PATHOPHYSIOLOGY
Overview
What is chronic joint pain?

- Joint pain that persists beyond the normal expected tissue healing time of 3 months
- A wide variety of conditions can cause chronic joint pain

**Mechanical**
e.g., osteoarthritis, soft tissue injury, etc.

**Inflammatory**
e.g., rheumatoid arthritis, bursitis, etc.

**Tumor-related**
Etiology
# Types of Joint Pain

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoarthritis</td>
<td>14,000</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>500–1000</td>
</tr>
<tr>
<td>Juvenile rheumatoid arthritis</td>
<td>100–200*</td>
</tr>
<tr>
<td>System lupus erythematosus</td>
<td>1–125</td>
</tr>
<tr>
<td>Polymyalgia rheumatica</td>
<td>5–60†</td>
</tr>
<tr>
<td>Giant cell arteritis</td>
<td>5–30</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>7</td>
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</tbody>
</table>

*In children
†In individuals >50 years of age

Ankylosing Spondylitis: Etiology

- Ankylosing spondylitis is a chronic inflammatory disease of unknown etiology
- It is considered an autoimmune disease
- HLA-B27 is the risk factor most often associated with ankylosing spondylitis
  - Mechanism of involvement is unclear
  - Subtypes and other features of the relationship between HLA-B27 and ankylosing spondylitis have been studied for years
Rheumatoid Arthritis: Immune-Mediated Disease of Uncertain Etiology

Genetic predisposition
- HLA genes
- Non-HLA genes

Environmental triggers
- Bacterial infection
- Viral infection
- Smoking
- Unknown

Immune-mediated response

Rheumatoid arthritis initiated

Overgrowth of synovium (membrane lining of joint) and joint destruction

HLA = human leukocyte antigen
Osteoarthritis: Multifactorial Disease Etiology

**Genetic influences**
- Biochemical abnormalities that cause bone and cartilage deformities
- Congenital hip dysplasia

**Acquired Risk factors**
- Age
- Obesity
- Metabolic conditions
- Misaligned joints
- Joint trauma or injury

**Structural damage to cartilage**

**Alteration in cartilage formation**

**Inflammation in the joint**

**Cytokine release**

**Bone remodeling**

Ankylosing Spondylitis: Uncertain Etiology and Pathogenesis

- Incompletely understood, but knowledge is increasing\(^1\)
- Immune-mediated mechanisms are involved\(^1\)
  - Increased concentration of T cells, macrophages and proinflammatory cytokines
  - TNF-\(\alpha\) is thought to play a role in the inflammatory reactions observed with the disease\(^2\)
    - Inflammatory reactions produce hallmarks of disease\(^3,4\)

Factors
- HLA-B27 – especially interaction between HLA-B27 and T cell response\(^1\)
- Inflammatory cellular infiltrates
- Cytokines (e.g., TNF-\(\alpha\), IL-10)
- Genetics
- Environment

HLA = human leukocyte antigen; IL = interleukin; TNF = tumor necrosis factor
Rheumatoid Arthritis Pathogenesis

Initiation*

A. Immune response

B. Inflammation

C. Synovial overgrowth

D. Joint destruction

*Initiation is typically attributed to a genetic predisposition or environmental trigger (not shown).

B = B-lymphocyte; C = complement; GM-CSF = granulocyte-macrophage colony-stimulating factor; IgG = immunoglobulin G; IgM = immunoglobulin M; IL = interleukin; M = macrophage; P = plasma cell; PGE2 = prostaglandin E2; RF = rheumatoid factor; T = T-lymphocyte; TGF-β = transforming growth factor-β; TNF-α = tumour necrosis factor-α

Osteoarthritis Pathogenesis

*Initiation is typically attributed to a genetic predisposition or environmental trigger (not shown). IL = interleukin; M = macrophage; MMP = metalloproteases; NO = nitric oxide; PGE2 = prostaglandin E2; TGF-β = transforming growth factor-β; TIMP = tissue inhibitor of metalloproteases; TNF-α = tumor necrosis factor-α

Factors Contributing to Osteoarthritis Development

Obesity
Anatomic abnormalities
Microfractures and bony remodeling
Loss of joint stability
Trauma

Aging
Genetic and metabolic diseases
Inflammation
Immune system activity

Abnormal stresses → Compromised cartilage → Abnormal cartilage

Biophysical changes
- Collagen network fracture
- Proteoglycan unraveling

Biochemical changes
- Inhibitors reduced
- Proteolytic enzymes increased

Cartilage breakdown

Mechanism-Based Treatment of Inflammatory Pain

**Pain Treatment Options**
- Acetaminophen
- nNSAIDs/coxibs
- Opioids
- Local anesthetics/channel blockers
- Intra-articular corticosteroid/hyalurinate injections

**Caption:** CNS = central nervous system; coxib = COX-2 inhibitor; nsNSAID = non-specific non-steroidal anti-inflammatory drug
Mechanism-Based Treatment of Chronic Pain in Osteoarthritis

- Sensitization of joint nociceptors
- Development of neuropathy
- Activation of thalamocortical nociceptive system and amygdala
- Reduction of gray matter
- Changes in descending inhibition and facilitation
- Sensitization of nociceptive spinal cord neurons with joint input
- Activation of microglia

Medications affecting central sensitization:
- $\alpha_2\delta$ ligands
- SNRIs
- TCAs
- Tramadol, opioids

CNS = central nervous system; coxib = COX-2 inhibitor; nsNSAID = non-specific non-steroidal anti-inflammatory drug
But... Patients with Chronic Pain of Just One Type of Pain Pathophysiology May be Rare

Therapies that work better for a particular patient are likely to depend on the mechanisms contributing to the patient’s pain.

Patients with mixed pain may benefit from combination therapy.

Neuropathic Pain in Osteoarthritis

• Some osteoarthritis patients may use terms such as “burning” or “numbness” to describe their pain
  – These verbal descriptors are suggestive of a neuropathic component
• Based on mechanism of action and preliminary studies, non-traditional analgesics such as $\alpha_2\delta$ ligands, TCAs and SNRIs, may be useful for treating this component
  – However, further studies are needed to clarify the role of these drugs in osteoarthritis

SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant
Neuropathic Pain in Osteoarthritis

• The exact cause of osteoarthritis pain remains unclear
  – Pathological changes in articular structures
  – Changes in central pain processing or central sensitization appear to be involved
    \(^1\)

• Some osteoarthritis patients may use terms such as “burning” or “numbness” to describe their pain
  \(^2\)
  – These verbal descriptors suggest a neuropathic component

• Based on mechanism of action and preliminary studies, non-traditional analgesics (e.g., \(\alpha_2\delta\) ligands, TCAs, SNRIs) may be useful for treating this component
  – Further studies are needed to clarify the role of these drugs in osteoarthritis

\(^1\) Girbés L. Phys Ther. 2013 Jun;93(6):842-51

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Central Sensitization in Osteoarthritis

• Central sensitization may contribute to osteoarthritis pain in a subgroup of patients (~30%)
  – Hypothesis supported by a variety of direct and indirect evidence

• Several interventions (including manual therapy, TENS, medication and joint replacement surgery) have been shown to modulate central hyperexcitability, but more research is required

TENS = transcutaneous electrical nerve stimulation
Summary
Pathophysiology of Chronic Joint Pain: Summary

• Chronic joint pain can be due to many causes: mechanical, inflammatory or tumor-related
• Many conditions associated with chronic joint pain are complex, multifactorial disease
  – Some conditions, such as rheumatoid arthritis and ankylosing spondylitis, involve immune-mediated mechanisms
  – Others, like osteoarthritis, are primarily due to mechanical stress and cartilage breakdown
  – Many conditions associated with chronic joint pain are complex, multifactorial disease
• Chronic joint pain due to arthritis is frequently inflammatory in nature
  – However, many patients with osteoarthritis and rheumatoid arthritis may also have a neuropathic component to their pain