

Variables	Group I (n=32)	Group II (n=32)	Group III (n=30)	P-value
gender (male/female)	10/22	4/28	3/27	**0.057**
Age(years)(mean ±SD)	66.1±13.4	66±10	63.4±10.7	**0.645**
Affected hand (right/left)	18/14	16/16	19/11	**0.57**
Affected hand (dominant/nondominant)	19/13	16/16	19/11	**0.549**
Wrist circumstance (cm) (mean ±SD)	17.2±1.3	17±1	17±1	**0.726**
Wrist diameter (mm) (mean ±SD)	59.8±3.9	59.7±4.2	59.8±3.7	**0.991**
hand length (cm) (mean ±SD)	17.5±1.3	17.5±1.1	17.3±0.8	**0.801**
Forearm length (cm) (mean ±sD)	23.1±1.5	23.3±1.3	23±1.5	**0.618**
hand power (kg) (mean ±SD)	**20.1±8.1**	**23.6±8.4**	**19.1±7.5**	**0.06**

Table 7: Study III **Outcome measures**

Primary outcome measure	Treatment group	Baseline	2-week	12 week	6 month	Friedman test
VAS (mean ±SD)	group I (n=32)	7.29±2.05*	4.24±2.09*	4.15±2.21*	2.43±1.93*	**<0.001**
	group II (n=32)	6.22±2.74*	4.81±2.39*	3.23±2.03*	2±1.44	**<0.001**
	group III (n=30)	5.8±1.88*	4.2±1.75*	3.19±2.12*	2.75±2.56	**<0.001**
Median DML (mean ±SD)	group I (n=32)	5.08±1.35*	4.70±1.2*	4.55±1.12*	4.32±0.66*	**<0.001**
	group II (n=32)	5.15±1.23	5.00±1.23*	4.80±1.23*	4.65±0.8*	**<0.001**
	group III (n=30)	4.69±1.51*	4.50±1.32*	4.45±1.19*	4.16±0.7*	0.887
Median SNAP (mean ±SD)	group I (n=32)	4.05±1.55	3.73±1.5	3.80±1.39	4.04±0.75*	**0.01**
	group II (n=32)	3.28±2.2	3.24±1.94	3.71±1.68	4.05±1.51*	**0.025**
	group III (n=30)	3.90±1.15	3.80±1.18*	3.96±0.93*	3.86±0.36*	**0.037**
Inlet CSA (mean ±SD)	group I (n=32)	11.73±2.53*	10.77±2.18*	10.78±2.39*	10.45±2.37*	**0.002**
	group II (n=32)	12.23±2.49*	11.55±2.4*	11.26±2.19*	10.26±2.34*	**<0.001**
	group III (n=30)	12.09±3.96*	11.23±2.72*	11.37±1.97*	10.76±2.05*	**0.007**
Boston (mean ±SD)	group I (n=32)	55.81±15.04*	41.95±11.26*	40.43±12.14*	34.06±10.25*	**0.001**
	group II (n=32)	47.70±11.70*	44.94±9.70*	43.41±10.97*	38.67±11.21*	**<0.001**
	group III (n=30)	45.22±13.84*	40.45±11.08*	41.27±12.65*	36.94±13.04*	**0.018**

Abbreviations: **CSA, cross-sectional area; DML, distal motor latency; VAS, visual analog scale; SD, standard deviation; SNAP, sensory nerve action potential.**

Table 8: Substudy III Between-group analyses

Primary outcome	Repeated measurement ANOVA (between group)
VAs	0.399
Median DML	0.03
Inlet CSA	0.512
Boston	0.756

Abbreviations: ANOVA, analysis of variance; CSA, cross-sectional area; DML, distal motor latency; VAS, visual analog scale.

Table 9: Boston Subscales Data Analysis

	Treatment Group	Baseline	3 month	6 month
Boston total score	Group I (n=32)	55.81 ± 15.04	40.43 ± 12.14	34.06 ± 10.25
	Group II (n=32)	47.70 ± 11.70	43.41 ± 10.97	38.67 ± 11.21
	Group III (n=30)	45.22 ± 13.84	41.27 ± 12.65	36.94 ± 13.04
FSS	Group I (n=32)	23.5 ± 6.29	17.02 ± 5.11	14.33 ± 4.41
	Group II (n=32)	20.23 ± 5.01	18.27 ± 4.62	16.2 ± 4.7
	Group III (n=30)	19.05 ± 5.64	17.37 ± 5.32	15.38 ± 5.5
SSS	Group I (n=32)	32.31 ± 8.76	23.4 ± 7.02	19.73 ± 5.84
	Group II (n=32)	27.47 ± 6.69	25.12 ± 6.35	22.46 ± 6.52
	Group III (n=30)	26.16 ± 8.2	23.89 ± 7.32	21.55 ± 7.55

Substudy 4: Figure 3 shows the study flowchart. We screened 92 patients with CTS; of these, 50 patients were eligible and were randomized into 2 study groups. All patients completed the study, so we analyzed all outcomes. Table 10 presents the demographic data; the difference between groups was not significant. Table 11 shows the primary outcome measures between the two groups. BCTQ, VAS, and ultrasonographic measures were significantly better among intra-flexor over within-tunnel group. Electrodiagnostic and grip scales did not have any significant differences. The function status subscale of BCTQ (p-value 0.016) had insignificant advantage of symptom severity scale (p-value 0.261) in intra-flexor group over the within-canal injection group. Almost all the above measures had significant post-injection improvement within groups. Image 17 shows the intra-flexor retinaculum and the near nerve with canal injection techniques and 6-weeks post-injection sonographic evaluation, in which the flexor retinaculum thickness was decreased post-procedure in the first group, from 3.2 mm in picture A to 2 mm in picture C.

Figure 3: Study IV Flowchart

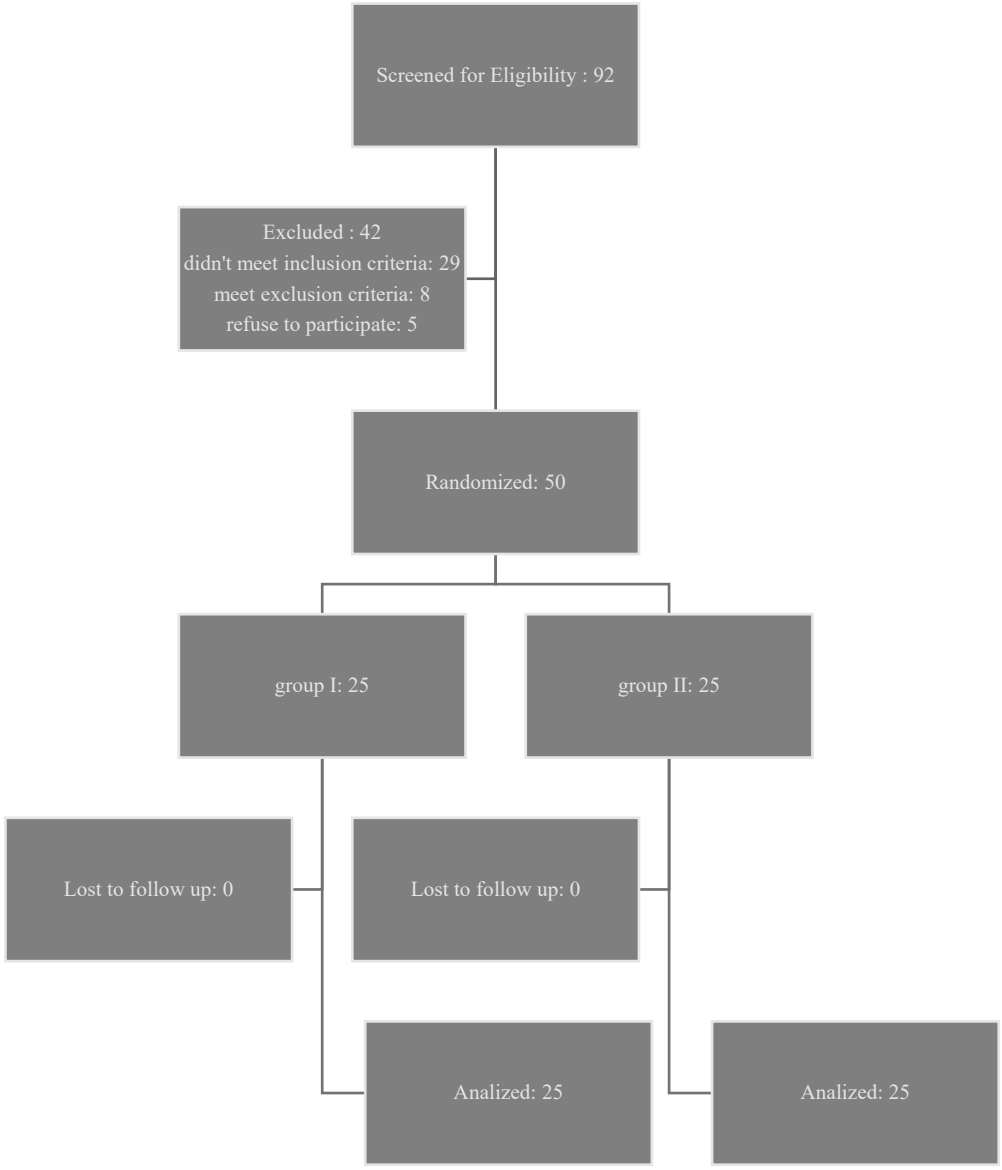
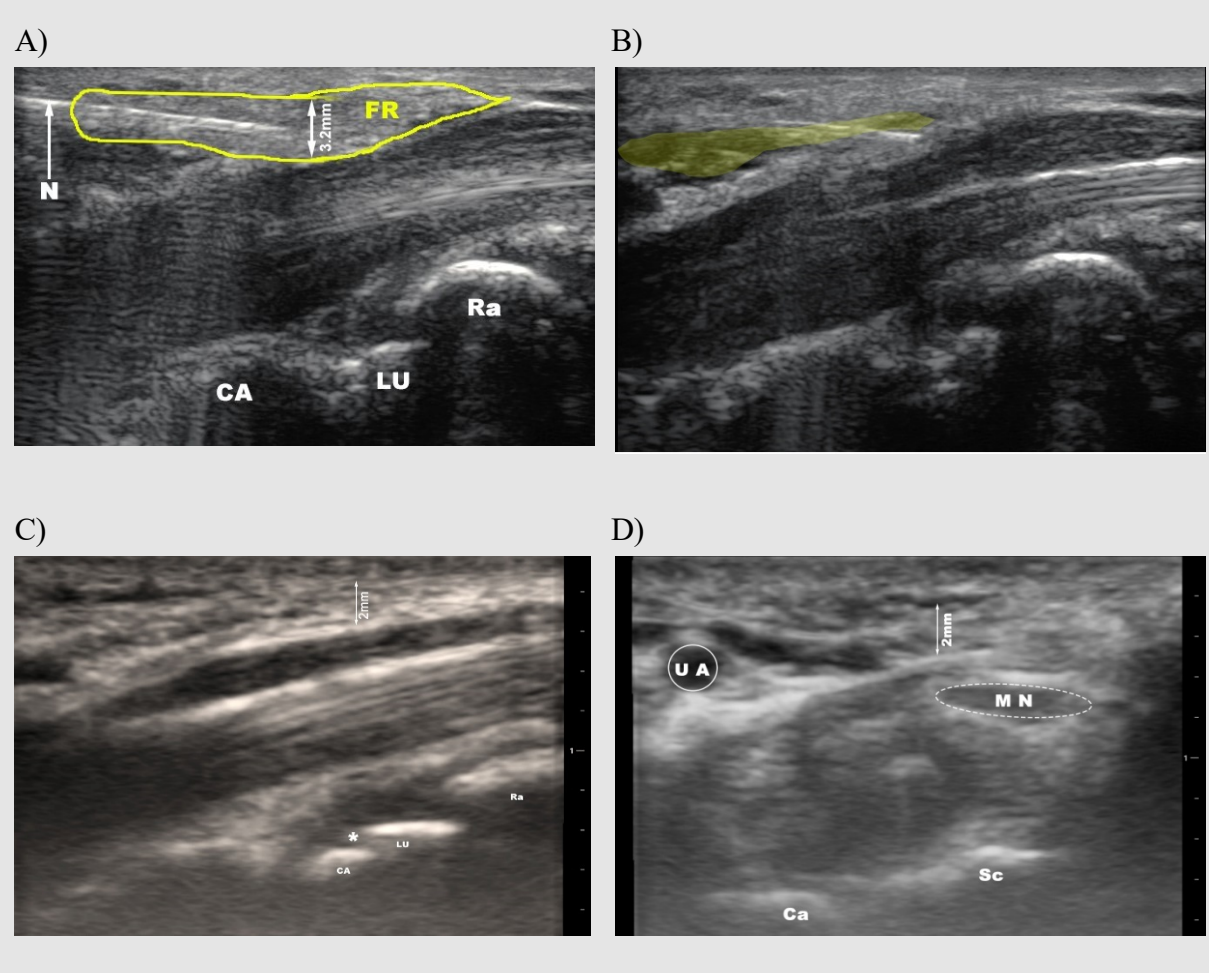


Table 10. Study IV participants' demographic data

	Group I	Group II	P-value
Age	65.72 ± 5.5	64 ± 8.16	0.387
Female/male ratio	68%/32%	80%/20%	0.333
Dominant/nondominant hand involvement	92%/8%	80%/20%	0.221

Image 17: Study IV: Intra-flexor retinaculum injection sonographic assessment.



A. Needle position in the FR longitudinal view (group 1); B. Needle advancement and drug infiltration between FR and MN (group 2), longitudinal view; C. Post-injection flexor retinaculum thickness, longitudinal view (group1); D. Post-injection flexor retinaculum thickness, axial view (group 1); * mid canal

FR: Flexor Retinaculum; Ra: Radius; LU: Lunate; Ca: Capitate; Sc: Scaphoid; N: Needle; MN: Median Nerve; UA: Ulnar Artery.

Table 11. Study IV: comparing with-in and between groups outcomes measures.

Primary outcome		Baseline measurement	Six weeks follow up measurement	Paired samples t-test	independent-samples t-test
VAS **Mean (SD)**	Group I	7.04 (2.65)	2.72 (1.67)	**<0.001***	**0.026***
	Group II	7.12 (2.33)	4.44 (1.50)	**<0.001***	
Median DML **Mean (SD)**	Group I	4.84 (0.99)	4.69 (0.82)	0.043	0.094
	Group II	4.78 (0.70)	4.46 (0.67)	**<0.001***	
Median SNAP **Mean (SD)**	Group I	4.48 (0.68)	4.38 (0.85)	**0.012***	0.526
	Group II	4.38 (0.55)	4.09 (0.46)	**0.001***	
BCTQ **Mean (SD)**	Group I	52.2 (12.79)	28.08 (10.46)	**<0.001***	**0.023***
	Group II	57.72 (10.28)	41.24 (9.37)	<0.001*	
BCTQ symptom severity scale **Mean (SD)**	Group I	29.88 (7.31)	15.8 (6.06)	**<0.001***	0.261
	Group II	34.92 (9.41)	23.44 (5.37)	**<0.001***	
BCTQ functional status scale **Mean (SD)**	Group I	22.32 (5.49)	12.28 (4.41)	**<0.001***	**0.016***
	Group II	22.8 (8.1)	17.8 (4.02)	**0.009***	
Inlet CSA **Mean (SD)**	Group I	12.08 (2.66)	9.44 (2.35)	**<0.001***	**0.004***
	Group II	12.4 (1.82)	11.82 (1.26)	**0.007***	
Grip **Mean (SD)**	Group I	23.52 (8.63)	28.52 (7.68)	**<0.001***	0.149
	Group II	22.95 (7.44)	30.26 (10.13)	**<0.001***	

* Statistically significant results

6. Discussion:

Substudy 1: Our main goal was to estimate the prevalence of neuropathic pain and determine its associated comorbidities among elderly Iranians in a large population-based study. Pain is common in older adults and has a bidirectional relation to many comorbidities and problems. Chronic NP prevalence in this study was 13.7%, slightly higher than other similar studies. A systematic review of a population-based study in France, and others in Morocco and the UK, reported NP prevalence between 6% and 10%.(61) The other study reported it 10% in the US.(62) There is some ambiguity for the higher prevalence of NP among older adults. They have the potential for pharmacokinetic-dynamic problems compared with younger adults due to the polypharmacy of multiple problems. They also faced cognitive dysfunction more than younger individuals, and this is a source of bias in precisely detecting pain. Finally, some believe that pain is considered a normal part of aging and some social factors such as ignorance of the elderly may result in underestimation and undertreatment of their illnesses.(63) In our study, the prevalence of neuropathic pain is driven based on a questionnaire, part of the DN4. In this study, more than one-third of subjects had chronic pain and two-thirds reported pain in overall. However, the body of different literature revealed that chronic pain prevalence is different in different populations, ranging from 20% to 51%.(64,65) Recall periods and pain definition may be the reason for differences in pain prevalence in different studies.(65) Similar to other studies, back and knee pain were the most common. In this age group, mild and benign pain are less common in older adults, while severe and disabling pain are more frequent.(62,64,65) Proper diagnosis and management of these types of pain can help improve the quality of life of the elderly.(66) Similar to other studies that saw more prevalence in women both in the cross-sectional and review studies and a cross-national study(67), our findings show less chronic pain in men. Although there is no scientific evidence to justify the reason for sex differences, this may be due to the perception threshold difference because of psychological, biological, cultural factors, and coping skills.(67) Pain, comorbidities, and frailty are always found together.(68) And in some studies, a significant association between pain severity and high comorbidities has been reported.(68) We found no cause-and-effect relation neither between comorbidities and pain nor for mental health and chronic pain because the nature of our cross-sectional study. A large community-based study and cluster sampling instead of help-seeking sampling are some of our study's positivity's. The association between pain experience and mental health is bidirectional.(69) Like other studies such as the one by Lopez et al.(70), a study in Sweden(71), and in a European cohort(72), we found that mental health is impaired more in

subjects with chronic neuropathic pain, although it may relate to pain disorder or other comorbidities.

Substudy 2: In this substudy, we focused on one of the common peripheral entrapment-originated neuropathic pains in the elderly that can be treated well if diagnosed on time. Older adults depend on their hand function in daily living, especially when they have many other limitations. Like countless other disorders, it is important to diagnose CTS accurately and early because it responds to noninvasive treatments in the early stages. Elderly patients usually have advanced CTS because of a late diagnosis, so it is important to detect it early with a screening method.(73) Blumenthal et al. reported that severe electro-physiologically detected CTS with mild symptoms was 3.2 times more common in the elderly than in younger patients. The authors suggest that older adults under-report their problems or have less pain perception and emphasize active screening by health care workers using clinical or paraclinical tools.(73) The gold standard of CTS diagnosis is clinical examination based on reliable guidelines; the gold standard paraclinical test for confirmation is EDX, but this test is uncomfortable for the patient and costly. We focused on a less invasive alternative. In this study, we found that ultrasonography examination to detect CTS in older patients has excellent accuracy, 96.9% sensitivity and 93.6% specificity. In addition, the results showed the cross-section of the median nerve at the mid-canal level was smaller than the outlet and inlet CSAs. EDX, the most common method for diagnosing CTS, has many shortcomings and is relatively invasive, and this has led physicians to investigate alternative methods. High-resolution ultrasonography has become a popular device to detect many disorders of internal organs. It is more accessible, low cost, noninvasive, and fast.(74) EDX assesses nerve physiology, but ultrasonography evaluates biomechanics and anatomy of nerves such as CSA, thickness of tendons, and adjacent tumors or aberrant vasculatures.(75) Aging affects axonal isolation and integrity by affecting myelination of fibers, leading to a decrease in velocity of nerve conduction, and axonal damage shows abnormal findings in an EMG, even in asymptomatic persons.(76) If these findings are detected in the median nerve at the wrist, they may be considered as false positive or reported as subclinical CTS. In contrast, in some studies similar to our work(77), the NCV may have a false negative up to 40%. The pooled sensitivity and specificity for the electrodiagnosis were 80.2% (95%CI 71.3%–89.0%) and 78.7% (95% CI 66.4%–91.1%) respectively.(78) The cutoff age to represent significant CTS changes varies in different studies, ranging from 55 to 80 years.(79) Some studies like our work, it is emphasized that ultrasonography and EDX have complementary roles at this time. Instead, it is proposed that US be used as an initial step in screening patients suspected with

CTS, and EDX is only performed if ultrasonography results were non-confirmatory.(44,80) The mean CSA normal values at the tunnel inlet vary widely, ranging from 6.1 mm^2 to 10.4 mm^2 in the general population.(81) The possible reasons are selection criteria of the subjects, CTS diagnosis gold standard, EDX criteria and normal value of CTS diagnosis, sonographer experience, and inter- and intra-rater reliabilities of CSA measurements among studies. Demographic characteristics such as age, gender, and handedness affect this normal range.(81) The reference standard is usually clinical criteria and some studies use EDX as a complementary method to diagnose CTS.(36) One source of shortcoming in the research studies is the use of only clinical criteria to detect CTS, while selecting asymptomatic persons as the control group. We discussed the subclinical CTS in the elderly, so clinical criteria in addition to EDX is a superior method and is preferred. Moreover, the EDX criteria for detecting CTS is not the same in different studies and is responsible for the wide range of sensitivity and specificity. There is still no systematic review to assess and compare both the intra and inter-rater reliabilities of measuring the CSA of nerves and considering it, and this is one of our study's strengths. However, in almost all studies, only one sonographer took the images and measures, and so did we. A meta-analysis and the literature suggest that the CSA at the carpal tunnel inlet (a line between scaphoid and pisiform) is the most precise and reliable diagnostic criterion for detecting subjects with CTS, with the best specificity and sensitivity.(82) Other anatomical measurements such as the wrist to nerve ratio, flattening index of the flexor retinaculum, and bowing indexes are suggested in some studies, but they are not better than CSA at inlet. In this study we calculated and determined the normal CSA cutoff point in the elderly and the range of CSA of median nerve at inlet for the CTS with different severities: mild, moderate, and severe.

Substudy 3: Prevalence of CTS is high in the general population and increases with age. It has two peaks: around 50 and 80 years. If it is not diagnosed and treated on time, it may lead to functional impairment and decreased dexterity, or lead to surgery, complications, and economic costs to the patient or their health care system. These reasons highlight the need to investigate proper diagnosis and management, especially in the elderly.(73) One of the popular treatments of CTS is steroid injection with or without an ultrasonographic guide. Some physicians inject the steroid in the tunnel, but in this study, we tried to separate the median nerve from its surrounding structure by hydrodissection. In addition, we evaluated different doses of steroid to find the optimum steroid dose in this age group. Analysis of almost all data including electrodiagnosis, ultrasonographic measures, and clinical criteria showed significant improvement within-group without significant difference between groups.

Lam and Thurston's and Vesey et al.'s studies showed the prevalence of CTS is significantly higher above 50 years old, and Bland and Rudolfer reported a bi-hump peak around 50–54 and 75–84 years.(83) Therefore, the cutoff point for elderly discrimination has significant variance in the literature. Fernandez et al. showed that the functional outcome and symptom relief after decompression were satisfactory, but severe nerve deficit and thenar muscle atrophy were more prevalent than in the younger age group.(84) In another study by Hobby et al., using five age-groups, functional improvement, and treatment outcome were less satisfactory in older groups.(85) Furthermore, older adults usually have multiple disorders, more comorbidities such as heart problems, hypertension and diabetes mellitus, and so they may have more complications after surgery or receiving higher doses of steroids.(85) With this evidence, we selected 50 years as a cutoff age for detecting and managing CTS early for the elderly. A meta-analysis has shown that steroid injections decrease symptom severity and improve function.(86) However, the adverse effects of steroids for diabetes and hypertension put a big question in front of its administration, especially in older adults with multiple disorders.

Local anesthetics such as lidocaine usually become mixed with steroids to reduce pain during and after injection.(87) Lidocaine induces the local anesthesia by blocking C and A-Delta fibers. It also leads to vasodilatation by blocking the natrium channels and manipulating secretion of nitrous oxide by endothelial cells.(88) An anti-inflammatory role is also proposed for lidocaine, through inhibition of nuclear factor-KB.29.(89) This could be an appropriate explanation for the findings we saw in group III, the only lidocaine group. Although we cannot rule out the placebo effect, it would be painful and our institution's ethics committee did not approve administering it to the placebo group. There are several hypotheses for the pathophysiology of CTS. Some reasons include increased pressure, adhesion of surrounding connective tissue or space-occupying lesion in the tunnel such as tumor, bone fracture, or synovial cysts.(90) Hydrodissection itself may decrease the adhesions and free the median nerve from its surrounding tissues,(91) and it may be another explanation for the effects that we saw in group III. Dernek et al. studied 67 CTS patients in two groups. Group I received 1 mL of betamethasone and group II received 0.5 mL of normal saline and 0.5 mL of lidocaine. The result was similar and they suggest the second for the treatment of CTS to avoid potential adverse effects of steroids.(92) Some studies suggest lidocaine injection instead of steroids for CTS management in patients with high risk of steroid injection.(93) Vahi et al. found that postsurgical complications are much more increased in patients who had multiple presurgical steroid injections.(94) For patients with severe CTS, who are in the waiting list for surgery, a lidocaine-only injection is a better choice.

This study's strengths are case selection based on clinical gold standards, use of electrodiagnosis to confirm cases, outcome measures such as the Boston Carpal Tunnel Questionnaire, and ultrasound parameters. Furthermore, it was a prospective study with a relatively complete follow-up and assessment for 6 months. Our study's limitations are the lack of comparison with younger patients, an absent placebo and/or an untreated/sham control group. And it has relatively short-term follow-up, 6 months instead of 12 months. We should also match the groups by considering baseline measurements, because the post-hoc analysis of baseline measures came up with a significant difference between Groups I and III for VAS. However, this study found that lidocaine-only hydrodissection was as effective as hydrodissection with either 40 mg or 80 mg of steroid.

Substudy 4: Although CTS prevalence and its related treatment costs are high, a definite treatment protocol is lacking regarding its optimal treatment.(95) We believe it is important to determine the most efficient and cheapest strategy for CTS treatment in the elderly. The American Academy of Orthopedic Surgeons (AAOS) recommends either local steroid injections or surgery as initial treatment for the population with CTS.(96) Pomerance et al. hold that surgery as a first step to manage CTS is the costliest treatment option.(97) However, other studies have contradictory conclusions,(98–99) and it may be due to psychosocial costs associated with a long course of nonsurgical management. Among many considerations on the final decision for CTS treatment, the out-of-pocket cost is considered the most important. The AAOS states that surgery has longer effects than steroid injection than splinting alone ordinarily.(96) Shi and MacDermid brought evidence of no significant differences between surgery and conservative management regarding functional or severity outcomes in 1 and 3 months.(100) It seems additional considerations such as patient preferences, comorbid issues, risk for complications, and magnitude of nerve damage are particularly important when differences between management options are small. Some experts suggest a course of conservative management before surgery,[193,194] and based on outcomes make step ups or not. We have introduced a new approach in this study in the management of CTS, based on the hypothesis that direct steroid injection in the flexor retinaculum can induce atrophy and may imitate surgery effects. If it works, it can benefit both surgical and nonsurgical methods. Considering ultrasonographic measurements, functional status, and symptom severity, we found better results in intra-flexor injection than with in-canal injection. Some studies estimated the incidence of local soft tissue atrophy after steroid injection of up to 40% depends on corticosteroid features, patients' traits, and the procedure's characteristics.(101,102) Local soft tissue atrophy is more prevalent in subcutaneous fat

tissue and in females. Long-acting steroids such as triamcinolone have more atrophying effects over short-acting agents like dexamethasone. Larger gauge needles, a larger volume, a higher concentration, and more scattered infiltration may exert more atrophying effects.(102) The current RCT strengths are exact administration of RCT design in drafting and taking exact steps and CONSORT statement in analysis and report, precise outcome measures such as NCS, the BCTQ, and ultrasound. Our study limitations are absence of a true placebo group, and/or a sham control group, nor comparison with surgery. We did not confirm atrophy on the flexor retinaculum by ultrasound, but only evaluated its secondary effects on CTS features. One of our major limitations was short follow-up time: 6 weeks rather than 6 and 12 months due to budgeting limitation. Although preliminary short-term results of our study are promising for intra-retinaculum steroid injection, we strongly suggest longer follow-up with the inclusion of a sham control group and a surgery group for future studies.

7. Conclusion:

Substudy 1: We determined the prevalence of chronic and neuropathic pain and its comorbidities in elderly adults living with their families in the community in an urban area of Iran. In this study, we found a somewhat higher prevalence than in other studies and thus, emphasize the importance of identifying neuropathic pain, its accompanying problems, and the adverse consequences it can have. Our findings can be used by health policymakers to manage this population's needs in Iran, and by young physicians who are at the forefront of elderly care for detecting and managing neuropathic pain effectively.

Substudy 2: High-resolution ultrasonography is a convenient and reliable test for detecting CTS in older adults with different severities. The median nerve CSA at the carpal tunnel inlet is the most sensitive and specific measure for detecting CTS and could be used as the first confirmatory method for clinical examination.

Substudy 3: Injecting in the carpal tunnel under ultrasonography with the hydrodissection method to manage CTS is an effective approach. We found that a lidocaine-only injection is effective as steroid containing suspensions and may be a better choice for elderly patients with multiple morbidities. However, larger studies that address our limitations are suggested.

Substudy 4: This study demonstrated superiority for the intra-flexor retinaculum over the carpal tunnel steroid injection in elderly patients with CTS, with respect to ultrasonographic measurements, functional status, and symptom severity. However, larger studies that address our limitations are highly recommended.

Limitations:

Substudy 1: The prevalence of neuropathic pain is driven based on the question part of DN4, and it may be underestimated. The Iranian cultural and sociodemographic definition of "elderly" is considered to be years of age above 60, which differ from the definition in the Western countries However, the mean age was found to be 68. Clinical examination in addition to questionnaires can improve diagnosis accuracy.

Substudy 2: Due to limited resources, we did not reach our target size (63 cases) in the severe CTS group, which should be addressed in the future. We did not compare the results of older individuals with younger patients, and a control group of younger patients seems needed.

Substudy 3: The lack of an untreated control group and comparison with younger adults are limitations in this study. Longer follow-ups are better, too. A significant baseline difference for VAS between groups I and III in post-hoc analysis may affect the conclusion, though other measures have no significant difference at the baseline.

Substudy 4: One of our project's major limitations was the restricted follow-up time of about 6 weeks. We also did not investigate direct atrophying effects of steroid in the flexor retinaculum by ultrasound and lacked a sham and a surgery group. Addressing these limitations in future studies will lead to conclusive findings.

8. Points of perspective

Overall, we focused on neuropathic pain in the elderly and focused on one of the common and treatable sources of peripheral neuropathic pain: the CTS. Due to demographics and cultural definition of elderly people in Iran and bi focal peaks prevalence of the CTS, we set our cutoff age for the elderly at over 60 years. We found a significant percentage of pain, both acute and chronic, nociceptive, and neuropathic in the elderly. With our findings in mind, we believe it is important to further identify, diagnose, and offer treatment to afflicted persons. We suggest a larger population-based study that will focus on pain and neuropathic in general and on CTS in specific. One should consider the elderly in nursing homes, because many of them cannot communicate well and our primary care physicians are not well trained in this area.

For the ultrasonography measures of the median nerve, establishing the cutoff point for detecting CTS and ranges for different severities, we recommend a study including younger age groups to determine whether there is any difference between the elderly and young adults.

For the interventional studies, we suggest sham, control, surgical intervention groups and longer follow-up periods.

Finally, despite these study limitations, chronic pain-related neuropathies are common in the elderly and should be addressed in future research. Early detection and management of CTS are crucial in older adults. Ultrasonography—a helpful, convenient, noninvasive method—is useful for detecting CTS. Nonsteroidal CTS injections could be considered for relieving CTS pain in the elderly with comorbidities. Intra-flexor retinaculum steroid injection may become an alternative to surgery.

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