Structural Part of the Matrix

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Bio for David Musnick MD

- Board Certified in Internal Medicine, Sports Medicine
- Certified in Functional Medicine (2014)
- Lecturer at the IFM annual meetings and AFMCP
- Creator of:
- DM Integrative and FM Approach to healing the brain after Concussion
- FM Approach to Chronic Pain
- FM Approach to Osteoarthritis
- Author of Integrative Approach to Treating Concussion and TBI in Integrative Neurology: Fall 2020 Oxford University Press
- Author of Chapter on Osteoarthritis in Metabolic Orthopedics 2019

Learning Objectives

- Use the concepts of structural integrity for clinical evaluation and treatment.
- Utilize clinical questions and a clinical framework to screen for certain structural integrity issues and to help frame a case

Asking the Right Questions

- Asking questions is a very important tool for a Functional Medicine practitioner
- They can help you figure out or frame a clinical issue
- Try using some or all of these questions on any structural case in your practice

Key Structural Questions

- Is there a loss of normal structure in this tissue, organ or organ system?
- What is the status of the remaining structure? Degenerative, necrotic, normal…
- How much functional reserve is there in this tissue?
- What structure would be ideal to add to the tissue, organ or organ system to improve function?
- Can new cells or matrix be added to the tissue or organ?
- What structural questions do I need to have to improve the function of this organ, organ system?

Key Structural Questions

- How long might it take to change this structure?
- How will I need to stage my structural interventions
- What modifiable Personal Lifestyle choice will need to be made to improve this structure?
- What matrix interventions might need to be done to improve this structure?
- What is the most important pathophysiology that has and still is damaging this structure?
- If this structure were improved what functional benefits might this patient see

Important Structural Priorities

- Support/protect mitochondria structure
- Protect or repair barrier tissues such as the blood brain barrier or gastrointestinal barrier of the small intestine
- Decrease inflammation and narrowing and improve compliance in arteries
- Protect DNA from cancerous changes
- Protect telomeres to improve cellular longevity
- Decrease fatty infiltration
- Decrease toxic load in the structure
- Decrease toxic release from the structure
- Improve the nervous system regulation of the structure

Important Structural Priorities

- Support bone density and treat Osteoporosis
- Support and protect key joints of the spine and extremities (OA)
- Support lean body mass and preserve muscle tissue (slow Sarcopenia)
- Protect renal tissue to preserve renal function, treat renal insufficiency and slow progression to preserve or improve detoxification and other renal functions
- Decrease scarring, adhesions and fibrosis
- Improve the collagen content of the skin
- Achieve balance in the TH1 and TH2 branches of the immune system
- May need to increase the TH1 aspect of the Immune system

Key Structural Concepts

- It is important to have structural priorities and structural questions for your patients
- Improving and protecting structures takes time and you must explain the potential benefits as well as the time and resource commitments required from the patient
- Resources and interventions placed to prevent structural problems can have significant beneficial impacts on later function and reduce the burden of later problems

Importance of Early Structural Intervention

- Many structural problems have long latencies and interventions may need to be at a preclinical stage
- Cancer prevention strategies and coronary structure interventions should be started at earlier ages (20, 30s, 40s) because of the long latencies of these problems
- Brain structure, neurodegenerative and dementia disorder prevention needs to begin earlier because of the long latency of this problem and the earlier onset we are seeing of mild cognitive impairment

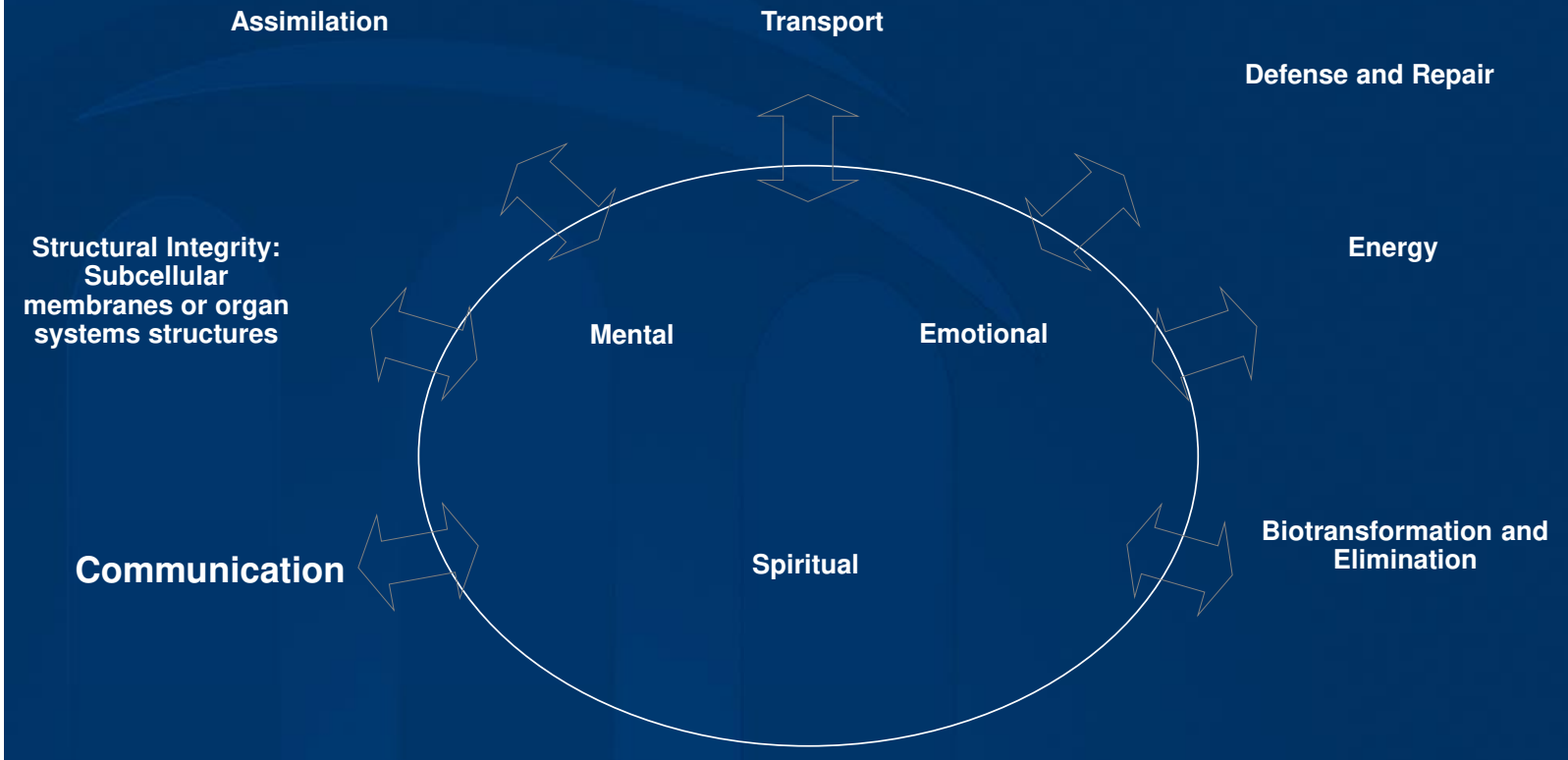
Early Intervention

- Bone structure intervention needs to start in adolescent years in order to ensure that the individual reaches maximum potential bone density
- Women in their 30s and 40s need to be monitoring bone turnover and start strategies to preserve bone mass

Matrix and Structure

- When approaching a structural issue ask "What are the effects of key aspects of the matrix on this structure that I am working on?
- What can be done to support the structure via matrix interventions and nutritional and lifestyle interventions?
- Can I effect improvement in other aspects of the matrix by doing this?

FUNCTIONAL MEDICINE MATRIX MODEL



Sleep	Exercise	Nutrition	Stress	Relationships

Date: ____ Name: _____ Age _____ Sex_____ Chief Complaints: _____

IFM
THE INSTITUTE FOR FUNCTIONAL MEDICINE

Other Structural Questions to Consider: Toxicity

- Is this structure a reservoir for toxins?
- Are toxin levels related to pain or dysfunction of the structure?
- If there is a mobilization or breakdown of this structure, how can the patient's body be protected?
- Example: Adipose tissue is a reservoir for fat soluble toxins. When fat is lost, toxins will be released and redistributed unless support is given for phase 1 and 2 detoxification

Structure and Toxicity

- During weight loss programs recommend foods that support phase 1 and 2 detoxification e.g., watercress, cruciferous veggies, onion family veggies, pomegranate juice and green tea
- Consider a supplement or a functional food that supports phase 2 detox pathways during weight loss programs

Structure and Toxicity

- Bone is a reservoir for Lead and Cadmium. Lead and Cadmium may be released during times of bone resorption in women and men.
- Cadmium may have an adverse effect on bone density
- Kidney structure may be damaged by cadmium exposure. (One mechanism of damage appears to be oxidative stress).
- Consider measuring blood lead and cadmium levels in menopausal women and in aging men especially if symptoms related to lead and cadmium are suspected.

Structure and Toxicity

- Consider measuring blood lead and cadmium levels in menopausal women and in aging men especially if symptoms related to lead and cadmium are suspected.

Structural Change Takes Time

- Time it takes before you can monitor a bone resorptive urine test: 3-4 months
- The amount of time you will need to monitor and treat bone density: 2Years and throughout the lifespan
- Time before an intervention begins to relieve symptoms of OA of the knee: 8 weeks
- Time to begin to change chronic pain in a patient with central pain sensitization: 12 weeks

Structural Change Timeline

- Small intestinal lining turnover time: about 1 week (stem cells in the crypts of the small intestine generate new absorptive, goblet, enteroendocrine, and Paneth cells and replace most of the lining each week)
- Time needed for avoidance of gluten for small intestine to heal: 4-6 weeks (appears to be slightly less for other food allergens)
- Time for peripheral nerve to heal after contusion: 10-12 weeks
- Time for ligament injury to heal with close to 100% strength: about 10 weeks

Structural Change Timeline

- Time it takes at the onset of an aerobic exercise program for new enzyme systems to occur in the muscles for a new level of aerobic fitness: about 8-12 weeks
- Time it takes to improve balance: 2-3 weeks
- Time it takes for tendons to become degenerative: approximately 3 months (to regenerate approximately the same)

Make Structural Goals Explicit

You are more likely to have a compliant patient for the long term if you:

- State your goal clearly and write it down
- Explain the short and long term benefits
- Explain how long it may take
- You may want to have a form that they read and sign that lists the benefits of a structural change program in order to improve compliance.

Forms/Programs

- Include:
  - The objective or goal for both structure and functional improvement
  - The objectives for prevention of worsening of the structure or other structures
  - The expected timeline
  - Tests needed
  - Interventions proposed
  - Recheck visits and the frequency
  - Methods of evaluation
  - A disclaimer line of "There is no guarantee."

Ask and Educate

- Frame your structural goal and time frame: "I would like to evaluate and treat your bone density and then check a lab test to monitor bone break down. We will need a recheck visit about 3 months after we start treatment. After that I would like to help you keep your bones healthy year after year as it it so important for your health."
- Are you on board with this?

Make Structural Goals Explicit

"I would like to improve the surface cartilage of your right knee so that you can participate in short hikes and skiing, maneuver stairs and do your ADLs. This will take at least 8 weeks to start noticing an effect but it is important that you stick to this plan for at least 6 months because the support of your cartilage is a long term structural endeavor."

Functional Medicine Approach to Chronic Pain: Sensitization, Genomics and Narcotics

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Speaker Bio

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- Certified in Functional Medicine
- Practice of Sports Medicine and Functional Medicine
- Put together the FM Approach to Pain in 2008 AIC
- Specialties in Hypermobility, Prolotherapy, Frequency Specific Microcurrent, Low Level Laser Therapy, Traumatic Brain Injury, DJD, Tendinopathy
- Chapter Author 1. Tendinopathy and Chronic Pain, 2. Osteoarthritis in Metabolic Therapies in Orthopedics
- Medical legal expert in Orthopedics cases

Objectives

- State what chronic pain is and the scope of the problem Describe normal pain processing
- Discuss pain sensitization and mechanisms of chronic pain
- Outline problems with conventional pain management approaches
- Discuss a Functional Medicine method of pain management which will take into account 1. TIP(**Tissues** causing pain, **Issues**(condition of the tissues) and the status of the pain **Processing** system 2. Regional Factors 3. Matrix and Lifestyle Factors

Objectives

- Describe Genomics of pain and when to order tests
- Outline Opioids, SEs, safe tapering and alternatives

Scope of the Problem

- There is an epidemic of patients with Chronic Pain
- In 2016 an estimated 20.4% (50.0 million) of U.S. adults had chronic pain and 8.0% of U.S. adults (19.6 million) had high-impact chronic pain. Women represent a higher percentage than men. CDC Morbidity and Mortality Weekly Report

Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults — United States, 2016

Weekly / September 14, 2018 / 67(36);1001–1006

Have you noticed that there are more and more patients that are complicated with diffuse pain or with non resolving regional pain?

Who are they?

- Patients with **regional** pain that has lasted more than 8 weeks that is easily triggered or is constant and is not cancer may have **regional sensitization**: ie spine pain, Neuropathy, knee or hip DJD with pain, trigger points, facet inflammation, tendinopathy, Migraines etc.
- Patients with more **diffuse pain** that is constant and has lasted more than 8 weeks have peripheral and **central sensitization**: FMS, Ehlers Danlos and Hypermobile Patients, RA and Autoimmune Conditions, Patients with SIBO and pain, MCS, multiple food allergies, mold biotoxins, diffuse Neuropathies

What Can Happen

- Labeling a Diagnosis and matching to one treatment
- Inadequate pain relief
- Side effects from NSAIDS or opioids
- Persistent pathology or worsening of pathology
- Expanding or worsening of pain
- Development of chronic pain
- Adverse effects of pain on sleep, mood, exercise, stress and energy

Problems with Pain Management

- Patients are labeled with a diagnosis that may not correctly identify the tissues generating the pain and the condition of the tissues
- Pain referral patterns may not be taken into account
- There is no to minimal attention to the mechanisms of chronic pain sensitization in the peripheral receptors, the cord and the brain. Thus nothing is done to treat the low threshold pain processing system

Problems with Pain Management

- Regional factors that are influencing the pain generating tissues are frequently not addressed
- Whole body issues(Matrix and Lifestyle factors) that are influencing the pain are frequently not addressed
- Co-morbidities contributing to pain are not addressed(Depression, Anxiety, Stress, etc.)
- Patients are given a prescription for NSAIDS despite chronic pain is not simply time limited inflammatory mediators, has numerous other mediators

Problems with Pain Management

- NSAIDS will be used because of their analgesic properties or because the provider does not know what else to do
- NSAIDS can damage small intestinal permeability as well as cause tissue damage to the stomach, liver, kidneys and large intestine
- Opioids are prescribed because the patient puts pressure on the provider to do something if an NSAID doesn't work. The narcotics sensitize the system, have numerous SEs and the patient can ask for increasing doses because of tolerance and then can get addicted.

Problems with Pain Management

- Opioids can cause sensitization and worsen chronic pain, depress Testosterone and can cause significant GI dysfunction(constipation, SIBO)
- Opioids can be seen as the answer by the patient but they should only be given for short term use for acute pain and not for chronic non cancer pain

Problems with Pain Management

- The clinician may not have an idea of a time course of how long an intervention might take
- The clinician may need to stage treatment depending on the condition of the tissue or the pain processing system
- Appropriate modalities are not used to treat the (TIP)tissues, the issues(condition) of the tissues and the sensitized pain processing system. (The most effective modality to treat tissues, issues with tissues and the pain processing system is Frequency Specific Microcurrent)

FM Model of Assessing Pain

- Your note should have the following written:
- Your ICD 10 names, numbers diagnoses are: _____
- The tissues generating your pain are: _____
- The condition of the tissues are: _____
- Other tissues or regions contributing to perpetuating the pain are: other joints, poorly recruiting muscles, facets, nerve, cord etc.

FM Model of Assessing and Treating Pain

- Your pain processing system is low threshold(Sensitized): Yes No How we will treat that is: _____
- Your contributing factors that can increase pain are: sleep, mood, scars, edema, diet, exercise, stress, attitude, toxicity, _____

How we will be addressing these are:

Refer to the Word handout that you can copy for your practice "FM Pain Dx and Blueprint"

Diagnosis

- An accurate diagnosis and discussion is important. It is not enough to give a single label for a diagnosis like : Neck Sprain, Abdominal Pain
- The diagnosis should include not only a name(label), ICD 10 diagnosis but also: All tissues generating pain
- A discussion of the status of the tissue or tissues
- Suspected mediators of pain and factors for the pain not resolving

History: Pain Diagrams

- Pain Diagram: ask them to shade in where they hurt
- Ask them to rate the pain on a scale of 1-10 where 10 is childbirth, a fracture or a renal stone
- Ask them to indicate the type of pain
- Ask them to put an I for intermittent and a C for chronic
- Ask them to write how many weeks, months or years they have had their pain

History: Pain Diagrams

- If they put a duration more than 2 months and indicate either I or C they likely have sensitization if Constant it is more likely
- If they shade in a small area and indicate it got bigger over time than they have secondary hyperalgesia
- If they shade in their neck and whole back(large areas that do not represent any anatomical structure or referred pain) than they likely have central sensitization
- Refer to this breakout session handouts for this type of pain diagram

Exam: Sensitization

- Mild palpation that leads to tenderness
- Wincing or withdrawal with mild pressure
- Tenderness in a whole region like C1-7, all of the paraspinals, the whole low back, the SI ligaments
- Numerous FMS tender points
- Tenderness in the IT Band
- Tenderness in the small intestine area with 2 finger palpation

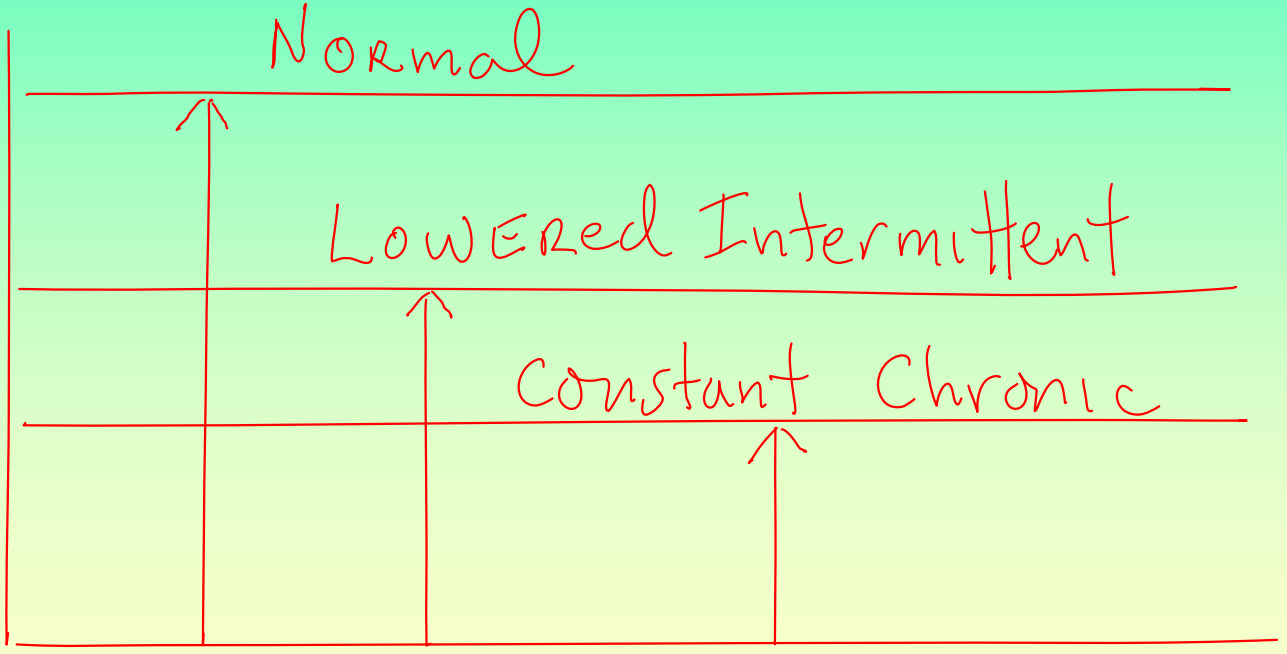
Sensitization

- Acute pain is usually useful and may serve a protective function
- If the pain becomes chronic there is not a protective function but rather a dysfunctional pain system that has become sensitized
- Sensitization is the lowering of the threshold for firing of a nociceptor or mechanoreceptor in the periphery or can occur in the cord in the dorsal horn or can occur in the brain in the thalamus
- When a patient's nervous system is sensitized the patient will perceive pain with less stimuli or will perceive pain constantly
- You then have a goal of educating the patient as to what sensitization is and how to improve their pain processing system

Sensitization Continuum

- At first there may be a perception of pain from less pressure or motion or mechanical or other factors
- The patient then can develop pain that is easier to set off and lasts longer
- The pain can be out of proportion to the stimulus
- As time goes on the patient can develop constant pain with intermittent worsening

Sensitization Continuum

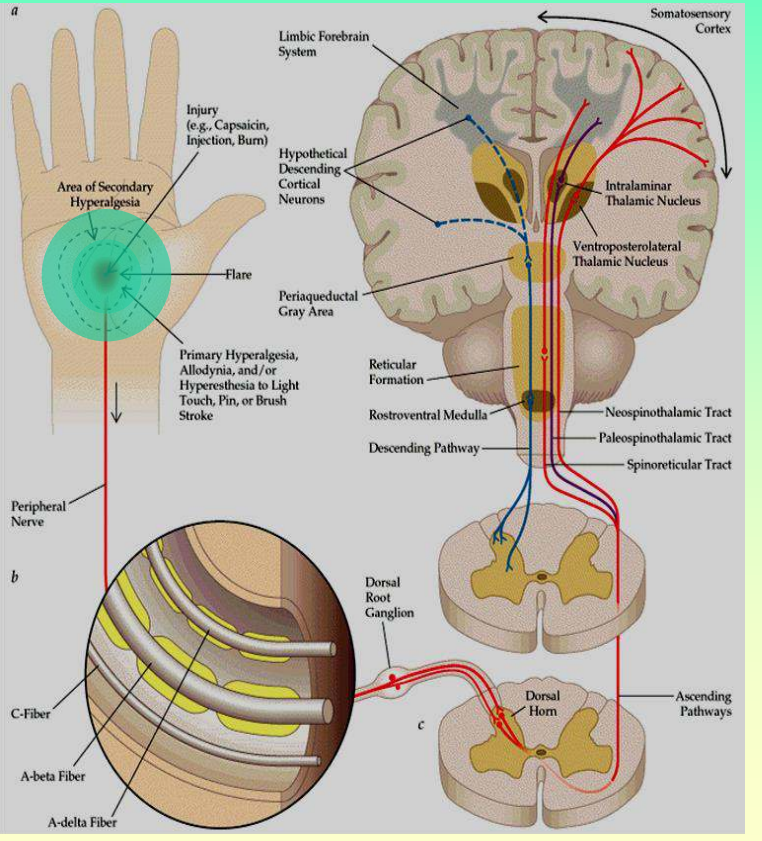


Sensitization

- Pain sensitization leads to chronic pain and has implications in the FM Matrix and can lead to or aggravate Depression, Sleep Dysfunction, Anxiety and Fatigue (co- morbid conditions) any of which can also be related to increasing pain sensitization
- Sensitization of receptors is related to inflammatory and noninflammatory mediators at the nociceptor or nerve ending causing excessively frequent firing changing the threshold to a lower threshold. Eventually the anatomy and physiology changes in the receptor, the cord and the brain with chronic sensitization.

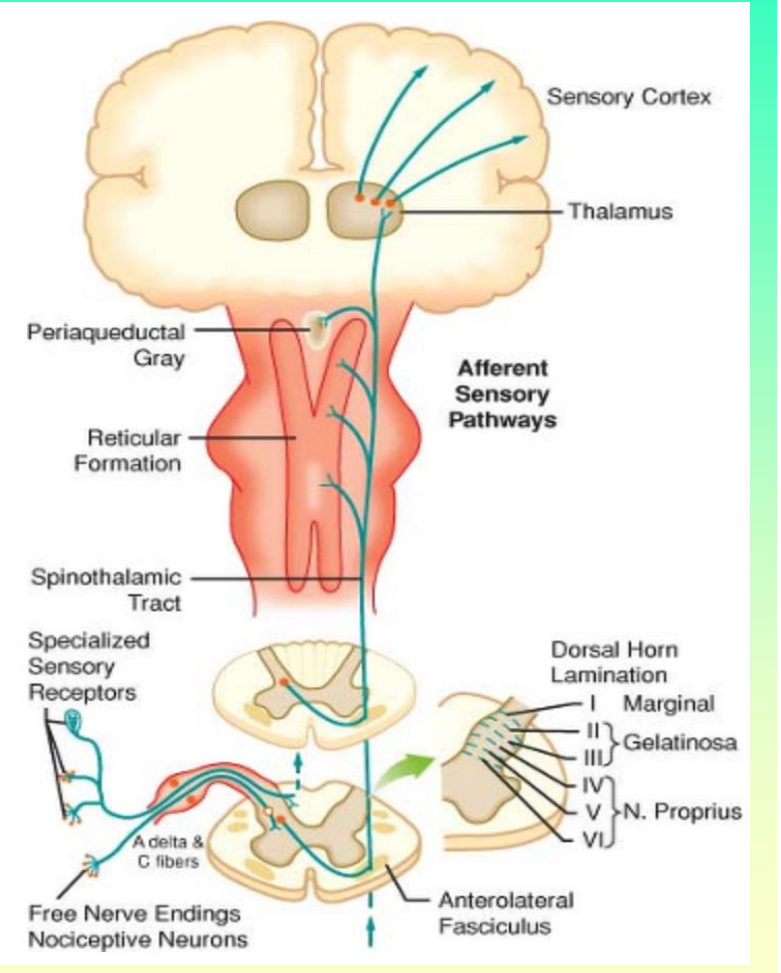
: Secondary Hyperalgesia

- Repeated impulse activity in C nociceptive neurons produces sensitization of spinothalamic tract neurons over time
- Previously subthreshold inputs reach threshold and initiate action potential (allodynia)
- Increases in spontaneous activity
- Spinal and supraspinal mechanisms
- Enlargement of the area in periphery where stimulus will activate neurons
- NMDA receptor, Substance P and other mechanisms



Pain Anatomy: Afferent

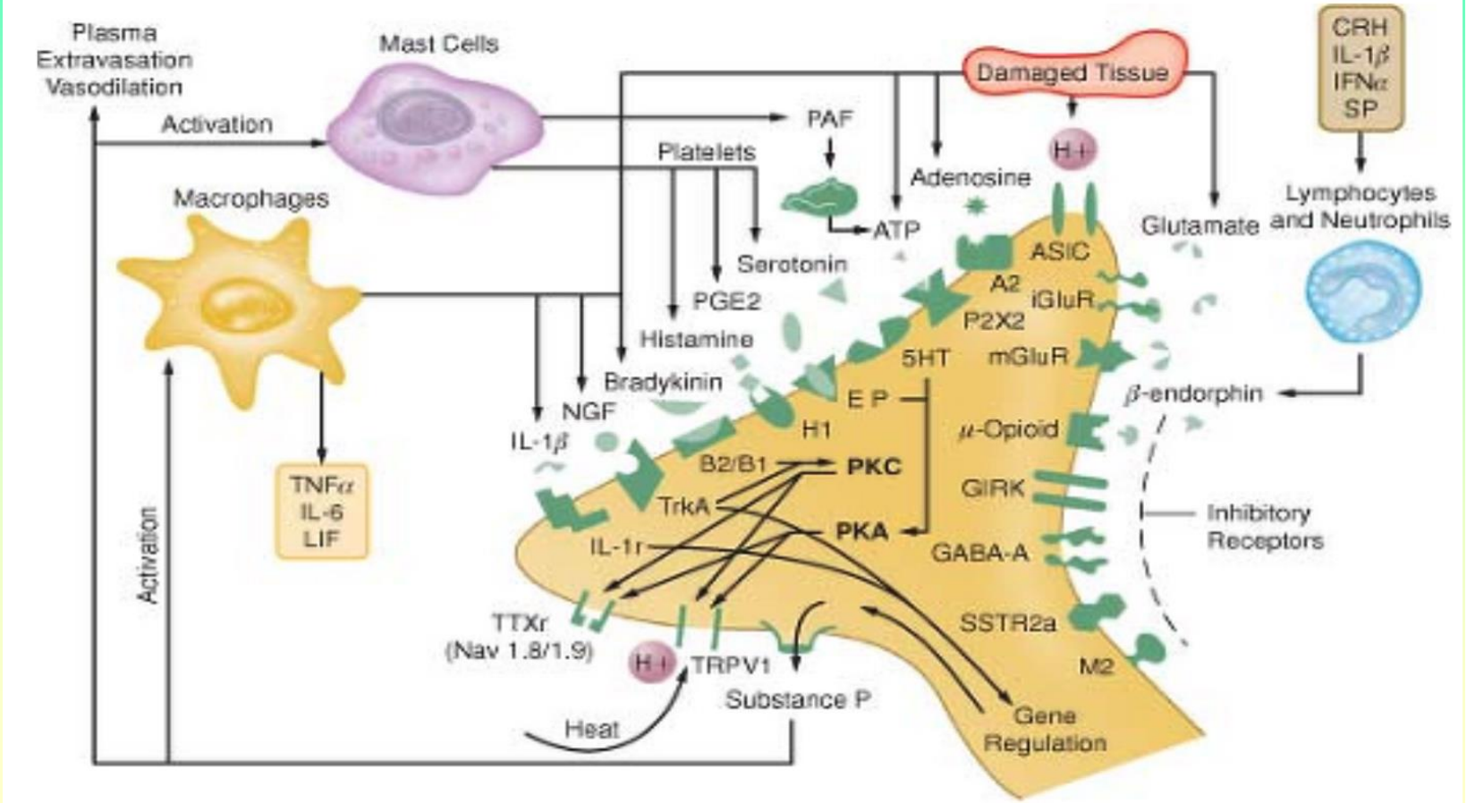
Pain is a signal from the peripheral nociceptor that is in A delta and C fibers. This signal is received in the dorsal horn of the spinal cord. Pain signals then travel up the Spinothalamic tract thru the brainstem and into the Midbrain(Thalamus) then to the sensory cortex



Peripheral Receptors and Axons

- C (unmyelinated) fibers(free nerve endings respond to mechanical, thermal or chemical). Many of the C fiber receptors are polymodal(PM) and respond to all 3 stimuli.
- PM receptors can be activated in a concentration dependent fashion by chemical mediators including: amines(5HT, histamine), Lipids (Prostaglandins), Kinins (bradykinin), Acidic PH with H+, Cytokines(IL1B, IL6, TNF alpha.) enzymes (trypsin and other mediators).

Neurochemistry: Peripheral Receptor



Nociceptor

- Bradykinin from Macrophages(Ms) activates Nociceptors(Ns)
- Serotonin from platelets activates Ns
- Histamine potentiates the response from Ns to bradykinin
- Prostaglandins and leukotrienes sensitizes Ns
- Excess H ions from tissue injury increases pain and hyperalgesia from inflammation
- Cytokines(TNF alpha,IL1B, IL 6) from Ms excite and sensitize Ns

Peripheral Sensitization

- Many different neurotransmitters from nerve terminal:
- Sub Pm CGRP, Aspartate, Glutamate, Neurotrophins(Nerve Growth Factor, BDNF, somatostatin
- Substance P activates Ms and Mast Cells
- Glutamate activates nociceptors

Note: Mediators that promote nociception in acute injury can also promote firing of nociceptors at lower thresholds with less noxious stimuli in chronic inflammation or ongoing mediator exposure from inflammation, Mast Cell Activation Check out www.chronicpaindrivers.com for a video

Peripheral Sensitization: Clinical

- Clinical Pearl: to alter or improve chronic pain consider making recommendations that will lead to:
- Substance P depletion(Capsaicin)
- Mast Cell Stabilization(Quercetin, Luteolin)
- Histamine blocking(decrease food and inhalant allergies
- PGE2 and Leukotriene reduction and blocking: Antiinflammatory diet Curcumin and Bosellia
- Cytokine blocking(esp TNF alpha(Curcumin, Resveratrol)
- NFKB blocking(decrease chronic or acute infection, decrease AGES)

Peripheral Sensitization: Clinical

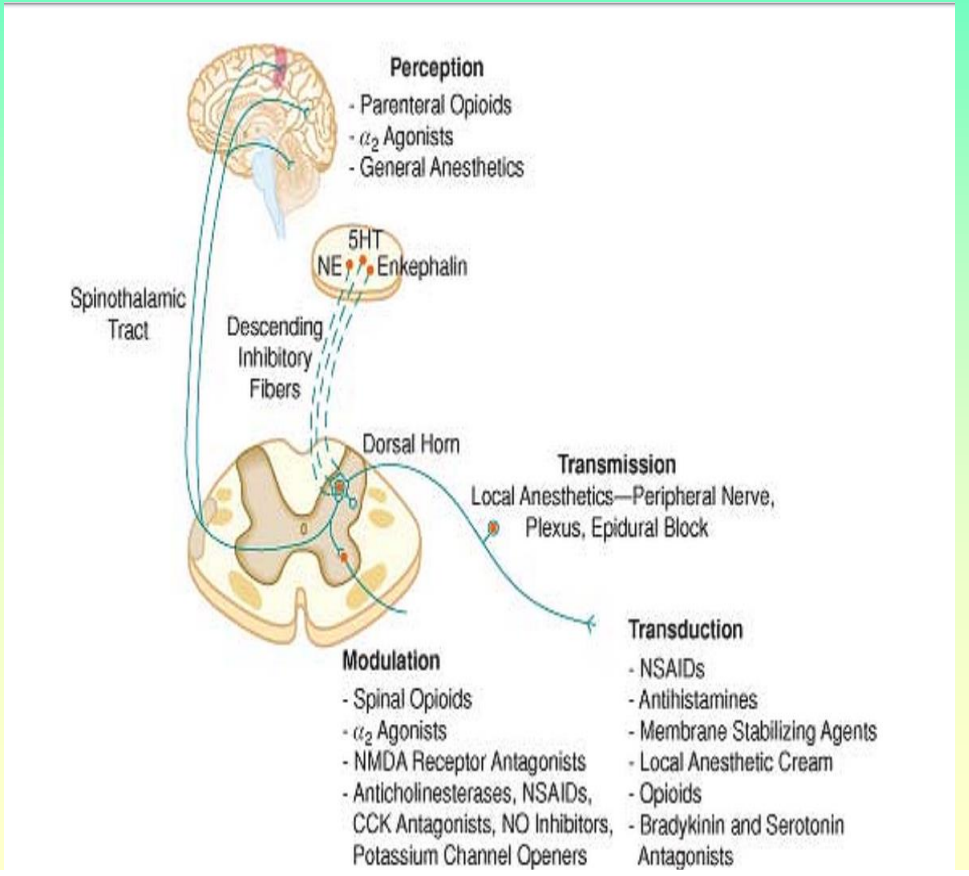
- Nociceptor neurons also express Toll Like Receptors (that is, TLR3, TLR4, and TLR7)
- TLRs can be activated by pathogen-activated molecular patterns, which include viral and bacterial components
- This could be a reason why patients with Chronic Lyme, co infections and chronic viral infections are more likely to develop and maintain chronic pain
- Because of this it is important to decrease chronic infection activity in chronic pain

Peripheral Sensitization:Clinical

- Also to decrease peripheral sensitization it is important to treat the tissues casuing the pain to help them to completely heal and the regions contributing
- Ie treat the tendinopathy with Laser, FSM or Regenerative injection
- Treat the periosteum with laser, FSM, local anesthetic
- Treat the nerve with manual work, laser, FSM
- Treat the visceral tissue ie bronchi, stomach, intestines by decreasing allergy, infection, inflammation and immune reactions

Transduction, Transmission, Modulation, Perception

- Transduction Peripheral: topical NSAIDs, control Inflammation, oral Curcumin, Boswellia, Lidocaine patch, Mast cell stabilizers, Homeopathic gels, Control histamine, decrease Tissue acidity Low level Laser FSM



Sensitization: Regional

- Assess for key Regional structural contributors that overload the pain system including: **Scar dysfunction, Trigger points, Joint Subluxation**, Ligament Laxity, Muscle recruitment dysfunction, Tendinopathy and Bursal Pain, joint capsule sensitization, **Neuropathic pain and Shoe Laxity**
- Determine Points of Leverage to Unload the Pain System to modulate pain and decrease pain sensitization Which regional things to work on first
- Educate your patient especially in regard to the staging and time required for the pain system to change
- Intermittently evaluate the efficacy of your treatment for pain sensitization and for improvement in the musculoskeletal system

Regional Pain

- Patients with regional sensitization and chronic pain need a regional approach to treat the TI(Tissues and Issues with the tissues) part of the TIP along with dealing with any regional factors that are leading to the tissues not healing (ie, scars, Trigger points, shoe laxity, pillows and sleep posture, use in exercise and ADLs, joint laxity, subluxation, joint hypomobility, joint inflammation, visceral inflammation or dysbiosis)

Sensitization

- Important to determine whether there are regional factors or whole body factors or both that are leading to sensitization
- Once you Gather and evaluate the the pain diagram, the patients history, and the physical exam you explain what sensitization and a dysfunctional pain processing system is by showing them the graph and saying something like

Regional Pain: Retell the Story

- After reviewing your pain diagram, your history, your imaging studies and your exam: I have concluded that the tissues that are sending pain signals are:_____

(periosteum, bone, tendon, muscle, nerve, joint, fascia, visceral tissue, blood vessel, scarred, etc.)

- I have concluded that the issue with these tissues are:_____

Torn, partial tear, inflamed, loose, tight, degenerative, bruised, spasm, compressed, poor nerve function, …

Regional Pain: Retell the Story

- I have concluded that there are some contributing factors near the tissue and these are:_____

(Spinal joint inflammation, subluxation, tight muscles, restricted joints near it, excessive motion at your feet or another joint, scar tissue, nerve dysfunction, weak muscles)

- I have concluded that the tissues that are sensitized are:__ and this means: "The receptors are too sensitive and are firing too often. This might be due to: inflammation, allergy, acidic tissue etc or simply how long this has been going on. My goal is to normalize pain processing".

Regional Pain: Retell the Story

- My plan to treat the tissue is:_____ and or to refer you to _____
- My plan to treat the regional contributing factors is: _____
- My plan to decrease the sensitized receptors at the tissue is: _____ Low level laser, Lidocaine patches, topical homeopathic, Frequency Specific Microcurrent, topical antiinflammatory, injection, exercise, etc.
- My additional suggestions to treat the pain are: _____

Regional Pain: Pearls

- For any chronic regional pain condition have a clinician that is experienced with Frequency Specific Microcurrent to evaluate and co treat the patient
- Make appropriate referrals to very experienced PTs, DOs, Chiropractic Drs for evaluation and manual work

Unload the Structural Issues Influencing the Pain System

- Decrease the synergistic inputs to the pain processing system if there is chronic pain or FMS
- Treat the trigger points
- Treat the scars with Neural Therapy injections
- Treat disc extrusions if dural or disc inflammation issues
- Treat the nerve roots and spinal cord if there is stenosis
- Improve muscle recruitment
- Remove the mechanical obstacles to healing and decrease the mechanical factors flaring the tissue up

Tissue Conditions: Issues with the Tissues

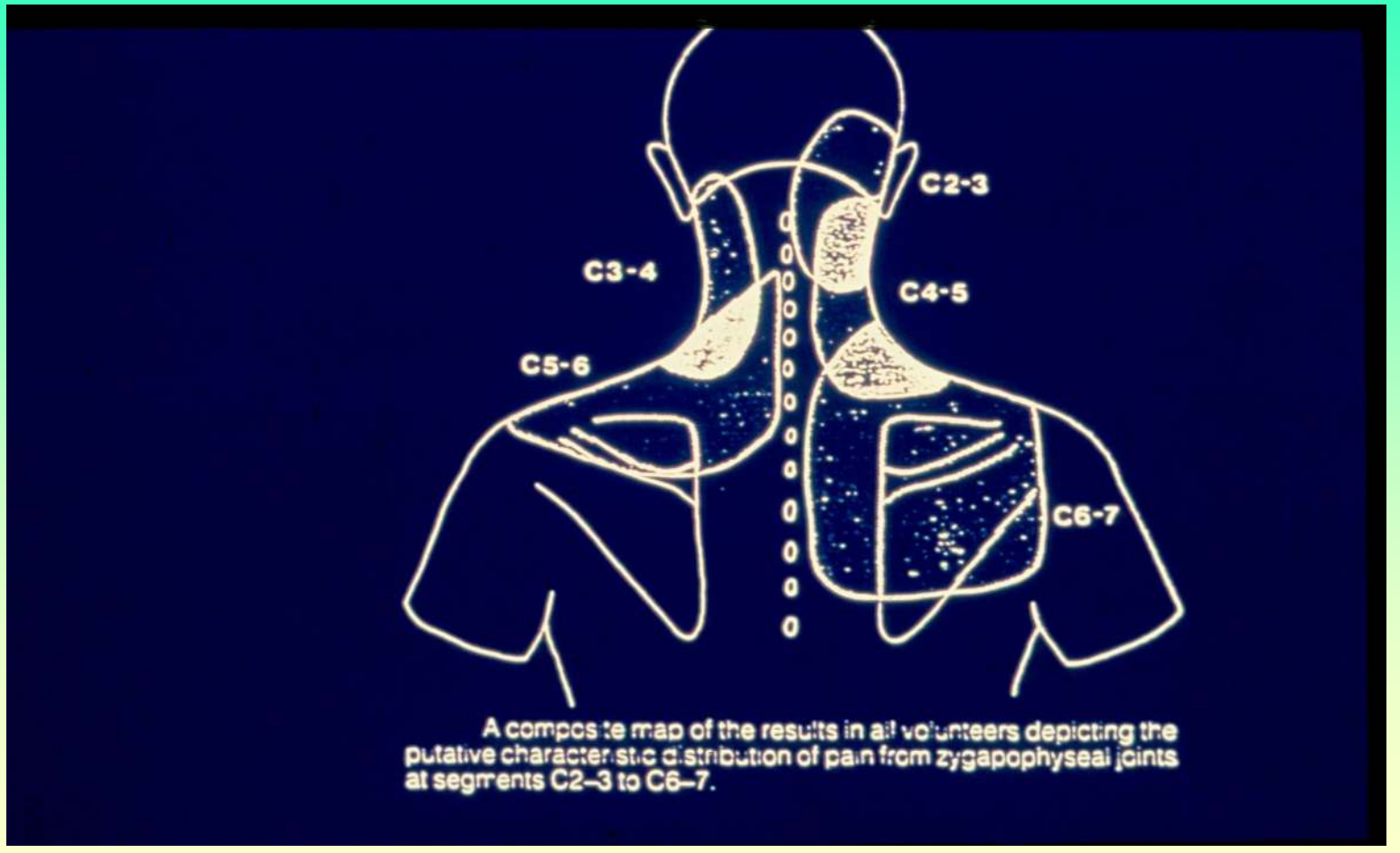
- Any tissue: inflammation, allergy, immune reactions to, tenderness, sensitized, infected, toxin damage, limbic system dysfunction
- Strain: partial or full tear of muscle or tendon
- Sprain: partial or full tear of ligaments
- Tendons: Degenerative, Tendinosis vs tendinitis ie tendinitis or golfers elbow
- Muscles: spasm, trigger points
- Ligaments: degenerative, partially torn, inflamed

Tissue Conditions

- Ligaments: degenerative, partially torn, inflamed or lax
- Note: Patients with hypermobility syndromes ie Ehlers Danlos Syndrome (EDS), Benign Hypermobile Joint Syndrome are at higher risk of developing tendon, muscle, ligament chronic pain because of the laxity especially with spasm and trigger points
- Nerves/Neuropathic Pain: compressed, inflamed, stretched, torn, damaged by toxins
- Joint capsules: ie shoulders can be overstretched, facet joints in the spine can be inflamed or sensitized

Tissue Conditions: Referred Pain

- Bone pain can be due to edema, fracture or sensitization of the **Periosteum**
- Referred pain patterns can help refine diagnosis
- Joint capsules in the cervical and lumbar spine can refer distally
- Ligaments can be felt locally or can refer distally
- Muscles with trigger points frequently manifest as referred pain and the cause is usually not the muscle itself but an issue with the ligaments, joint, nerve , cord etc.



A composite map of the results in all volunteers depicting the putative characteristic distribution of pain from zygapophyseal joints at segments C2–3 to C6–7.

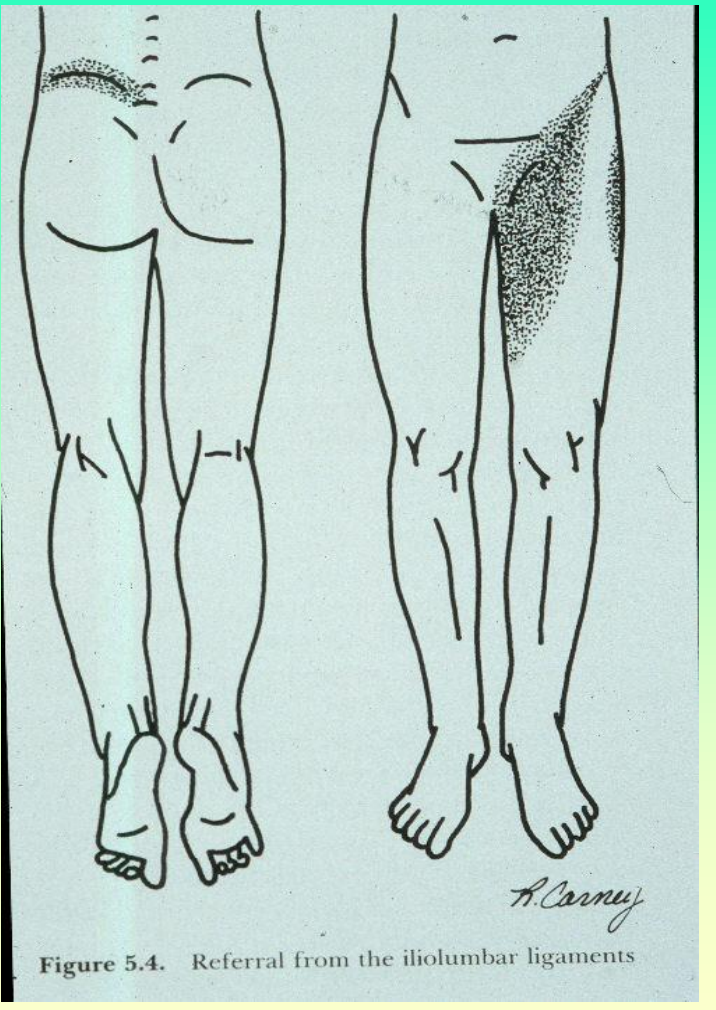
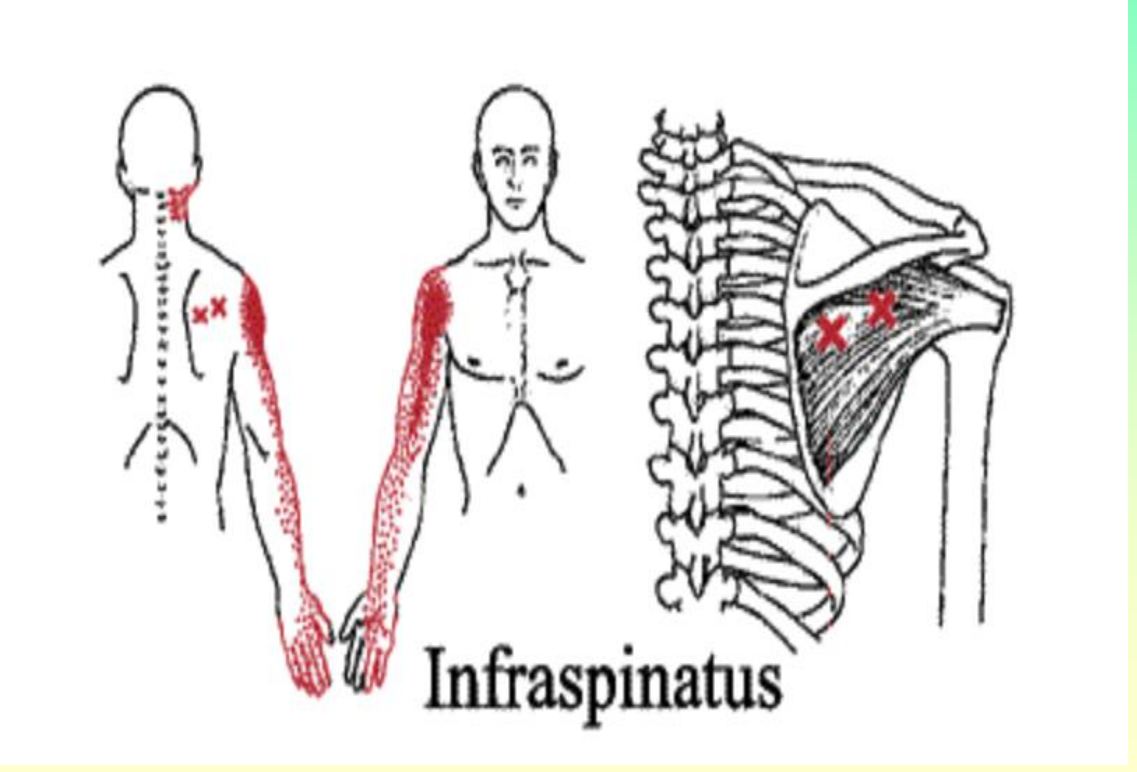


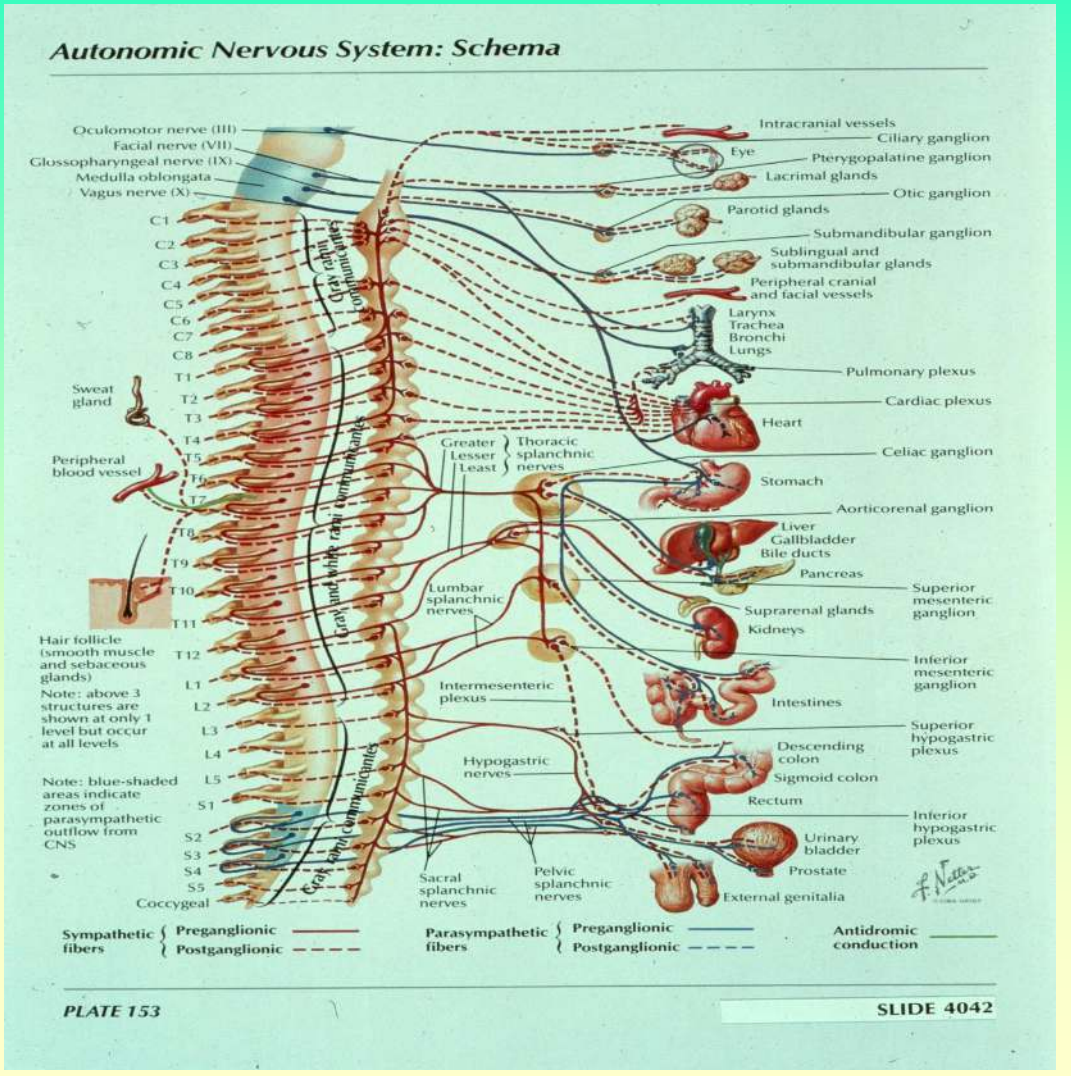
Figure 5.4. Referral from the iliolumbar ligaments

Tissue Conditions: Referred Pain Trigger Points



Tissue Conditions

- Spinal Cord: can be compressed, inflamed, infected but is most often sensitized
- Visceral tissues: lined by a parietal and visceral pleural membrane which can get inflamed and or sensitized
- Visceral organ dysfunction can lead to sensitization of the cord at the levels that the organ is innervated and then cause pain sensitization in the MSK tissue innervated at the same level


Autonomic Nervous System: Schema
Oculomotor nerve (III)
Facial nerve (VII)
Glossopharyngeal nerve (IX)
Medulla oblongata
Vagus nerve (X)
C1
C2
C3
C4
C5
C6
C7
C8
T1
T2
T3
T4
T5
T6
T7
T8
T9
T10
T11
T12
L1
L2
L3
L4
L5
S1
S2
S3
S4
S5
Coccygeal
Gray and white rami communicantes
Gray and white rami communicantes
Sweat gland
Peripheral blood vessel
Hair follicle (smooth muscle and sebaceous glands)
Note: above 3 structures are shown at only 1 level but occur at all levels
Note: blue-shaded areas indicate zones of parasympathetic outflow from CNS
Greater
Lesser
Least
Thoracic splanchnic nerves
Lumbar splanchnic nerves
Intermesenteric plexus
Hypogastric nerves
Sacral splanchnic nerves
Pelvic splanchnic nerves
Intracranial vessels
Ciliary ganglion
Eye
Pterygopalatine ganglion
Lacrimal glands
Otic ganglion
Parotid glands
Submandibular ganglion
Sublingual and submandibular glands
Peripheral cranial and facial vessels
Larynx
Trachea
Bronchi
Lungs
Pulmonary plexus
Cardiac plexus
Heart
Celiac ganglion
Stomach
Aorticorenal ganglion
Liver
Gallbladder
Bile ducts
Pancreas
Superior mesenteric ganglion
Suprarenal glands
Kidneys
Inferior mesenteric ganglion
Intestines
Superior hypogastric plexus
Descending colon
Sigmoid colon
Rectum
Inferior hypogastric plexus
Urinary bladder
Prostate
External genitalia
Sympathetic fibers
Preganglionic
Postganglionic
Parasympathetic fibers
Preganglionic
Postganglionic
Antidromic conduction
PLATE 153
SLIDE 4042

Treating Pain in the Tissues

- Decrease Inflammation: FSM is the preferred modality. Topical Voltaren if very localized and near the surface. Modify use. Work on food allergies, immune reactions(LDI) or other mechanisms of inflammation.
- Regenerate a degenerative tissue: May first start with a modality like FSM, Low Level Laser for tendinosis or mild laxity Note it can take multiple treatments to regenerate a tendon or muscle with FSM or LLLT
- For tendinosis that does not respond: use Prolotherapy or PRP. For degenerative joints refer for Prolotherapy if the ligaments are loose

Treating Pain in the Tissues

- To confirm degeneration in a tendon can use Diagnostic Musculoskeletal Ultrasound
- If a patient is using topical Testosterone may have them apply some of it intermittently over the tendon area to improve regeneration
- Prolotherapy with dextrose and testosterone with or without GH is more effective than with dextrose alone

Treating Pain in the Tissues

- Degenerative joints do not always hurt unless there is sensitization or inflammation of the synovium, capsule or the periosteum
- Short term goals: decrease pain in the synovium, joint capsule and periosteum
- Long term goals: improve the cartilage density, joint space and the synovial fluid and decrease calcification and osteophyte formation

Treating Pain in the Tissues: Degeneration

- Short term goals: decrease pain in the synovium, joint capsule and periosteum
- Decrease pain in the above tissues by decreasing joint inflammation with highly absorbable Curcumin(Meriva, Theracumin, BCM 95), moderate dose Omega 3s especially EPA up to 4 grams per day
- May use proteolytic enzymes for brief periods of time in between meals to decrease joint inflammation

Treating Pain in the Tissues:Degeneration

- Do not simply use Arnica except initially after an injury
- A number of combination homeopathic topicals are helpful to apply 2-3 x a day
- Homeopathic can be used for Nerve pain but the underlying cause must be addressed
- Long term goals: improve the cartilage density, joint space and the synovial fluid and decrease calcification and osteophyte formation

Treating Pain in the Tissues:Degeneration

- Use stabilized vegan Glucosamine Sulfate to provide sulfur precursors for chondrocytes. 750 mg 2 at one time for one large joint or 750 mg 2 2x a day for 2 major areas
- Wait at least 8-10 weeks before judging results
- Add MSM to increase sulfur precursors
- Use Omega 3s and Curcumin

Treating Pain in the Tissues:Degeneration

- Consider Hyaluronic Acid if the problem is in the knee, hip or even the shoulder
- Consider stem cells with signaling factors as they become available and are within the budget of the patient

Treating Pain in the Tissues:Muscles

- Most muscle spasm and pain has an underlying cause that may be related to overuse but may also be related to joint or nerve innervation issues
- Goal is : full strength and recruitment, no spasm or trigger points
- Need to look at motor recruitment for reasons for poor recruitment
- Need to evaluate and treat spinal facet inflammation or malalignment(subluxation) as the facet effects the muscles

Treating Pain in the Tissues: Muscles

- If many muscles are involved think about Fibromyalgia and Cord Sensitization especially in the neck
- If it occurred after a neck injury think about Post Traumatic Fibromyalgia
- Options for treating muscle pain are: Massage(often does not get at underlying cause and may aggravate a TP)
- FSM is probably the best modality because it can treat the underlying factors

Treating Pain in the Tissues: Muscles

- IMS or trigger point injections can treat individual muscles
- Prolotherapy may be needed if TP keep recurring in the setting of hypermobile joint regions
- Magnesium oral and topical should be given for increased tone and spasm
- Physical therapy can be used for improving recruitment
- Chiropractic can be used to normalize subluxations and improve spinal joint position

Exercise Modulates Pain

- Aerobic exercise done in a 70-80% heart zone is essential for any regional or generalized pain
- It helps release the body's own endogenous opioids
- It releases stress and decreases excessive tone in muscles
- It helps lymphatic drainage

Diffuse Chronic Pain: Central Sensitization

- For these types of patients you must deal with sensitization in the periphery as well as the Cord and brain in order to have lasting effects on their pain
- Evaluate what you presume is in their tissues setting off the nociceptors as well as what is sensitizing their CNS
- Analyze lifestyle factors as well as parts of the matrix in each patient to determine which may be the most important to work on
- Determine how you will stage your interventions, explain why you will be treating these in regard to their pain

Sensitization Cord and Brain

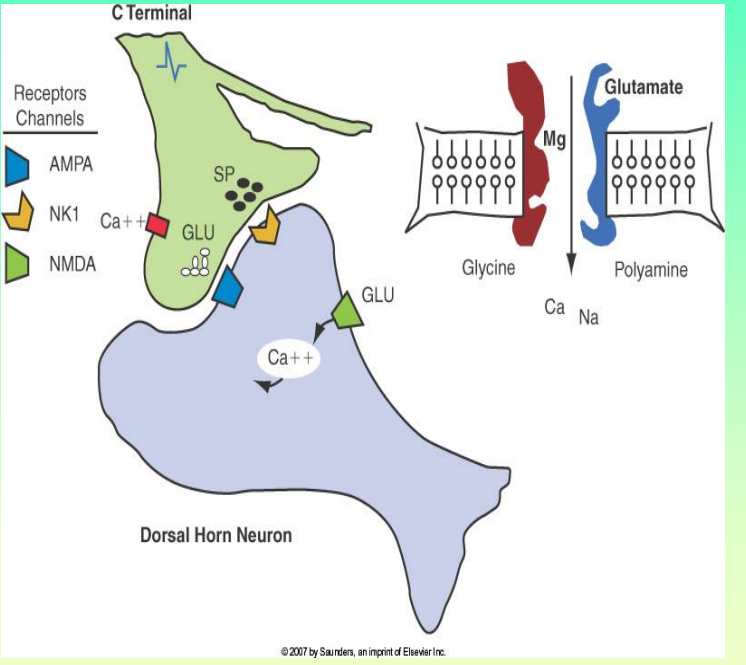
- The sensitization of central nociceptive neurons can occur in the spinal cord, trigeminal nucleus, brain stem and cortex

Spinal Cord Anatomy and Physiology Review

- Afferents terminate in the dorsal horn of the spinal cord (SC)
- There are nociceptive specific and Wide Dynamic Range neurons WDR
- WDR neurons may be affected by low frequency repetitive stimulation of C fibers until the neuron is in a state of continuous discharge “Wind up”
- Clinical Pearl: Poor posture in sitting, sleeping or standing is important to correct because it can send repetitive stimulation and lead to wind up

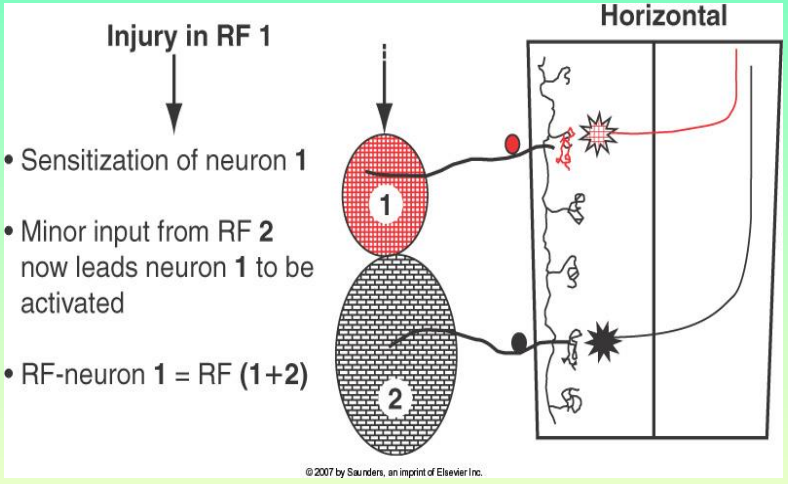
Spinal Cord Anatomy and Physiology Review: NMDA Receptors

- There are modulatory systems in the cord
- One of the modulatory systems in the cord is regulated by NMDA receptors
- This is a picture of a synapse of a C fiber and dorsal horn neuron



Consider a trial of an NMDA blocker to be more effective like Dextromethorphan. Decrease free calcium in supplements

Spinal Cord Anatomy and Physiology

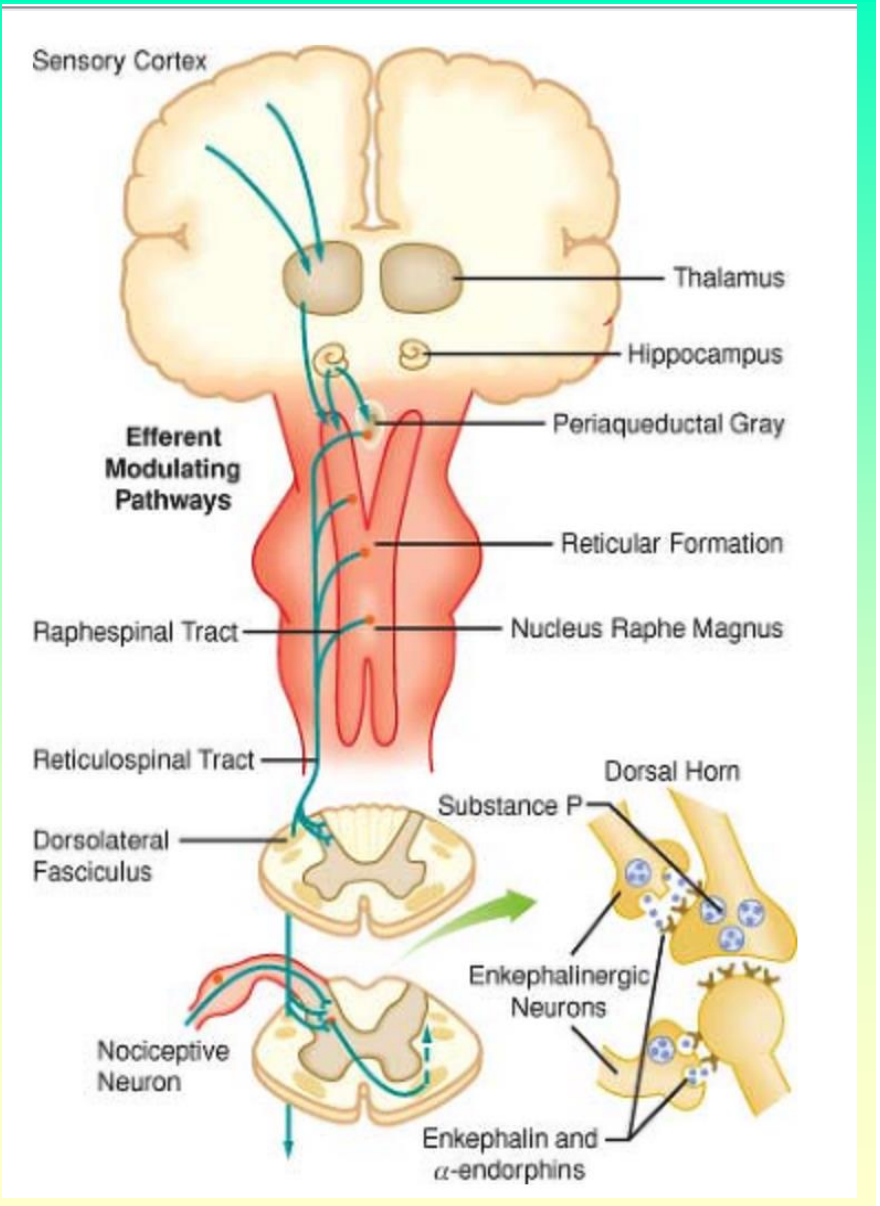


This is why working on regional factors are very important to decreasing cord sensitization. For example a scar

- Primary afferents also send axons rostrally and caudally
- Input from a single level can influence the excitability of neurons in segments a number of dermatomes away from the chronic pain problem

Descending System

- This system acts on motor function as well as effects inhibition. Limbic System is also involved in regard to the memory and emotional component of pain



Transduction, **Transmission, Modulation**, Perception

- Transmission

Peripheral Nerve:

FSM

Manual Therapies

Modulation Cord:

NMDA antagonist:

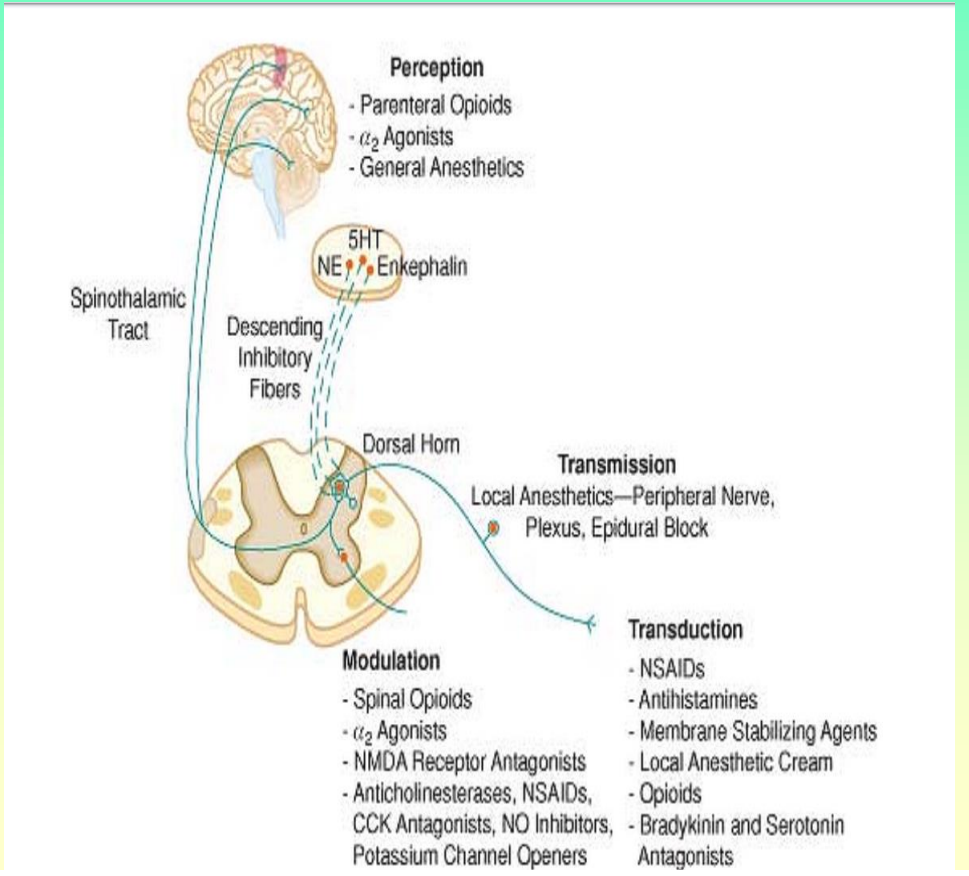
Dextromethorphan

Control inflammation

Treat noxious MSK pain

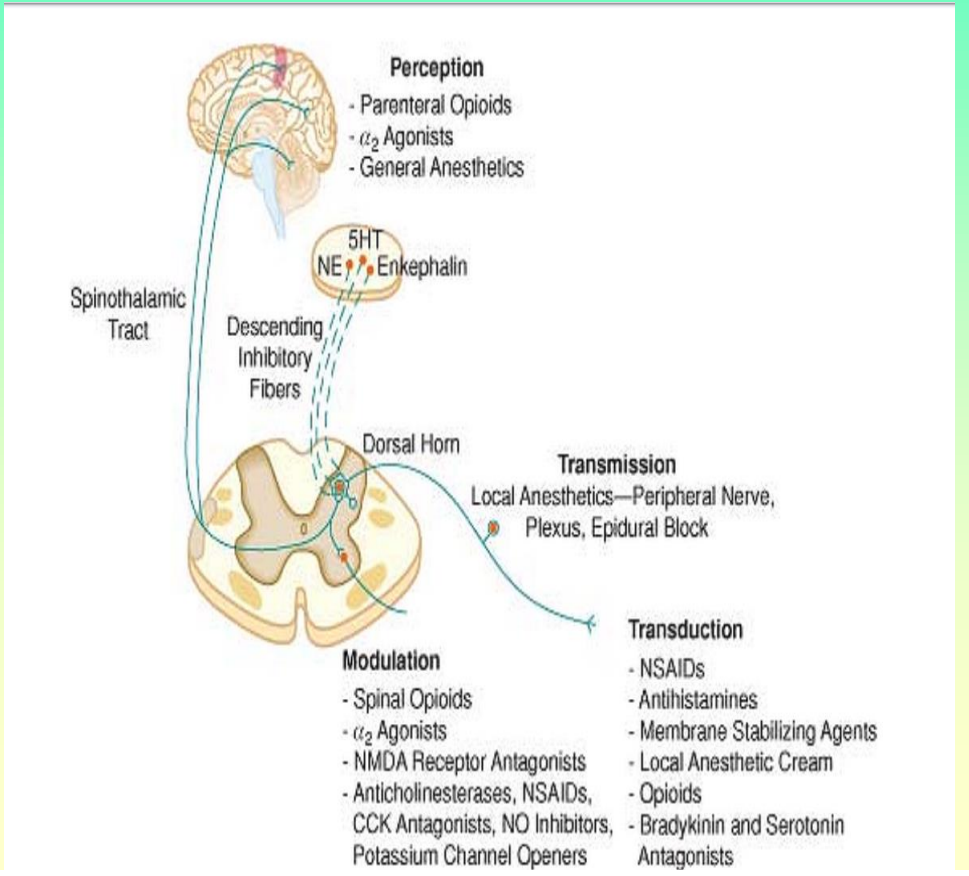
Generators,Aerobic exercise

FSM



Transduction, Transmission, **Modulation, Perception**

- Modulation Thalamus and cortex
- Aerobic exercise
- FSM
- Counseling
- Tapping(EFT)
- Mindfulness
- Stress management
- Control neuroinflammation
- Decrease excitotoxicity



Sensitization Cord and Brain

- There are very few methods to directly modulate sensitization and inflammation in the cord and the brain
- Frequency Specific Microcurrent(FSM) is a uniquely capable modality to treat the sensitization in the peripheral tissues as well as the cord and the brain. It has condition frequencies like 40 for inflammation, 9 for allergy, 94 for removing trauma to the nervous system and 10 for the cord and 89 for the Thalamus and mid brain that enable it to be used to directly improve pain processing. For further information look at the book FSM in Pain Management or the research articles: https://frequencyspecific.com/papers

Central Sensitization: Clinical

- A number of receptors may play a role in Cord and brain sensitization including TLR4 and NMDA receptors
- Central sensitization is very related to neuroinflammation with activation of glial cells, such as Schwann cells in the nerve, satellite glial cells in the ganglia and microglia, and astrocytes and oligodendrocytes in the spinal cord and brain

Central Sensitization: Neural Inflammation

- **Neuroinflammation in the spinal cord can be a major mechanism of chronic pain via neuron–glial interactions and central sensitization**

Central Sensitization: Neural Inflammation

- Limiting and blocking TNF alpha (expressed by microglia, astrocytes and primary sensory DRG neurons) may have significant effects on decreasing cord sensitization
- Blockade of TNF-α rapidly inhibits pain responses in the central nervous system.*Hess A, Axmann R, Rech J, Finzel S, Heindl C, Kreitz S, Sergeeva M, Saake M, Garcia M, Kollias G, Straub RH, Sporns O, Doerfler A, Brune K, Schett G*
- *Proc Natl Acad Sci U S A. 2011 Mar 1; 108(9):3731-6*
- For patients with diffuse Chronic pain measure antibodies to the BBB and treat to heal the BBB if positive

Central Sensitization: Neural Inflammation

- Resolvins and Protectins may be able to block TNF alpha and be useful in modulating central nervous system inflammation in chronic pain

Nat Rev Drug Discov. 2014 Jul; 13(7): 533–548.
Published online 2014 Jun 20. doi: 10.1038/nrd4334

Emerging targets in neuroinflammation-driven chronic pain

Ru-Rong Ji,[1] Zhen-Zhong Xu,[1] and Yong-Jing Gao[2]

Central Sensitization

- The key contributors include: Lifestyle: Sleep, Mood, Stress, sedentary, inflammatory high toxin GMO diet
- Start by working on sleep and diet then exercise and then stress

Key Matrix factors affecting sensitization: Biotransformation(mold, toxins in the tissues) Defense and Repair(autoimmune, chronic inflammation, chronic infections) Assimilation(GI inflammation, Dysbiosis nutritional deficiency) Energy: (mitochondrial dysfunction), Communication (Adrenal fatigue, hypothyroid, Sex Hormone dysfunction), Attitude Dysfunction

When approaching Matrix issues you will need to figure out what interventions will make the most difference in pain with the least expense and time.

Start with an approach to normalize the GI tract, work on cognitive and emotional aspects of pain, then correct Hormone issues …

Sensitization: How to Tell the Story

- "After gathering all of this information I have determined that one of the issues regarding your pain is that your pain processing system is sensitized. This means it sends pain messages with a lower threshold which means it takes less to trigger the pain or you can experience a higher level of pain. If their pain is constant include the following: It also appears that your pain processing system is involved with generating pain messages and creating constant pain. In order to relieve your pain for the long run we will also need to improve your pain processing system.

Sensitization: How to Tell the Story

- One of my goals for you is to move you up in the pain processing graph towards or to the normal level
- For this I am recommending:_____”
- If you want to get more specific for a complex case you can also say: To work on the tissues near the pain receptors I recommending: _____
- To Work on the nerve endings and connections in the spinal cord processing I am recommending:_____
- To work on the brain centers for pain processing I am recommending: _____

Sensitization: Central: Pearls

- Watch for EDS patients with diffuse chronic pain
- They will need Frequency Specific Microcurrent and a close look into triggering factors and perpetuating factors under Defense and Repair
- They seem to be developing not only regional pain but expanding central sensitization pain from things like mold biotoxins, chemical exposures, Mast Cell activation Syndrome, and possible autoimmune mechanisms. They can develop other problems like POTS, Hypertension, Vagal Nerve dysfunction, SIBO…

Opioid Use

- Opioid use is very common for patients with MSK and non MSK non cancer pain because clinicians are practicing labeling and matching approaches to pain ie You have _____ . I will prescribe that _____
- Also some patients are already on Opioids and are asking for them because some other clinician retired or started a no narcotic policy in their office.
- Patients have been put on an opioid for acute moderate to severe pain conditions and now have progressed to tolerance, addiction and or Chronic pain sensitization

Opioids:Common Clinical Scenarios:

- The patient is on a narcotic and you see them for SIBO, Constipation, IBD or IBS. You are having trouble getting the GI condition better because the Narcotic is effecting GI motility.
- The patient makes an appointment with you for a MSK pain and at the end of the visit is insisting on a Narcotic because they have been on one previously. You feel uncomfortable and don't know what to do because you want to do a FM approach to their pain and they are not interested in that.

Opioid Use

- The patient agrees to work with you because they think FM is cool but later does not comply with your recommendations to get to the causes and simply wishes to keep filling a narcotic
- You see a man with Low T and wonder if it is the Narcotic they are on
- You see someone with EDS who is on lower dose narcotics(is is requesting higher doses) for generalized muscle spasm. She has multiple associated conditions: Asthma, SIBO, severe regional joint hypermobility.

Opioid Use

- The patient is on moderate to high doses of a Narcotic and they have decided to wean the narcotic with your help. How do you safely do this?
- A FMS patient is already on a Benzo, a Narcotic and a muscle relaxant and is seeing you for pain and anxiety. He has significant fatigue, low T, anxiety, muscle pain and Depression. What are the risks of these 3 medications together and what are the risks of weaning this patient?

Opioid Use

- You see a patient for Traumatic Brain Injury who was put on Percocet for neck pain. He sees you because his brain and gut are not working well. What should you do about the Narcotics?

Opioid Receptors

- Endogenous opioids are inhibitory neuropeptides in the dorsal horn of the spinal cord or the brain.
- Enkephalins, dynorphin, and β-endorphin arise from intrinsic spinal interneurons
- They bind to G protein-related receptor complexes that fall into three major classes: the μ-opioid receptors (MOR), the κ-opioid receptors (KOR), and the δ-opioid receptors (DOR).
- Ballantyne, Jane C.,Fishman, Scott M.,Rathmell, James P.. Bonica's Management of Pain (Kindle Locations 8651-8653). Wolters Kluwer Health.

Opioid Receptors

- MOR Mu 1 receptors in the brain: pain relief, physical dependence
- Mu 2 respiratory depression, euphoria, dependence
- Mu2 in the cord decreased GI motility

Opioid Receptor Actions

- These receptors influence pain, stress responses and affect
- Actions of Opioid receptor binding:
- MOR agonists promote pain reduction, a feeling of reward, euphoria and stress modulation
- They work at Spinal and Supraspinal locations

MOR binding leads to stress reduction via direct inhibition of norepinephrine locus coeruleus (LC) neurons and tones down the activation of this central stress response system

Opioid Mechanisms:References

- Curtis AL, Bello NT, Valentino RJ. Evidence for functional release of endogenous opioids in the locus ceruleus during stress termination. J Neurosci. 2001;21:RC152.
- Curtis AL, Leiser SC, Snyder K, Valentino RJ. Predator stress engages corticotropin-releasing factor and opioid systems to alter the operating mode of locus coeruleus norepinephrine neurons. Neuropharmacology. 2012;62:1737–45

Opioid Side Effects and Risks

- Tolerance, Escalating Dose
- Addiction and dependence
- Depression, Insomnia, Brain Fog
- Anxiety especially during breakthrough periods
- Respiratory Depression
- Lowered Testosterone
- Constipation
- SIBO
- Respiratory Depression

Opioid Side Effects and Risks

- *The risk of Depression as a side effect of Narcotics appears to increase significantly after 90 days on the medication*
- *"Some of these include opioid-induced resetting of the brain's 'reward pathway' to a higher level, which means the chronic use of narcotic pain killers can elevate the threshold for a person's ability to experience pleasure from natural rewards"*

J Gen Intern Med. 2014 Mar;29(3):491-9. doi: 10.1007/s11606-013-2648-1. Epub 2013 Oct 29.

Prescription opioid analgesics increase the risk of depression.

Scherrer JF[1], Svrakic DM, Freedland KE, Chrusciel T, Balasubramanian S, Bucholz KK, Lawler EV, Lustman PJ.

Opioid Side Effects: Testosterone

Opioids(especially Hydrocodone, Oxycodone and Morphine) use can lead to low testosterone levels and decreases in libido and adverse changes in body composition. Tramadol does not seem to cause this SE.

- Opioids can down-regulate the hypothalamic–pituitary–gonadal axis to produce very low testosterone levels.
- Opioids may suppress adrenocorticotropic hormone secretion from the anterior pituitary.
- All patients on Opioids for more than 4 weeks should have their T levels checked
- Testosterone replacement in patients on Opioids with low T can actually improve pain response to opioids and may enable tapering of the dose

Opioid Side Effects: Testosterone

ELSEVIER

Drug and Alcohol Dependence

Volume 149, 1 April 2015, Pages 1-9

Review

Testosterone suppression in opioid users: A systematic review and meta-analysis ☆

Monica Bawor [a, b], Herman Bami [c], Brittany B. Dennis [b, d, e], Carolyn Plater [f], Andrew Worster [f, g], Michael Varenbut [f], Jeff Daiter [f], David C. Marsh [f, h], Meir Steiner [i, j, k], Rebecca Anglin [g, i], Margaret Coote [j], Guillaume Pare [b, e], Lehana Thabane [e, l], Zainab Samaan [b, e, i]

Opioid Side Effects: Estradiol

Tramadol, Fentanyl and Gabapentin have been shown to lower levels of free Estradiol in woman

Lyrica does not appear to have as much of this effect

Drug Testing and Analysis / Volume 9, Issue 10

RESEARCH ARTICLE

An exploratory study Evaluating the impact of opioid and non-opioid pain medications on serum/plasma free testosterone and free estradiol concentrations

Julie A. Ray ✉, Mark M. Kushnir, A. Wayne Meikle, Jill E. Sindt, Frederick G. Strathmann

First published: 09 February 2017

Opioid Tolerance

- Tolerance is a phenomenon that occurs when patients have been on Opioids for a while(and may even start after one month of Opioids) in which the same dose leads to less pain relief
- Clinically this results in more pain and requesting escalating dose of Opioids or pain behaviors or new injuries to get higher doses of opioids
- A patient may request a higher drug dose ie 30 mg of Oxycodone and will insist that a lower dose does nothing and that they do not want it

Opioid Dosing Problems

- Higher dose requests or using medications faster than one month can lead to:
- Escalating doses and running out early with demands for early refills
- Periods of adequate pain relief and breakthrough pain because the half life of the Opioid is short
- Periods of adequate pain relief and withdrawal because they run out of the medication
- Major stress for the Clinician and the front desk!

Opioid Tapering, Weaning

- Tapering Opioid doses is indicated in many clinical situations:
- The patient or family members requests to taper
- The patient has nerve pain and is not responding to Opioids
- The patient has SIBO and or Constipation and you can not get control of it
- They are not showing a 30% reduction in symptoms from the dose of opioid
- They are above 50 mg Morphine equivalents and you cannot get a Pain Management Dr to agree that they need the dose that they are on

Opioid Tapering, Weaning

- You are treating their tissues and pain sensitization and they do not need as much or any narcotic
- A woman on narcotics is showing signs of low Estradiol

Weaning Opioids

- Weaning Opioid doses needs to be done slowly to avoid withdrawal symptoms
- Withdrawal Sx: N, V, tachycardia, anxiety, abdominal pain, Hypertension
- When to wean:

There are guidelines according to the CDCand for individual states:

Opioid Dosing Weaning Problems

- Most opioid problems result from short half life medications, tolerance, too high a dose of a medication ie 2 10 mg of Hydrocodone or 30 mg of Oxycodone and breakthrough pain as well as the side effects listed previously.
- When tapering Oxycodone or Hydrocodone or weaning try to get the patient on a longer acting medication to avoid break through pain like:
- Oxycontin, Hysingla or long acting MS
- Try to get them off dosing of higher doses such as 30 mg of Oxycodone 2-3 x a day or Norco 10 mg 2 at a time 3-4x a day

Opioid Dosing Weaning Problems

- Consider tapering the dose by 10% every 2-4 weeks after you have educated them regarding the reasons for tapering
- While tapering address the following:

Underlying causes of pain in the tissues

Treat the pain processing system

Increase exercise if possible

Treating Low T in men on Opioids can reduce dosage

Make recommendations re anxiety, Sleep and mood issues

Consider referral for Frequency Specific Microcurrent to treat the underlying tissue

Set office policies for Opioids

Opioid Dosing Policies

Set office policies for Opioids:

Use a Narcotic Agreement for every patient and use a new one at least every 2 years

Have every patient fill out a Pain and function questionnaire at least 3x a year

Have every patient on Opioids do a urine drug screen one time per year

If a patient is on more than 50 mg Morphine equivilants have them see a Pain management specialist to do a pain consult to determine if that Dr agrees with the dosing as is or has specific recommendations for changing it.

Opioid and Pain Genomics

- Mu-opioid receptors (MOPRs) are very important in the modulation of pain and analgesia by Opioids
- The **G** allele variation OPRM1A118G, rs179997 has been linked to reduced expression of OPRM1.
- This variation has been linked to higher pain intensity and slower recovery from certain injuries such as a herniated disc.
- Patients with the **G** allele may need higher doses of opioids to achieve pain relief compared to **A/A** controls.

Opioid and Pain Genomics

- COMT genotype may impact response to opioids
- COMT Val/Val (higher COMT activity) individuals may require higher doses of Opioids
- RS4680 Val 158/Met COMT activity can lead to increased opioid receptors and enhances opioid analgesia and lead to more side effects from Opioid drugs
- COMT Met/Met (low activity) patients can get analgesic effects with lower doses

Opioid Biotransformation and Pain Genomics

- Opioid Biotransformation:
- Fentanyl is metabolized predominantly metabolized in the liver by CYP3A4-mediated N-dealkylation Patients with the CYP3A5*3 SNP can have higher fentanyl levels for the same dose given to a patient without this SNP
- Morphine is metabolized to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) via glucuronidation by phase II metabolism of UDP-glucuronosyl transferase 2B7 (UGT2B7)
- There are two variants of the UGT2B7 gene

Opioid Biotransformation and Pain Genomics

- Tramadol is metabolized in the liver by demethylation, oxidation and conjugation
- O-demethyl-tramadol (M1), is the main active metabolite and is the result of the action of CYP 2D6 and is two to four times more potent than the parent compound.
- Poor metabolizers have 14-fold lower concentrations of the active metabolite and may have less analgesic efficacy

Opioid Biotransformation and Pain Genomics

- CYP2D6 is involved in the metabolism of Codeine, Tramadol, Oxycodone and Hydrocodone into their more potent metabolites
- CYP2D6 Ultra rapid and poor metabolizers should avoid the above drugs as they could be very hard to arrive at a reasonable dose

Opioid Biotransformation and Pain Genomics

The genes that most affect pain are Summarized in the table to the right. Consider screening for these genes in Cancer patients with pain, as well as patients that are difficult to taper or difficult to control their pain.
You could also make it a requirement in your practice that you would screen these genes in any patient that wants to be on an opioid for more than 2-3 weeks.

CYP2D6 genotype: Ultrarapid metabolizer *1/*1×N; *1/*2×N; *2/*2×N; Extensive metabolizer: *1/*1; *1/*2; *2/*2; *1/*9; *1/*10; *1/*41; *10/*10; *41/*41; *1/*3; *1/*4; *1/*5; *1/*6; Intermediate metabolizer: *4/*41; *5/*9; *4/*10; Poor metabolizer *3/*4; *4/*4; *5/*5; *5/*6. COMT (rs4680)-also identified as G472A, G586A, Val108Met and Val158Met. OPRM1 rs1799971.

Opioid and Pain Genomics

- The reference below is the best summary of genomics in pain management

Mol Med Rep. 2019 Mar;19(3):1423-1434. doi: 10.3892/mmr.2018.9792. Epub 2018 Dec 24.

Pain polymorphisms and opioids: An evidence based review.

Vieira CMP[1], Fragoso RM[1], Pereira D[1], Medeiros R[2].

Opioid and Pain Genomics

- The reference below is a summary of other genetic biomarkers that may predict the development of more significant pain or visit for pain to an Emergency Room. Of interest a number of these could be modulated favorably by Vit B6 and B12. Thus every patient with pain should be on a multiple Vit or B complex.

Molecular Psychiatry
https://doi.org/10.1038/s41380-018-0345-5

IMMEDIATE COMMUNICATION

Towards precision medicine for pain: diagnostic biomarkers and repurposed drugs

A. B. Niculescu[1,2,3] · H. Le-Niculescu[1] · D. F. Levey[1] · K. Roseberry[1] · K. C. Soe[1] · J. Rogers[1] · F. Khan[1] · T. Jones[3] · S. Judd[1] · M. A. McCormick[1] · A. R. Wessel[1] · A. Williams[3] · S. M. Kurian[4] · F. A. White[2,3,5]

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Osteoarthritis and Joint Degeneration

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More than 40 million Americans have osteoarthritis (OA).

Introduction

- Chondrocytes comprise the entire cellular matrix of the joint. The substrate of the extracellular matrix is comprised of collagen and polysaccharides known as glycosaminoglycans (GAGs). Substantial GAGs in the extracellular matrix include hyaluronic acid, chondroitin-4-sulfate, chondroitin-6-sulfate, dermatan sulfate, and keratan sulfate. The primary roles of the extracellular matrix include absorbing shock, maintaining viscosity, and nourishing chondrocytes. The primary role of the chondrocytes is the ongoing synthesis of matrix components.

Introduction

- Chondrocytes may be affected by a number of factors, including: cytokines, polypeptide growth factors, matrix components and biomechanical stimuli.
- The Structural Integrity of the joint is dependent on the function and quality of the chondrocyte and the extracellular matrix.
- The loss of structural integrity of a knee or hip affects a persons ability to walk and or exercise

Introduction

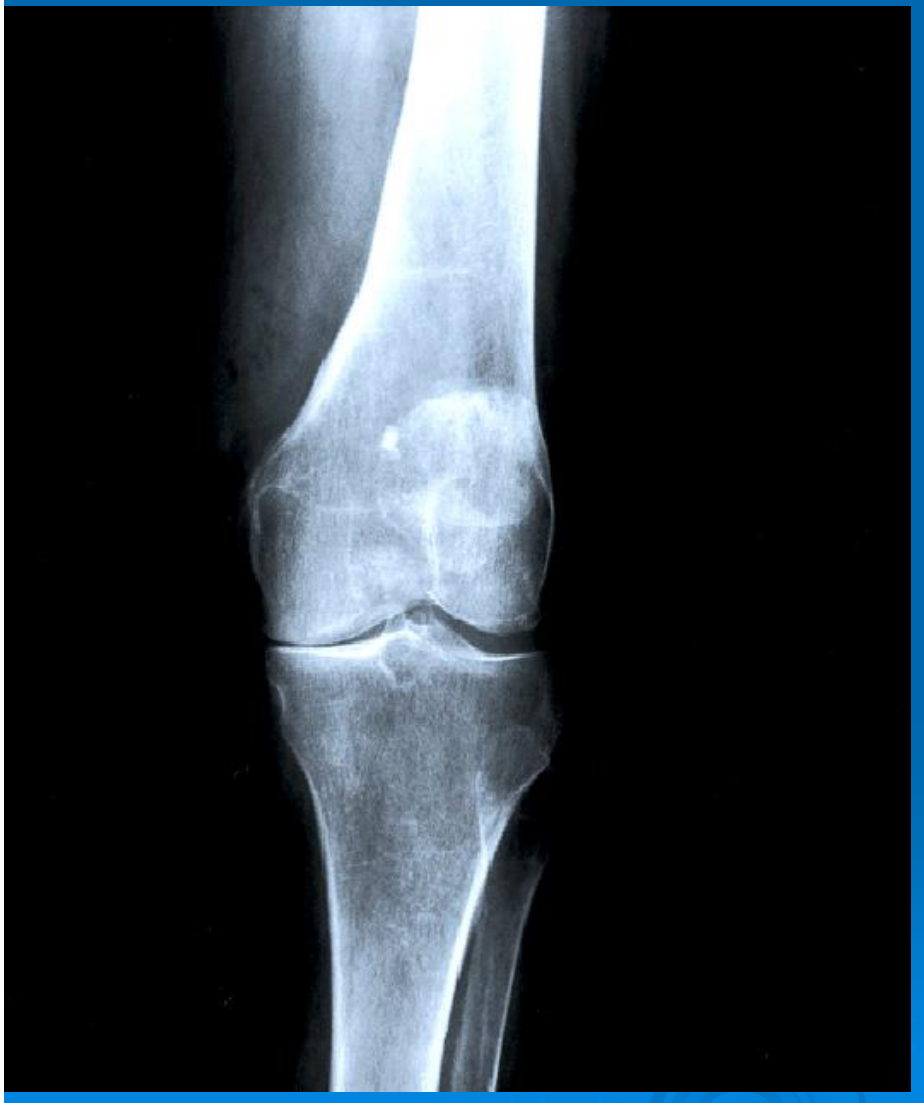
- Loss of structural integrity can lead to less ability to exercise leading to increased stress and poorer sleep
- That in turn can lead to systemic and/or brain inflammation and decreased insulin sensitivity

Introduction

- OA progresses when tissue regeneration cannot keep pace with the rate of cartilage loss.
- Joint damage may occur when the biomaterial properties of the articular cartilage are inadequate or the load on the joint is excessive.

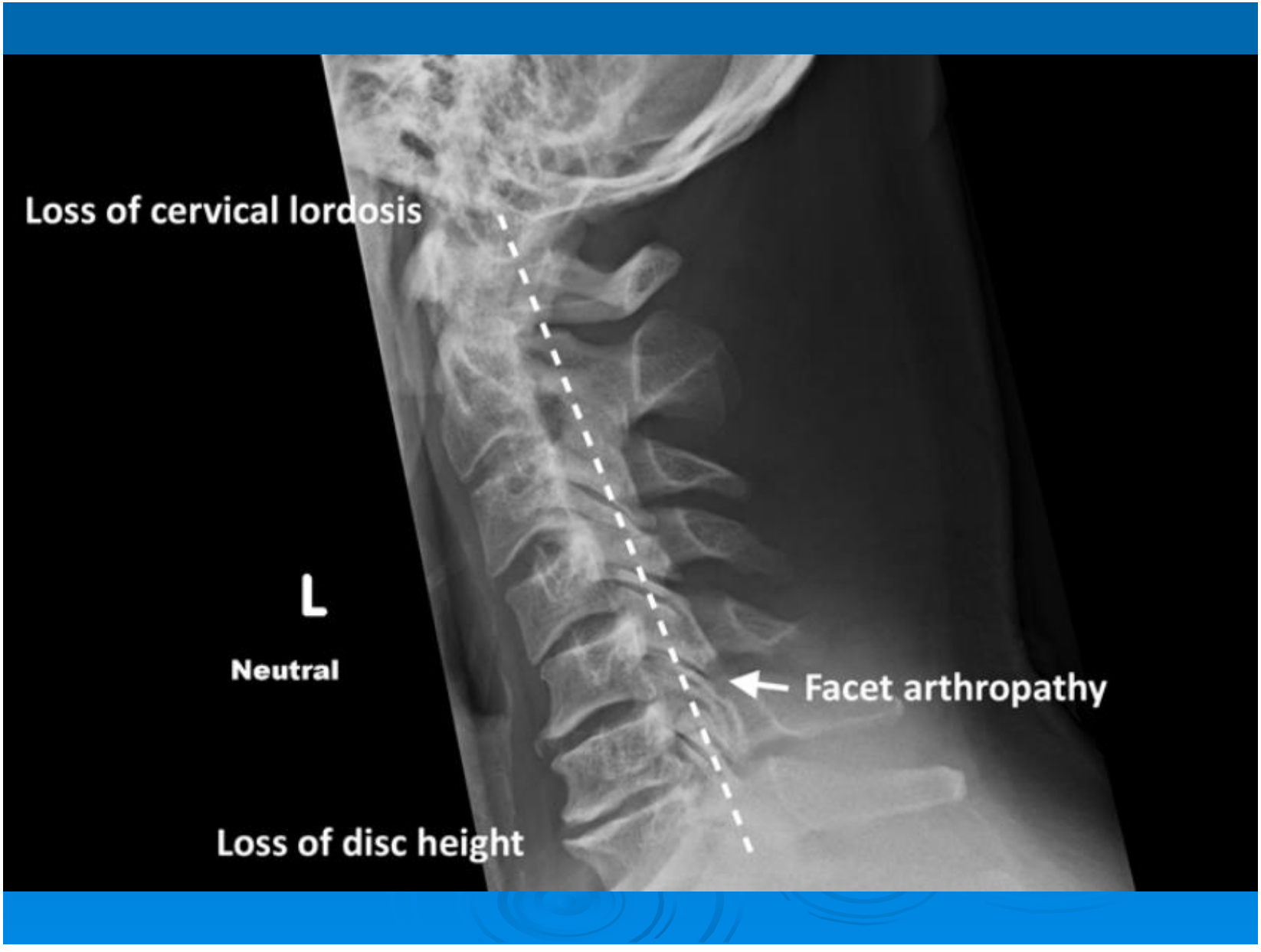
Osteoarthritis (OA)

- Most people that have OA have it in the knee, hips and/or spine
- OA can cause pain, cessation of exercise and enjoyable activities and can contribute to excessive stress, Insomnia, Type 2 Diabetes,
- OA consists of changes of:
- Joint space narrowing, bony spurs, cysts
- Thinning or loss of parts of the articular cartilage or of the meniscus cartilage (if the knee)
- The changes are not symmetrical
- There can be bone changes with edema



Spinal Joint Pathology

- All of the above plus disc degeneration and decreased height and function
- Facet joint arthropathy with narrowing and spurring and possibly facet cysts
- Facet arthropathy with decreased range of motion or facet inflammation
- Stenosis of the foramen or central canal with cord or nerve root symptoms


Loss of cervical lordosis
L
Neutral
Facet arthropathy
Loss of disc height

OA Post Traumatic

- Certain patients that have OA or DJD may have it asymptomatic
- Asymptomatic OA can become symptomatic after a sprain injury because of the damage to cartilage and or bone
- This can set up inflammatory mediators
- It is very important to recommend biomechanical and supplement approaches very soon after the trauma to limit cartilage loss

Pathophysiology

- Cartilage fibrillation
- Cartilage swelling
- Chondrocyte clusters
- Phenotypic change to “hypertrophic chondrocyte” producing type X collagen and matrix metalloproteinase (MMP)-13
- Production of proteases triggered by proinflammatory cytokines and fragments of matrix proteins
- This leads to more loss of chondrocytes
- Synovitis develops and can be a source of pain

OA Pathophysiology

- Inflammation(COX(PGE2), LOX(Leukotrienes) and inflammatory cytokines, NFK B)
- Enzyme breakdown(proteases)
- Synovial fluid dysfunction
- Decrease in nutrient support for chondrocytes and decreased repair and maintenance of cartilage

Pathophysiology: Bone

- Bone pathology:
- Thickening of subchondral bone(sclerosis)
- Bone spurs
- Facet Arthropathy
- Bone edema
- NOTE: pain generation can be from bone edema or from periosteal pain
- Exam: always palpate the bony surfaces in a patient with OA
- Goal: decrease bone edema and treat Periosteal pain with laser or Frequency Specific Microcurrent(FSM)

Articular Cartilage

- Articular Cartilage lines every joint
- It is composed of Chondrocytes and Matrix
- It is different than the meniscus cartilage of the knees(Only the outer 1/3 of the meniscus cartilage in the knee has a reasonable blood supply)
- The nourishment for the cartilage comes from the synovial fluid

Articular Cartilage

- It provides a gliding surface for the joint
- It may loose depth or become come completely denuded
- It can be damaged slowly by abnormal mechanical forces such as malalignment due to loose ligaments or very tight muscles or quickly by trauma
- Cartilage can be bruised, heels slower than ligaments and tendons. may not fully repair and both degenerative cartilage and meniscus benefit from support

Antecedent Factors

- Obesity is a major contributor to long term joint degeneration.
- Macrophages in adipose tissue produce proinflammatory cytokines, IL-6 and TNF-alpha.
- Adipocytes produce leptin and leptin can have damaging effects on joints
- SNPS: genes that code for growth and differentiation factor (GDF)-5, which is a bone morphogenetic gene that plays a role in joint development

Antecedent Factors

- Aging changes(not the same as DJD)
- Inflammatory, GMO, Toxin filled diets (and or Nightshade) filled diet can contribute to joint inflammation
- Altered mechanics that place excessive and abnormal loads on a joint can activate mechanotransduction pathways that result in increased production of inflammatory mediators and proteolytic enzymes

Altered Biomechanics(AB)

- AB can lead to abnormal forces on a joint that can lead to loss of cartilage surface.
- Causes:
- Flattened arches or overpronation can contribute to knee, hip or back OA
- Weak muscles will not move a joint properly and if they go on long enough can lead to progressive OA
- Hypermobility

Mechanical Factors: Hypermobility

Mechanical forces from:

lose or hypermobile joints lead to abnormal forces on joint cartilage and matrix with loss of cartilage and inadequate repair and lead to progression of OA

Examples: Knees with loose MCL, LCL or posterior lateral corner(stress test varus valgus and posterior lateral corner)

Laxity of the neck at C2,3 C5,6,7(flexion extension of the neck)

Laxity of the Lumbar and Sacroiliac(H and I test and Sacroiliac stability tests

Mechanical Factors: Hypermobility

For the long term strategy for joint health consider doing ligament stability tests referring for Prolotherapy for a patient that is hypermobile in a joint that is developing OA

It is an injection done one time per month for 3-6 sessions to proliferate fibroblasts and collagen

Usually done with Dextrose but that may not be enough of a stimulus Adding small amounts of Testosterone can improve the outcome

Feet and Shoe Factors

- Feet that are relatively flat(Pes Planus) can lead to excessive forces from Pronation on the knee and the hip, the Sacroiliac joint and lumbar spine
- Shoes that are not supportive enough can lead to excessive forces on the knee cap, the knee, hip
- Evaluate your patients shoes for stability and watch them walk

Unstable Shoe wear

- Check the stability of shoe wear in every patient with foot, ankle, knee, hip or back pain
- Shoe wear tests: Pronation and ring it out stress test
- Check the sole: Fold test
- Rear: press and pinch test
- Rx: prescribe shoe wear criteria
- Like Shoes N Feet order form

Modalities for OA

- Low Level Laser Therapy especially in the 904hz range can be very helpful to decrease sensitivity of the periosteum as well as to treat the meniscus(knee)
- Pulsed Electromagnetic Field Treatment (NES MiHealth) can be especially helpful to decrease pain and augment cartilage repair and building

Modalities for OA

- Frequency Specific Microcurrent can be used to decrease swelling, inflammation and pain of peripheral joints.
- It is extremely helpful to decrease pain from neck and back facets as well as to help to heal nerve roots, discs and even spinal cord(stenosis)
- It can address inflammation and may aid in increasing the survival of cartilage cells
- For more information or training go to www.frequencyspecific.com

Topicals for OA

- For pain: consider a Homeopathic combination cream like Topricin Sports or Celergesic
- For Chondrocyte repair(OA of the fingers, knee, Chondromalacia, foot, ankle, wrist) topical Glucosamine Sulfate(Vegan) 7.5% with dmso

Script: dmso 100% with 7.5% Vegan glucosamine apply one time per day 50 ml renew prn

Supplements for OA

- Supplements should be given along with addressing dysfunctional mechanics and can be started well ahead of modalities
- They should be compared to NSAIDS so patients do not simply go back to taking NSAIDS
- Use supplements based on their mechanism of action so you do not have a lot of overlap
- Inflammation: Cox, Lox, NFKB, TNFalpha, Cytokines
- Support Chondrocytes and Matrix(GS, Collagen Type 2, Avocado Soy unsaponifiables)
- Modulate Proteases(EPA)

Supplements

- Tell patients that they need to be “patient” and give any OA intervention about 8 weeks to start showing its effect
- Most OA supplements work on inflammatory mediators: Curcumin, Boswellia, Green Lipped Mussel, Scutellaria baicalensis ,Acacia catechu,

EPA/DHA, THIAA-a(NFKB), Vit D

Important to make sure that the major mediators of inflammation are addressed COX2, LOX, TNF alpha , NFKB, inflammatory interleukins .

Curcumin is a good baseline OA antiinflammatory

Curcumin

- Mechanism: primarily antiinflammatory (COX, LOX and Cytokines)
- Nuclear Factor-kB, TNF alpha
- IL 1 and IL 6), protein kinases (such as mammalian target of rapamycin, mitogen-activated protein kinases, and Akt) and other enzymes (such as cyclooxygenase 2 and 5 lipoxygenase)
- Also upregulates NRF2

Supplements: Curcumin

- Note: Curcumin has effects on many Cytochrome pathways and may inhibit drug metabolism
- If your patient is on a drug look up its interaction with Curcumin
- Curcumin is a good idea as a foundation of any OA program unless they have a drug interaction or do not tolerate it
- Use Curcumin 400-500 mg 2-3x a day)a highly absorbable Curcumin(Liposomal,BCM95)

Supplements

- Few supplements may be able to block MMPs proteinases
- Some supplements may be able to provide support to maintain chondrocytes and matrix and thus may be thought of having anabolic roles: Glucosamine and Chondroitin Sulfate, Bone Morphogenic Protein (BMP), and Type 2 undenatured collagen(and some other collagen products)
- Creating new Chondrocytes and matrix in bare areas is beyond the scope of this talk because a scapholding is needed with stem cells

EPA/DHA

- Omega 3s esp EPA may have effects on inflammation, enzyme breakdown as well as anabolic effects
- Researchers “found culture for 24 hours with omega-3 fatty acids resulted in a decrease loss of GAGs, reduced collagenase cleavage of type II collagen, a dose-dependent reduction in aggrecanase, and all studied modulators of inflammation (COX-2, 5-LOX, FLAP, IL-1α) and joint destruction (ADAMTS-4, MMP-3, MMP-13) were abrogated or reduced.”

Supplements

- Use moderate to high dose with a bias toward EPA in most of your patients with OA
- Avocado Soy Unsaponifiables may have cartilage repair and regeneration effects

Glucosamine Sulfate

- Glucosamine is an amine sugar found in glycoproteins and Glycosaminoglycan(GAG). Glucosamine is a major rate limiting step in GAG and proteoglycan synthesis
- It can be used to augment sulphur and improve articular cartilage and meniscus tissue in degenerative joints or in recently injured joints to prevent OA
- **Stabilized** GS has more studies supporting it than any other supplement for OA
- Use it as part of a foundation program for OA

Glucosamine Sulfate

- This should be in the form of Glucosamine Sulfate not Glucosamine HCL and it should be a form that is stabilized
- Supplementation with 1500 mg at one time is useful in injuries involving articular cartilage (kneecap, ACL or meniscus injury, etc.)
- Use 1500 mg 2x a day if more than one large joint or a spinal area and a peripheral joint like the neck and a hip

Glucosamine Sulfate

- Use for chronic problems with DJD of the knee as well as other joints with OA
- Consider also in patellofemoral syndrome as a supplement on a more continuous basis (or during a particular season)
- If an acute injury to a joint start supplementing immediately after an injury involving surface cartilage and use for 8-10 weeks after the injury to go along with the inflammatory histological cycle

Glucosamine Sulfate

- This is not a pain pill and must be taken daily
- It may have some minor antiinflammatory benefits
- Many studies done on it that have shown efficacy
- After 6 weeks it was rated more effective than Ibuprofen
- Regular GS is from shellfish and has excessive lead and mercury so I prefer a non gmo vegan GS
- NOTE: It is also available by prescription as a topical Glucosamine and can be applied to the joint lines and around the knee cap 2x a day

DJD/Nutritional Support

- Chondroitin Sulfate is a large molecule and may be poorly absorbed. It may block absorption of other nutrients(fat soluble vitamins)
- Most of it is from pooled Bovine trachea(windpipe)but may also be from pork and bird wind pipes
- Dose is 1200mg per day minimum
- GS 500 and CS 400 low molecular weight
- It may also black Mast Cells if the patient also ahs mast cell activation syndrome

Other Supplements

- SAM-e 200 mg 3x a day has been shown to be effective to decrease pain and improve function in OA
- Doses:
- It is very expensive compared to GS or CS
- MSM provides sulfur for cartilage and one needs about 4 grams per day of a high quality MSM
- Fish oil may be helpful at 4 grams per day
- 360-450 mg of EPA at 2 2x a day

Supplements: BMP

- Bone Morphogenic Protein (BMP)

May support meniscus and articular cartilage

Mechanism: may inhibit metalloproteinase and stimulate and aid chondrocyte and matrix growth

BMP-7 increases matrix synthesis and does not stimulate uncontrolled fibroblast proliferation and osteophyte formation.

BMP-7 may be a suitable growth factor for stimulation of meniscal cell and collagen formation.

BMP

- *BMP-2 treatment may lead to a reparative response in chondrocytes after cartilage injury or osteoarthritis*

Type 2 Collagen

- undenatured type II collagen
- When normal collagen is processed, it becomes “denatured”: its molecular shape changes and it loses its bioactivity.
- Collagen protein may not actually support joints
- Dose from studies is 40 mg per day

Medications

- NSAIDs such as Ibuprofen, Aleve may decrease pain but can decrease cartilage repair and have side effects on the GI and Kidney organs
- If on an NSAID need to be monitored for liver and kidney function every 3-4 months
- If a Diabetic it is even more risky
- Be careful taking NSAIDS on a hot day to avoid dehydration

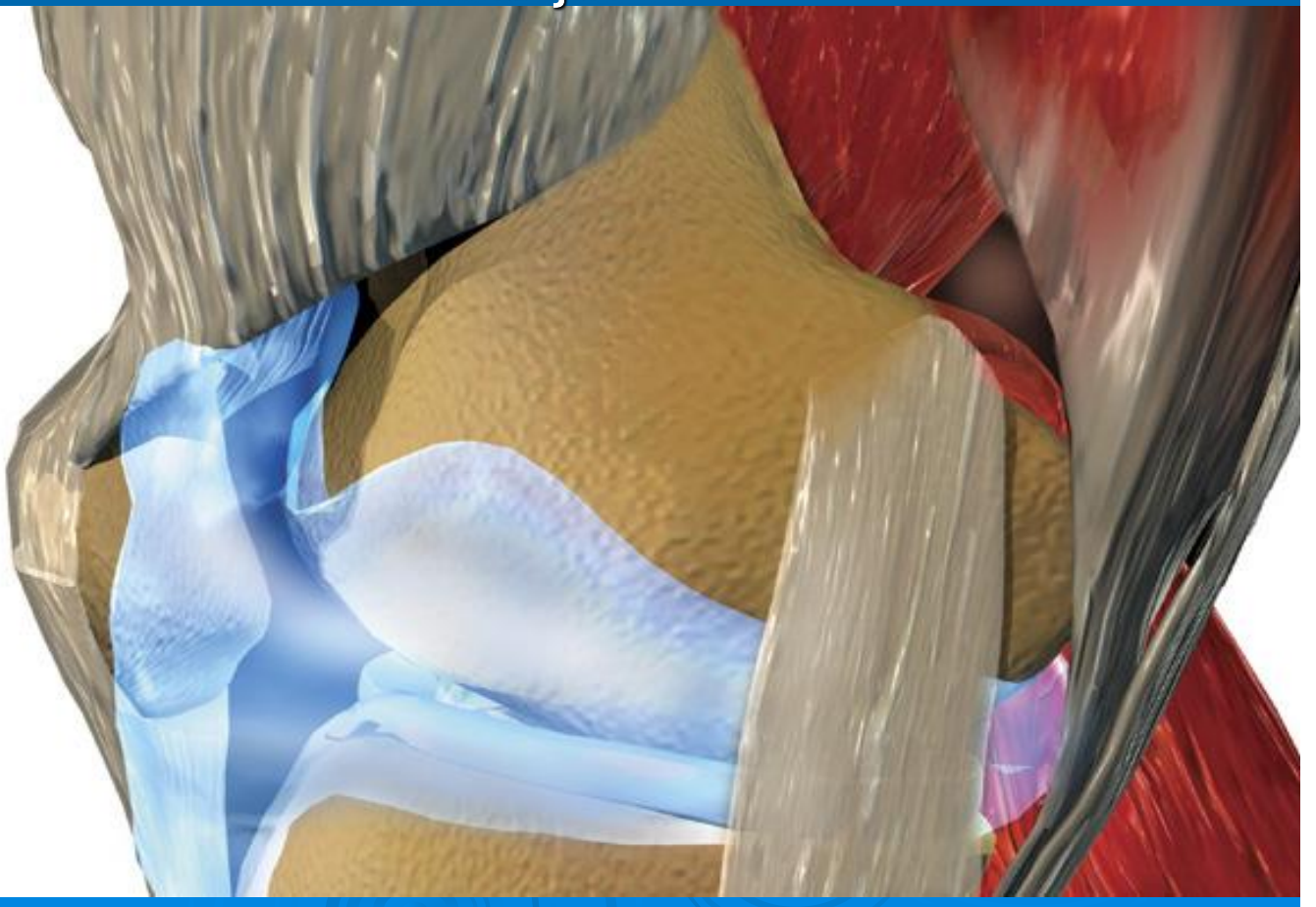
STEP(Scientific Therapeutic Exercise Progression) Exercise

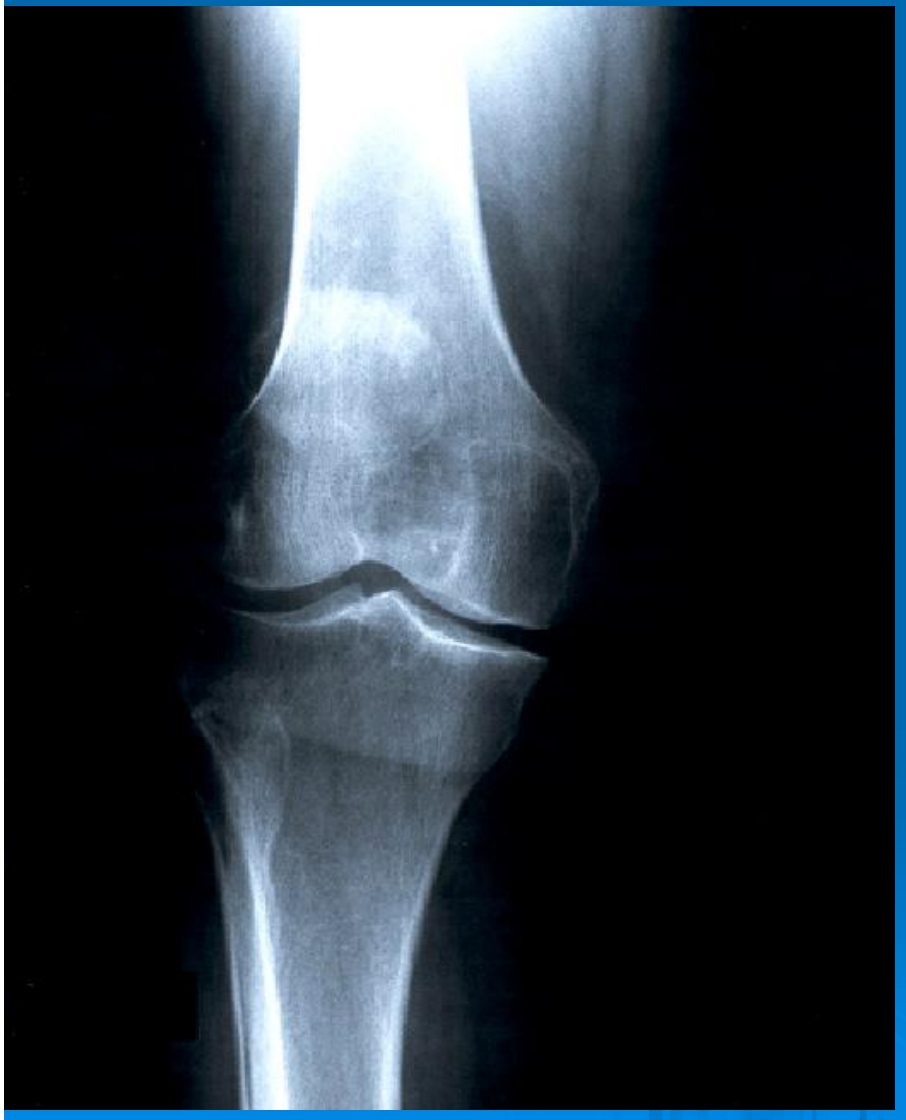
- Surface and meniscus cartilage may heal better with forces of compression, decompression and gliding
- Exercises should be designed to stimulate cartilage healing with these forces soon after an injury or in conjunction with a DJD program
- Reps should be high 20-30, 4-5 sets a day

DJD: Injections HA

- Bone on bone changes in a knee or hip may be a reason for minimal or no effect from supplements
- Injection of a synovial fluid analogue Synvisc, Hyalgan or Euflexxa
- These injections can improve function and decrease pain
- Injections are 1X/week x 3
- Improvement may last for up to 9 months

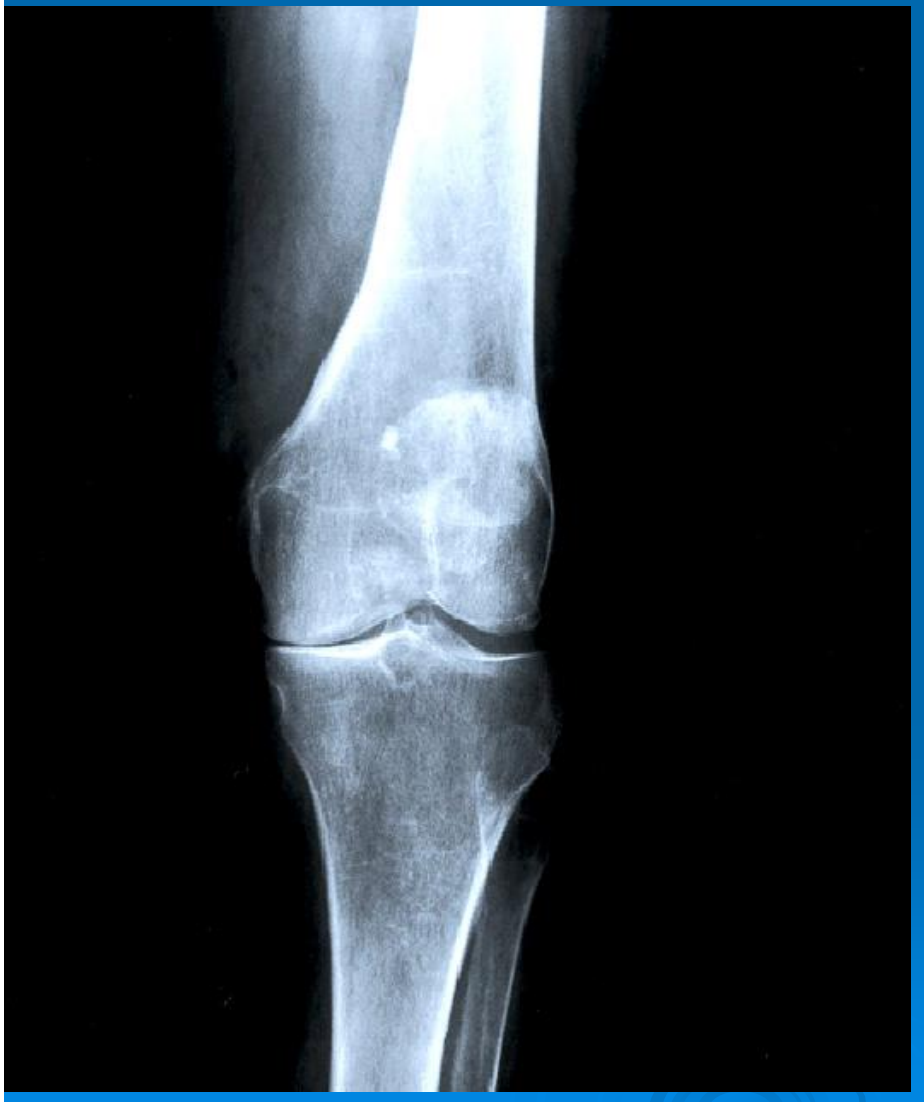
HA cushions, lubricates, and supports the knee joint.





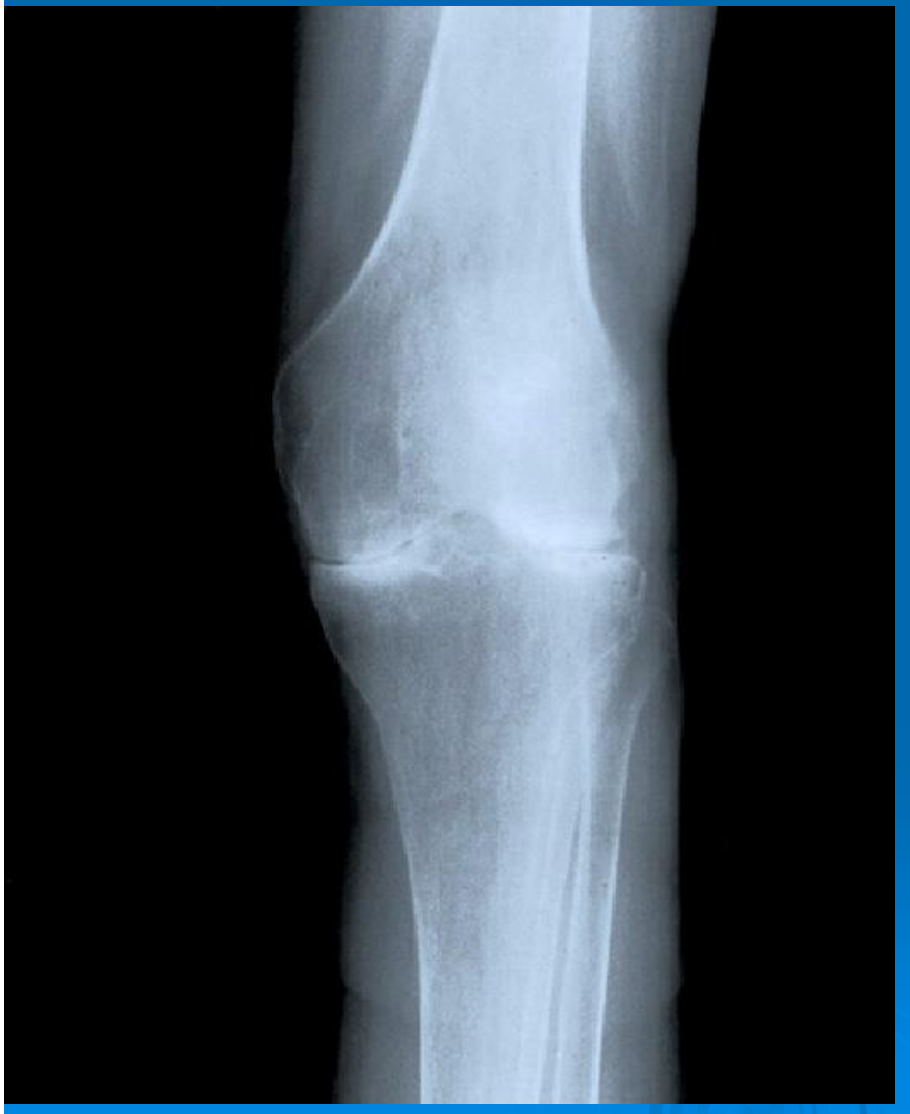
x-ray of grade II (mild-moderate)

80% of patients reported as better/much better.



x-ray of grade III (moderate-severe)

76% of patients reported as better/much better.



x-ray of grade IV (severe)

58% of patients reported as better/much better.

Other Injections

- PRP injections may be helpful to decrease inflammation
- Stem Cell treatments should be reserved for patients that do not want total knees and have tried oral, topical, modalities and Physical Therapy

FGF-18

- Recombinant form of human fibroblast growth factor 18 which is under development by Merck and Nordic Bioscience for the treatment of osteoarthritis.
- Fibroblast Growth Factor-18 has been shown to "attenuate cartilage degradation, increases Collagen II deposition and suppresses matrix metallopeptidase 13 (MMP13) expression in rat post-traumatic osteoarthritis (PTOA). At the cellular level, FGF18 promotes chondrocyte proliferation through PI3K-AKT signaling and migration through PI3K signaling. We found that FGF18 attenuates IL-1β-induced apoptosis, restores mitochondrial function and reduces Reactive Oxygen Species (ROS)"

Summary

- Evaluate and treat OA with diet and supplements
- Refer for modalities in patients with spine or extremity pain, nerve root compression
- Evaluate shoe wear
- Recheck patients for OA
- Refer when you need additional opinions re joint laxity, prolotherapy and other injections
- Treat your own OA if you have it