Causes and treatment of joint pain

St. Vincent's University Hospital

Aims

- Major rheumatic conditions
    1. Autoimmune
    2. crystal-related
    3. 'degenerative'

- Origins of joint pain - inflammatory or damage-related

- Therapeutic options
    1. Analgesia (simple, NSAIDs)
    2. Disease modifying (MTX, biologicals)
    3. Corticosteroids

- Industrial placement opportunity

Therapeutic aims

↓ Pain

↓ Stiffness

↓ progressive joint damage

? Repair joint damage

Maintain functional capacity and quality of life

Origin of joint pain; inflammatory or non-inflammatory?

Inflammatory: redness, heat, pain, swelling and loss of function

Symptoms worse in morning
Eased by exercise

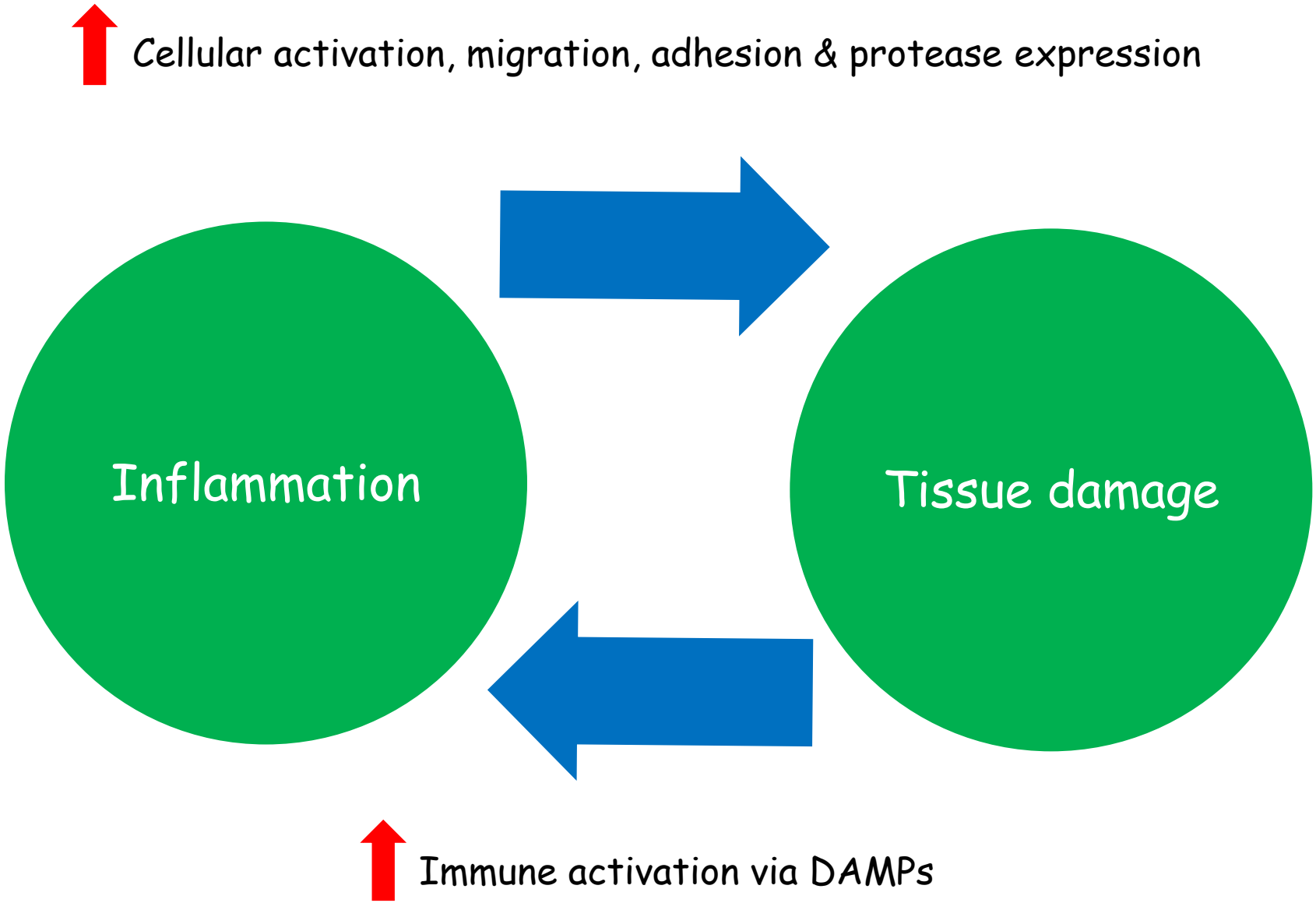
Non-inflammatory joint pain

Worse in evening
Exacerbated by use

Origin of pain: Inflammation and tissue damage coexist

	Inflammation	Tissue damage
Rheumatoid Arthritis	+++	++
Ankylosing spondylitis	+++	+++
Polymyalgia	++++	-
Crystals (eg gout)	++++	++
Osteoarthritis	++	++++

Relationship between inflammation and tissue damage



Rheumatoid arthritis

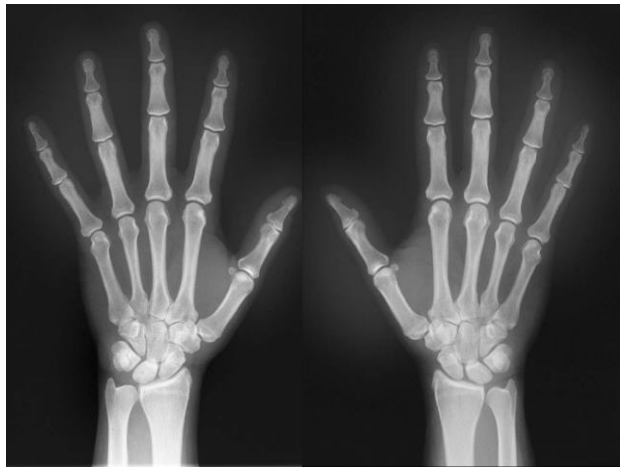
- Autoimmune disease – 1% prevalence, M:F 2.5:1

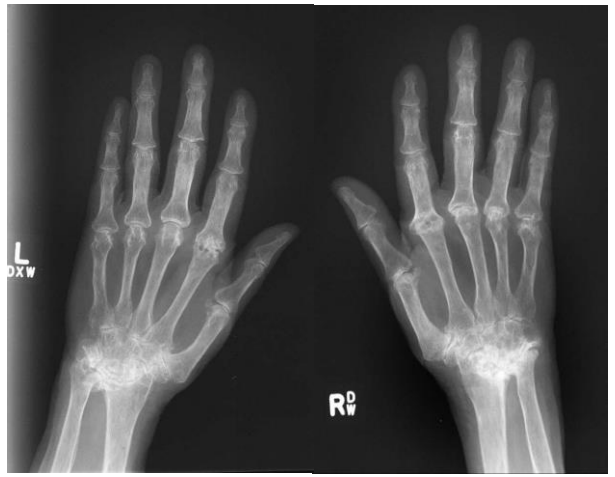
- Multifactorial

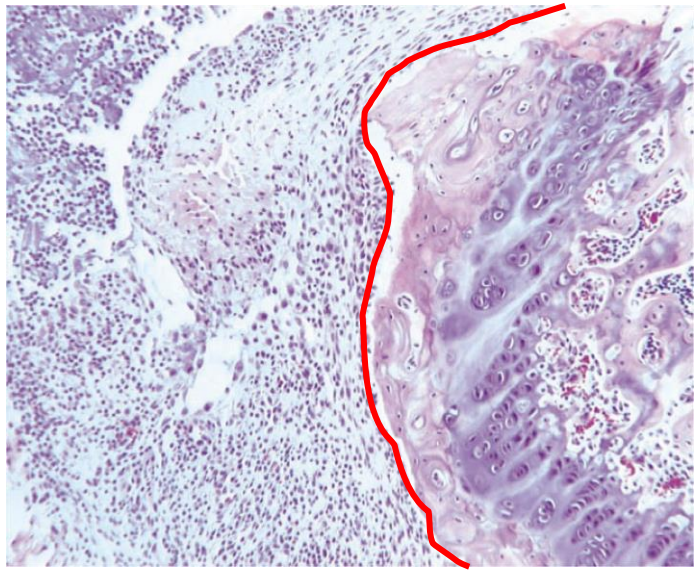
  Environmental – smoking↑, alcohol↓

  Genetics - Heritability 60%,

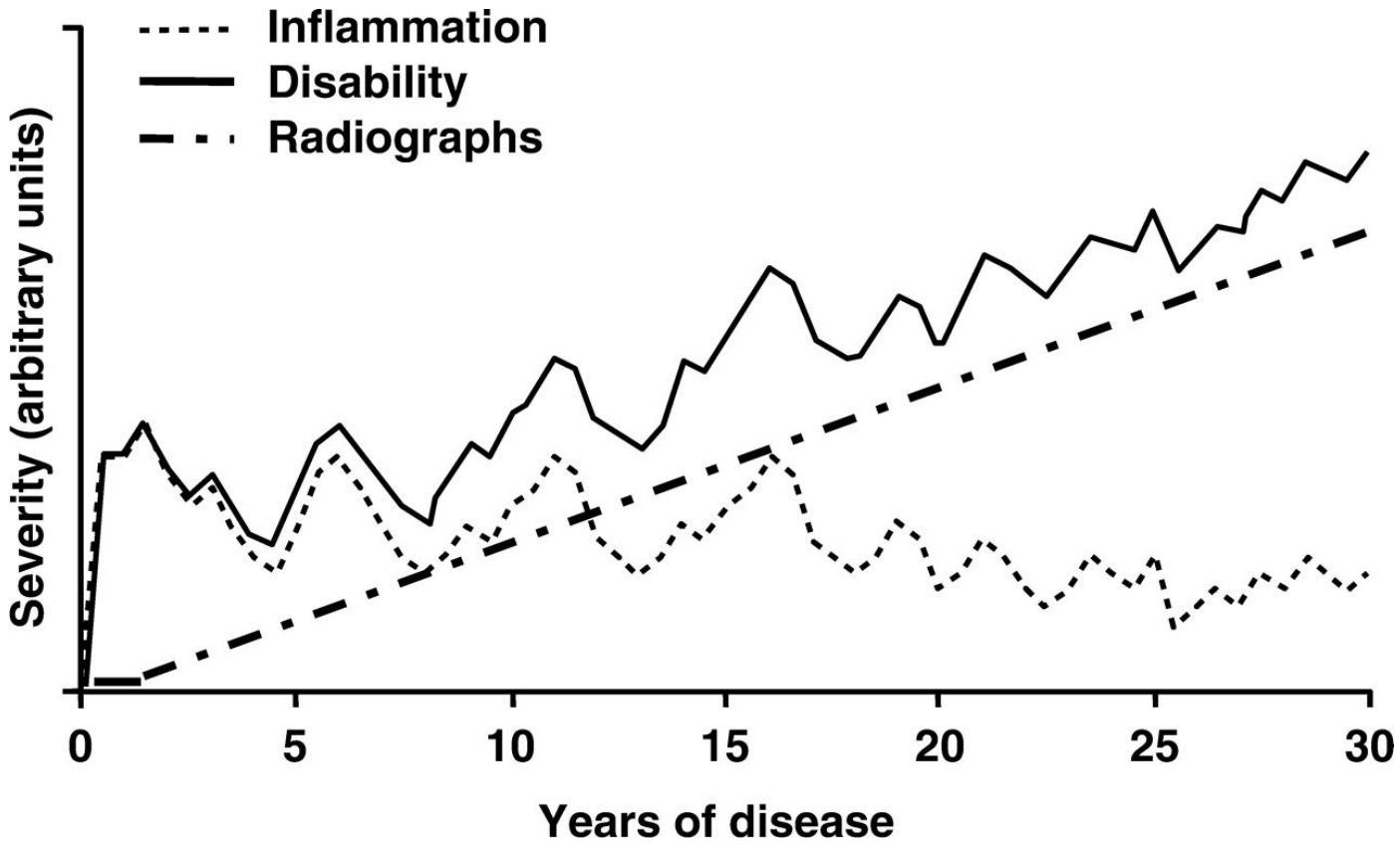
  >100 loci identified ($p<0.5\times10^{-8}$)







Disease progression in RA

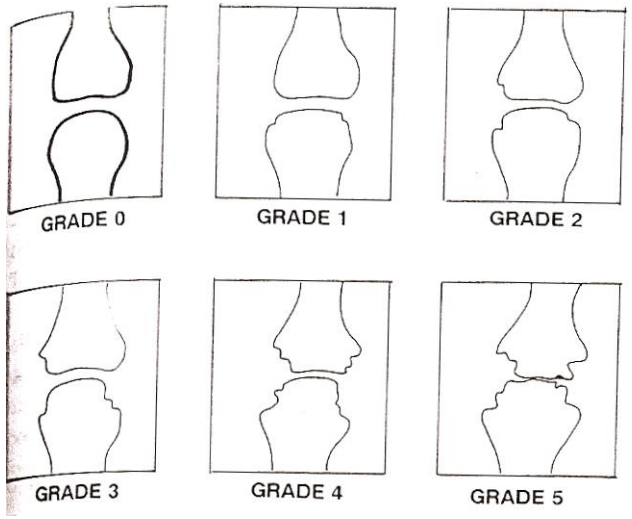


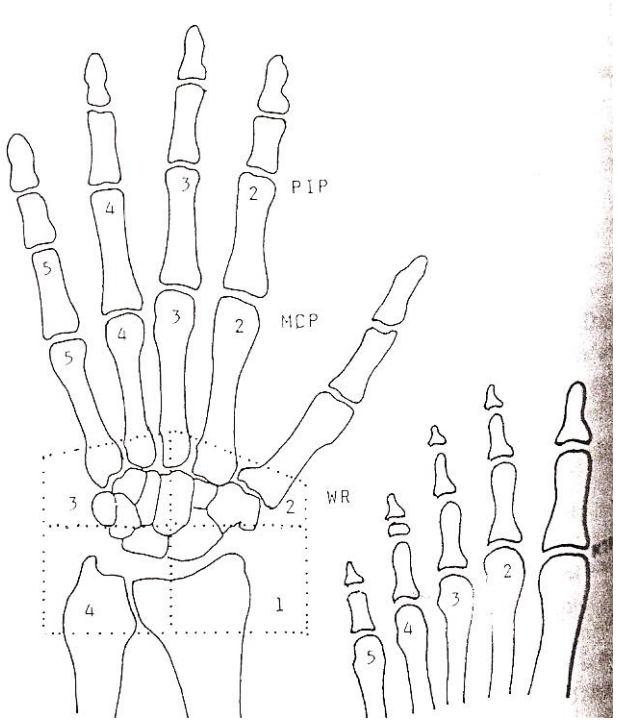
Inflammation (CRP) x time = damage

Rheumatology 2008 47:392-398

Radiological damage in RA

- Modified Larsen score
- 32 joints of hands & feet
- Score 0-160

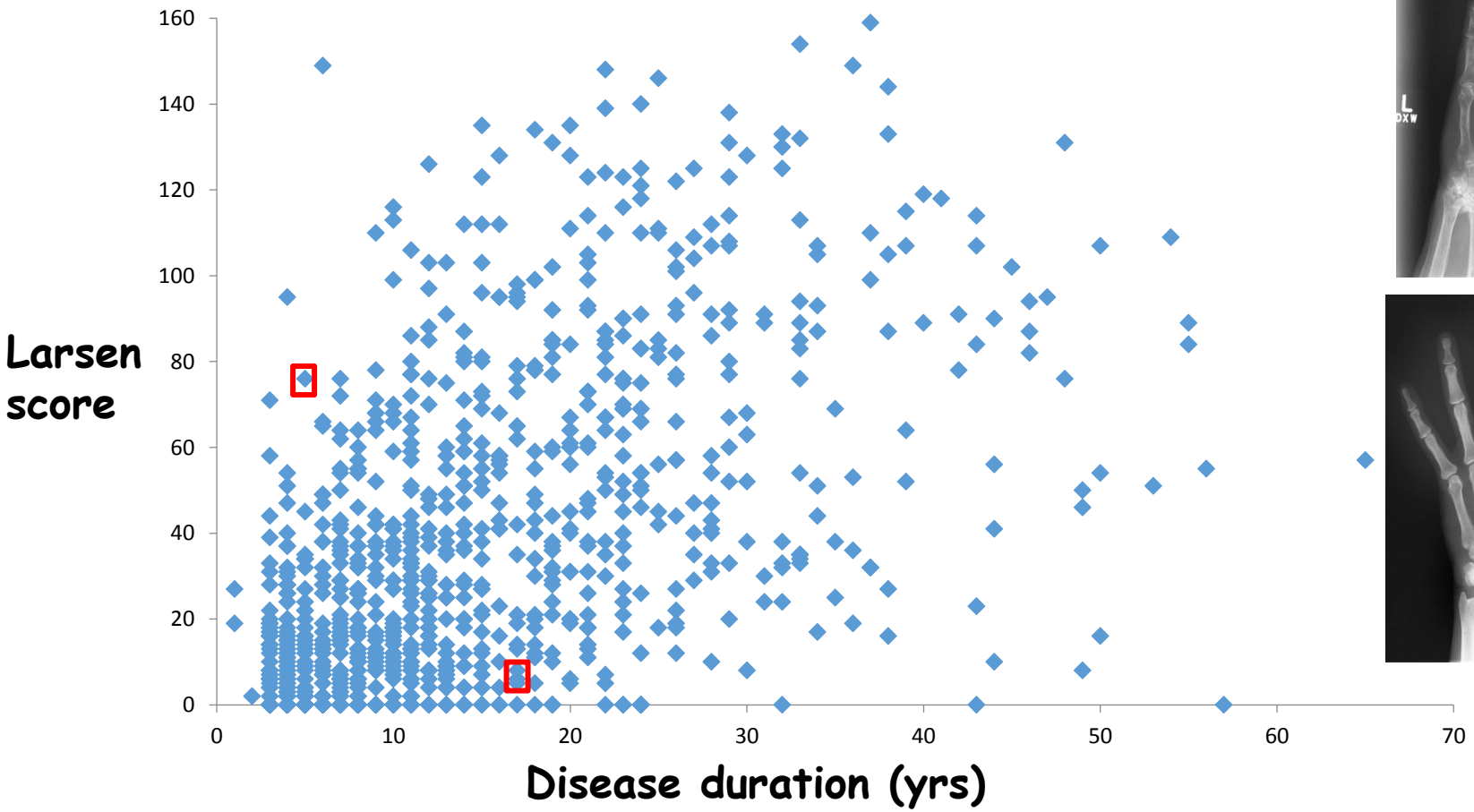


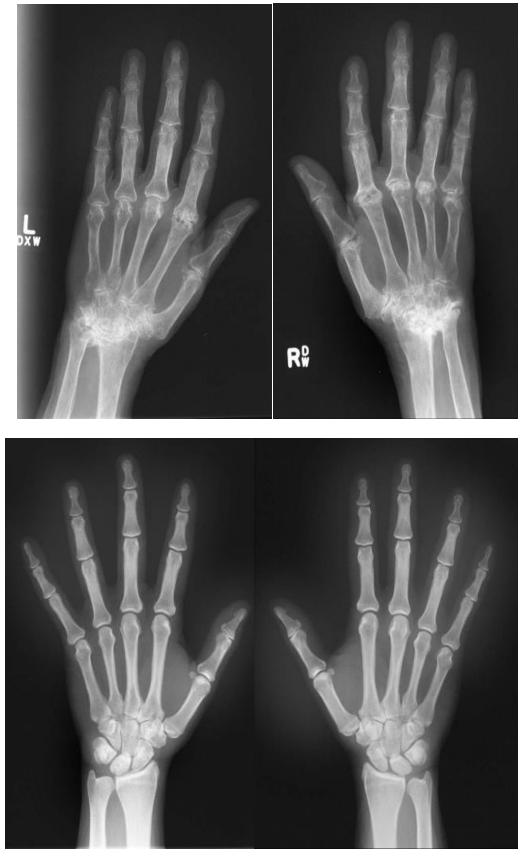


Larsen, A. 1995. J Rheumatol 22:1974-75

Radiological damage in RA

Genetic of Rheumatoid Arthritis (GoRA) study
1,007 patients attending Rheum OP (Sheffield)





Analgesia

Paracetamol 1gm qid (prn)

Paracetamol/codeine preparations

Non-steroidal anti-inflammatory drugs (NSAIDS)

Cyclooxygenase inhibition

Opioid derivatives

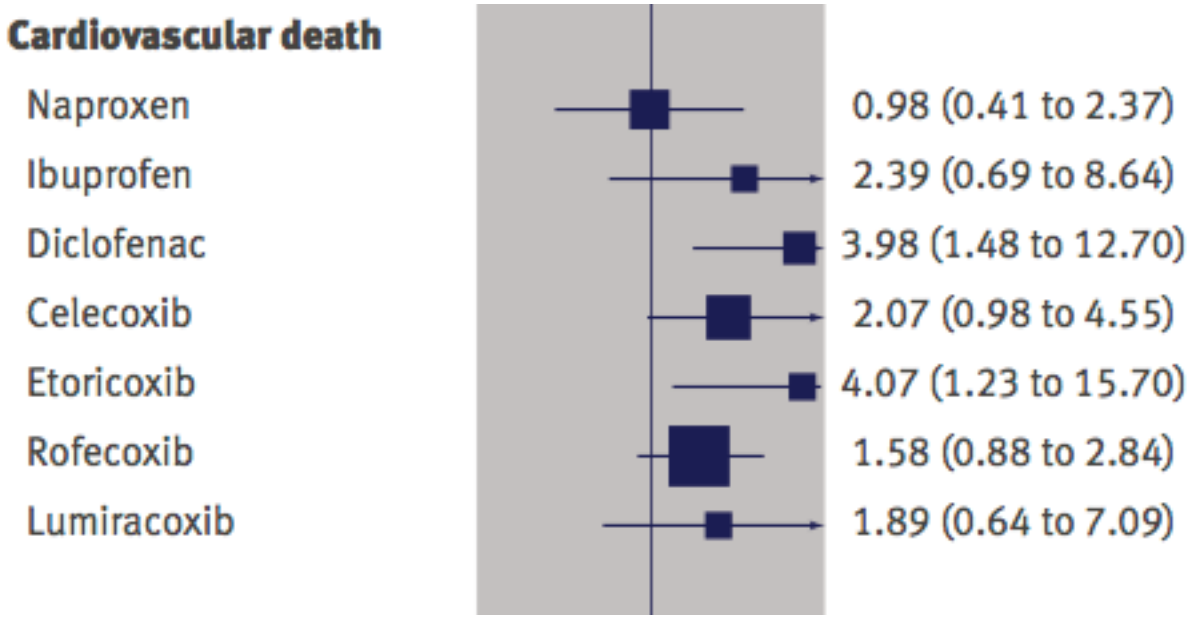
Classification of NSAIDs

Groups	
Salicylic acids	Acetylsalicylic acid
Acetic acids	Diclofenac
	Etodolac
	Indomethacin
Propionic acid	Ibuprofen
	Naprosyn
Enolic acids	Phenylbutazone
	Meloxicam
	Piroxicam
COX-2 specific	Celecoxib
	Etoricoxib

NSAIDs

Enzyme	COX 1	COX 2
Production	Constitutive	Inflammation-induced
Function	Physiological prostaglandins: vascular tone, gastric protection, renal function	Proinflammatory prostagladins eg PGE_2 and PGI_2
Inhibition by NSAIDs	COX 1  COX 2 Indomethacin Aspirin Ibuprofen Diclofenac Coxibs	

Cardiovascular safety of non-steroidal anti-inflammatory drugs



- All NSAIDs associated with increased cardiovascular risk
- Naprosyn seems least harmful

BMJ 2011;342:c7086.

Anti-inflammatory treatments - corticosteroids

Potent anti-inflammatory agents

Down-regulate production of many inflammatory molecules

Hydrocortisone (produced by adrenal) is short acting

Act through specific cytoplasmic receptors

Disease modifying – reduce CRP and x-ray progression

Oral, intra-muscular or intra-articular

Anti-inflammatory treatment: Disease-modifying antirheumatic drugs (DMARDs)

- Slow onset (6 weeks +)
- Systemic inflammatory response (CRP)
- Improve functional status
- Slow radiological progression
- Monotherapy or combination
- Use at onset since early 1990s v after 2-3 yrs 1980s
- Hydroxychloroquine, sulphasalazine, methotrexate

Anti-inflammatory treatments: biological agents

Anti-TNF agents: infliximab, etanercept, adalimumab, golimumab, certulizumab

Anti-IL-6: tocilizumab

Anti-IL-17: secukinumab

Anti-IL12/23: ustekinumab

B cell depletion: rituximab

Immune cell cross-talk: abatacept

Treatment of early RA

Initial

Analgesia – paracetamol ± codeine
NSAID

Anti-inflammatory - corticosteroids im
- methotrexate/suphasalazine

Treat to target – nurse led clinics

Add 2nd DMARD if poor response

Add biological agent

Osteoarthritis

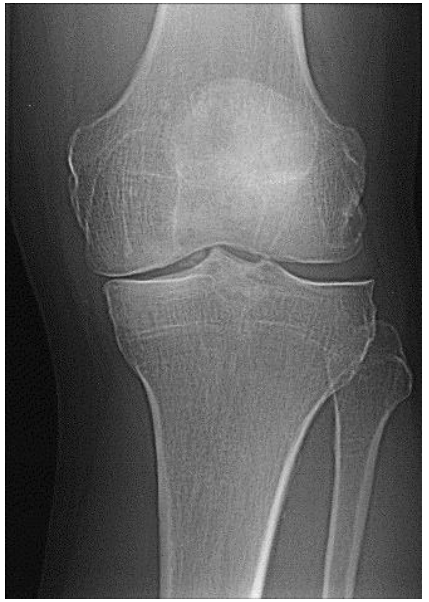
Age-related 'wear and tear' arthritis

Hands, spine, hips, knees, 1st toes commonly

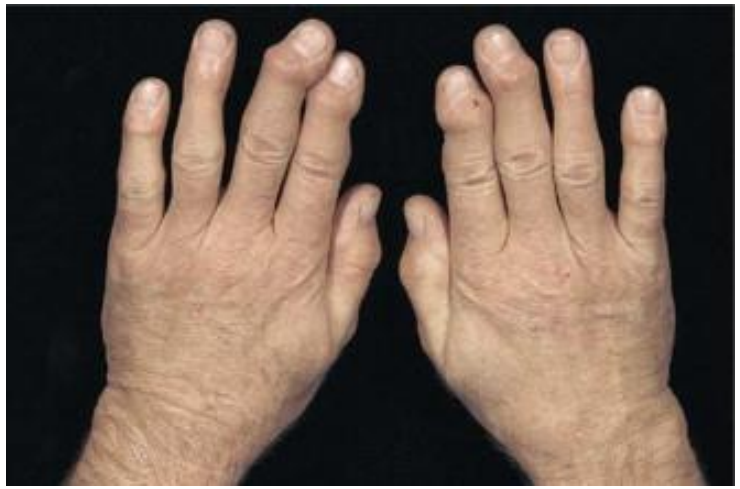
3 main components:
i. cartilage loss
ii. bone sclerosis and osteophytes
iii. inflammation (especially early)

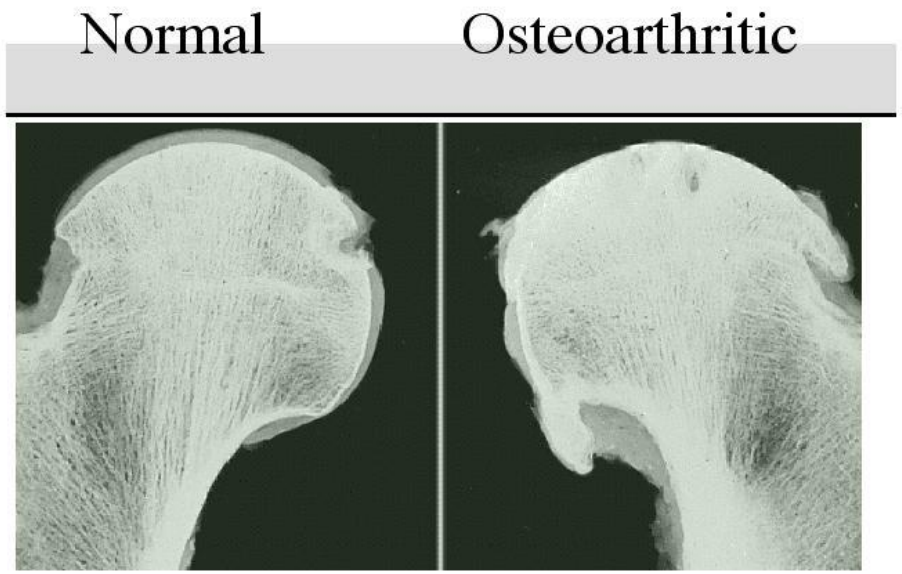
No disease modifying treatment except weight loss

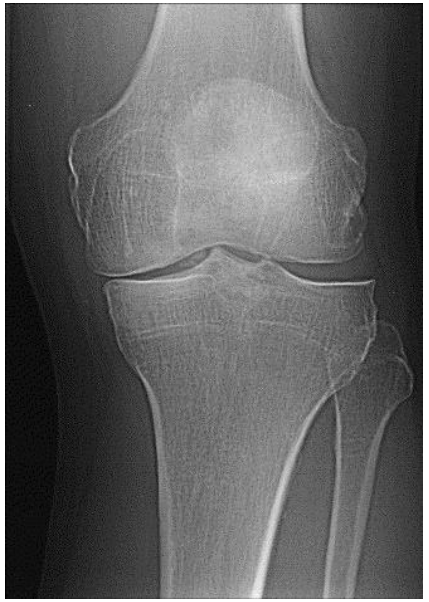
Treatments:
simple analgesia
NSAIDs
intra-articular steroids (if inflammed)
Joint replacement



Lancet 2005,365;965-73




Normal
Osteoarthritic



Poor correlation between structural damage and joint pain in OA

Pain is primary clinical symptom in OA

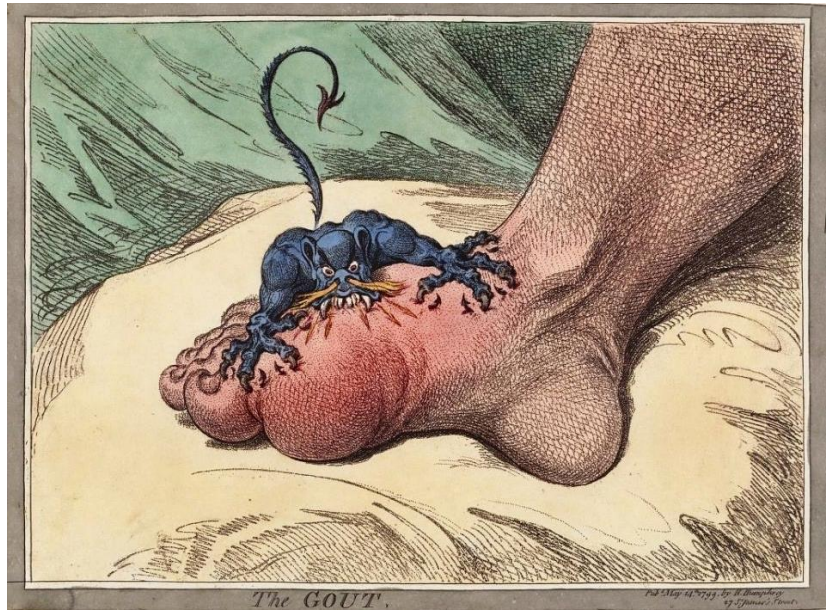
Origin and mechanism of pain in OA poorly understood

Frequent discordance between OA tissue damage and joint pain

Variants in pain pathway genes associated with asymptomatic v symptomatic OA

COMT, *SCN9A* and *TRPV1*

Gout

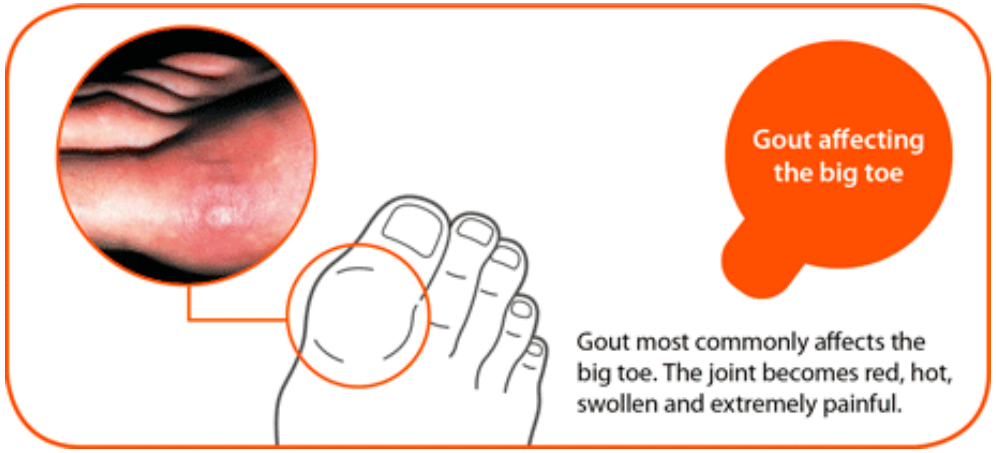


Acute episodes of arthritis

NLRP3 inflammasome activation by uric acid crystals

Extreme joint pain is the central feature

High serum uric acid and crystals in joint aspirate



Patient frequently reports:

1. Unable to weight bear
2. Cannot put bedclothes over foot
3. Pain exacerbated by movement of others in locality

Pain management in acute gout

NSAIDs

Corticosteroids orally or intra-articular

Colchicine – inhibits microtubule formation resulting in:

I. ↓ NLRP3 activation

II. ↓ NFκB activation

III. ↓ adhesion molecule expression on endothelium

IV. ↓ superoxide radicle production

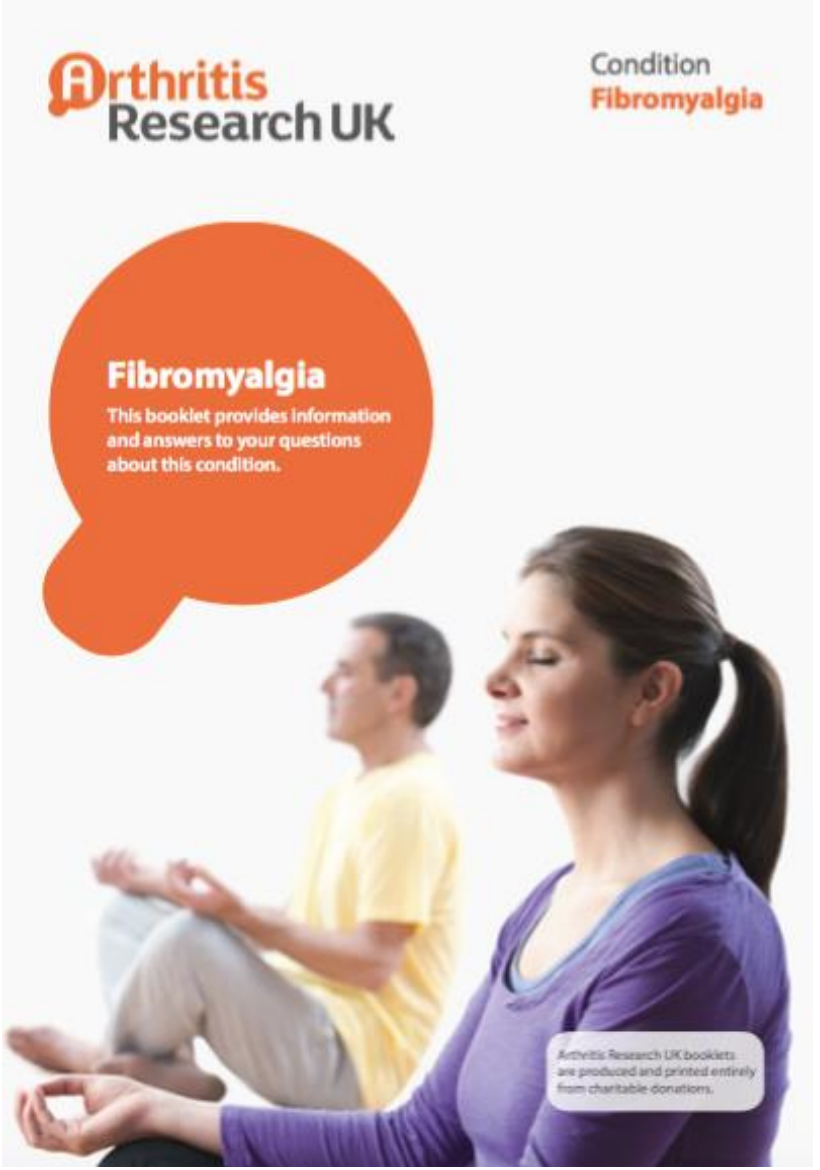
Fibromyalgia

Chronic widespread pain

Prevalence of 2% to 8%

Accompanied by fatigue, memory problems, and sleep disturbances

Not related to inflammation or tissue damage

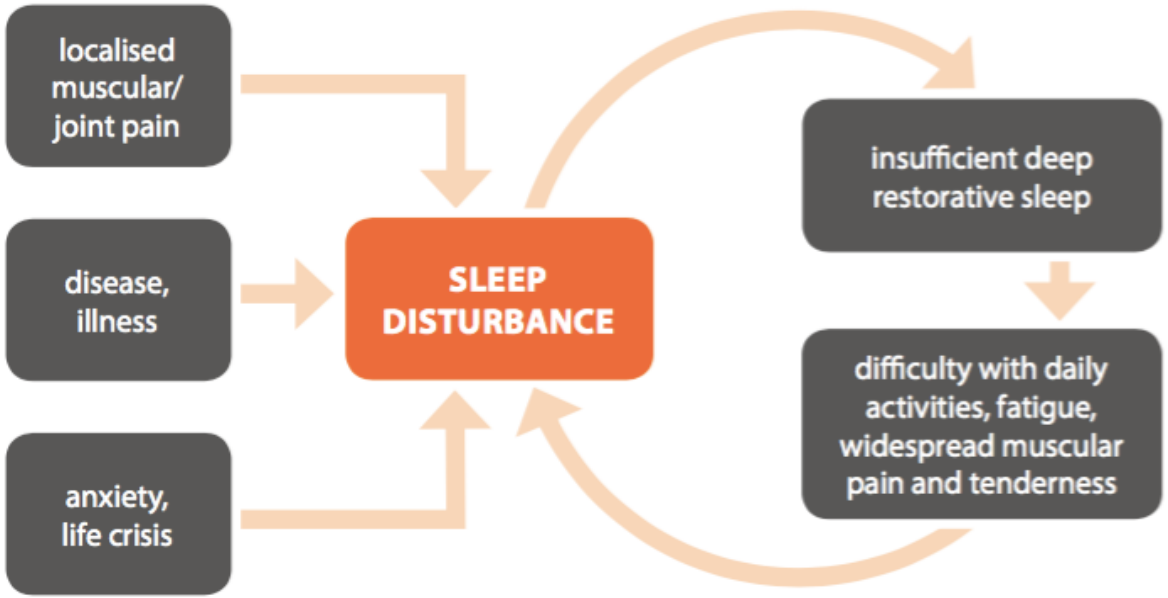


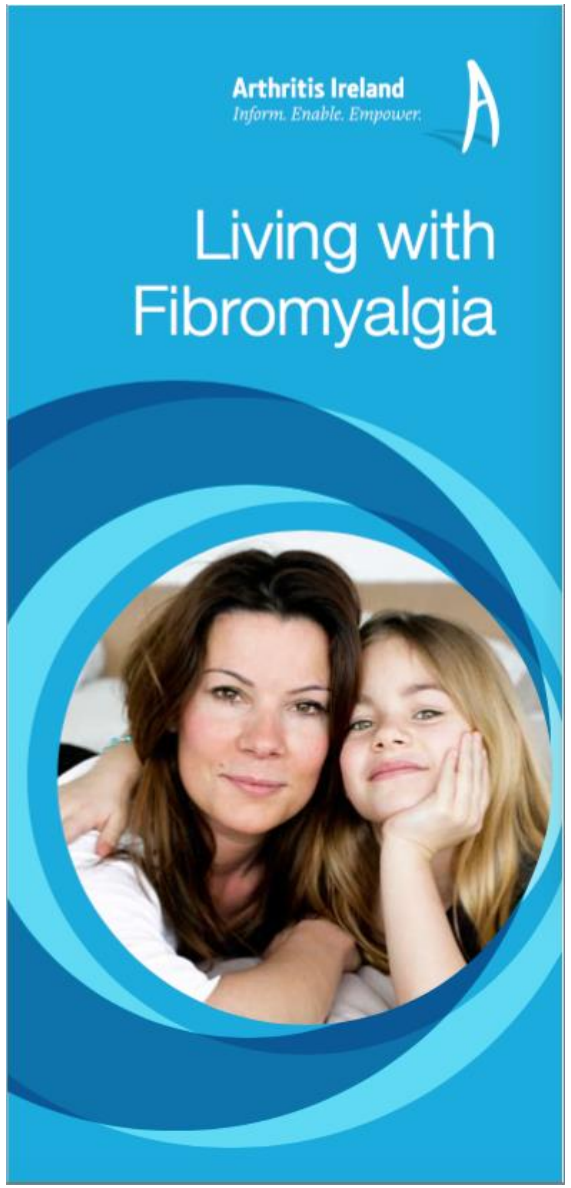
What is fibromyalgia?

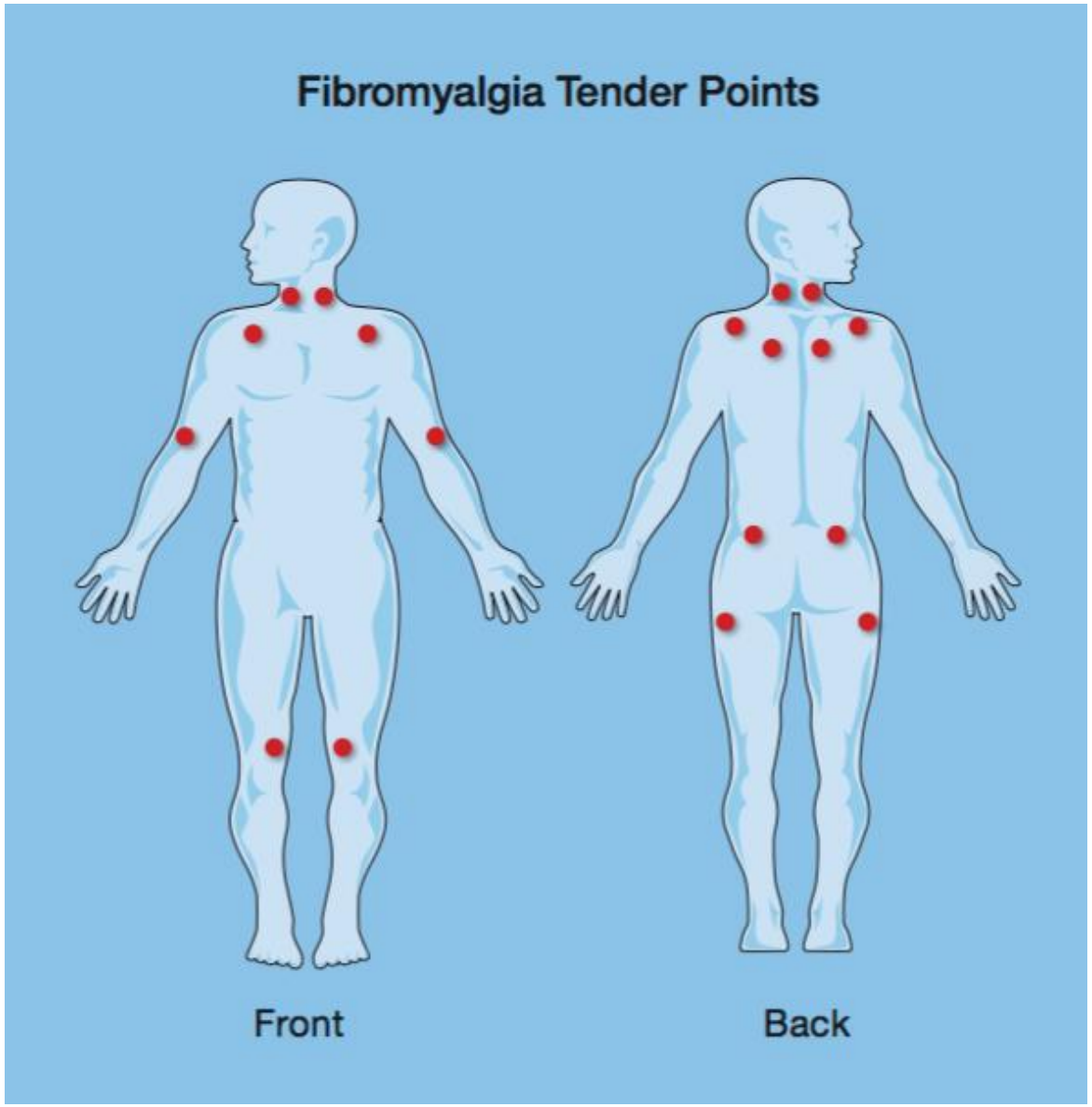
Fibromyalgia is a condition that causes widespread pain. It's not life-threatening or progressive but it can still have a major impact on your quality of life. In this booklet we'll explain the symptoms and possible causes and look at how fibromyalgia can be treated. We'll also suggest where you can find out more about living with fibromyalgia.

At the back of this booklet you'll find a brief glossary of medical words – we've underlined these when they're first used.

www.arthritisresearchuk.org




Arthritis Ireland
Inform. Enable. Empower.
Living with Fibromyalgia


Fibromyalgia Tender Points
Front
Back

EULAR management recommendations of fibromyalgia

Full understanding of fibromyalgia requires comprehensive assessment of pain, function and psychosocial context.

Fibromyalgia should be recognised as a complex and heterogeneous condition where there is abnormal pain processing and other secondary features.

Optimal treatment requires a multidisciplinary approach including non-pharmacological and pharmacological treatment modalities tailored according to pain intensity, function, associated features, such as depression, fatigue and sleep disturbance in discussion with the patient.

Simple analgesics such as paracetamol and other weak opioids can also be considered in the treatment of fibromyalgia.

Corticosteroids and strong opioids are not recommended.

Antidepressants/pregabalin frequently used

Exercise, hydrotherapy, cognitive behavioural therapy

Ann Rheum Dis 2008;67:536-541

Summary

- Joint pain arises from inflammation and/or tissue damage
- Rapid resolution of inflammation reduces pain and prevents tissue damage
- Revolutionary therapeutic advances over past 20 years for inflammatory joint diseases
- Major area of unmet need in understanding causes of fibromyalgia
- Osteoarthritis increasing prevalence with no disease-modifying treatments

Industrial collaboration opportunity: pain research

Asahi Kasei Pharma – JAPAN

Starting from April 2017 we would like to send a Guest Researcher for 1 yeare to a facility that has a focus on running clinical trials and evaluating pain

The general objectives for sending out a Guest Researcher to be hosted at a Pain Research Group are:

1. To understand how to run a clinical trial in a pain indication in a global context
2. To understand how to put a protocol together to run a successful pain study (and to understand the differences between a protocol being established in Japan vs a global setting)
3. To understand specific pain assessment tools and the advantages and disadvantages of each
4. To understand which pain assessment tools to implement in which type of protocol
5. To establish relationships with pain related research teams around the globe

The proposed candidate will hold a Master's degree and will have worked in Asahi Kasei Pharma for no longer than 5 years since graduating university. As they are native Japanese, they will also be sent to intensive English school before joining the host research team.