Osteoarthritis

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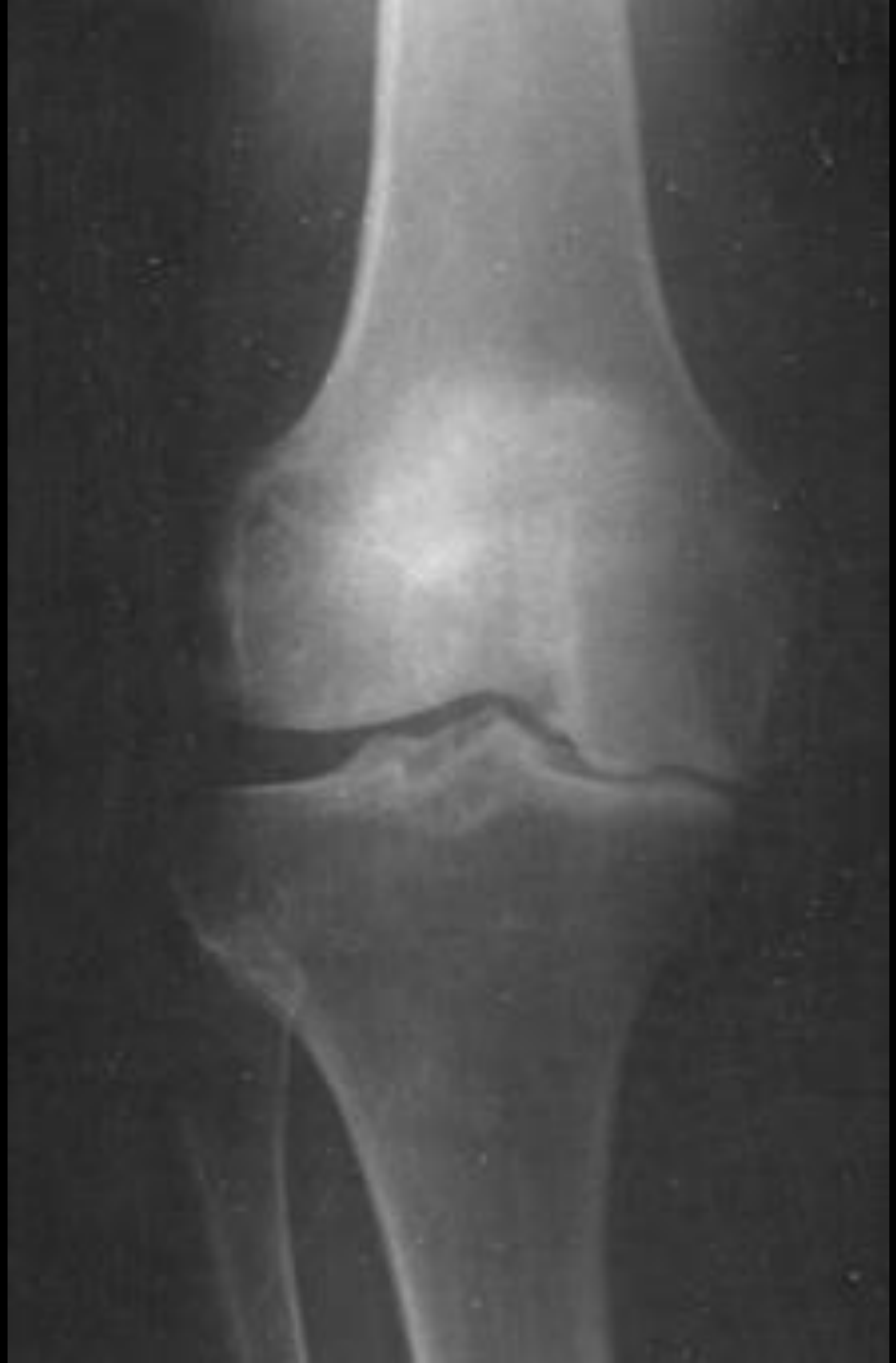
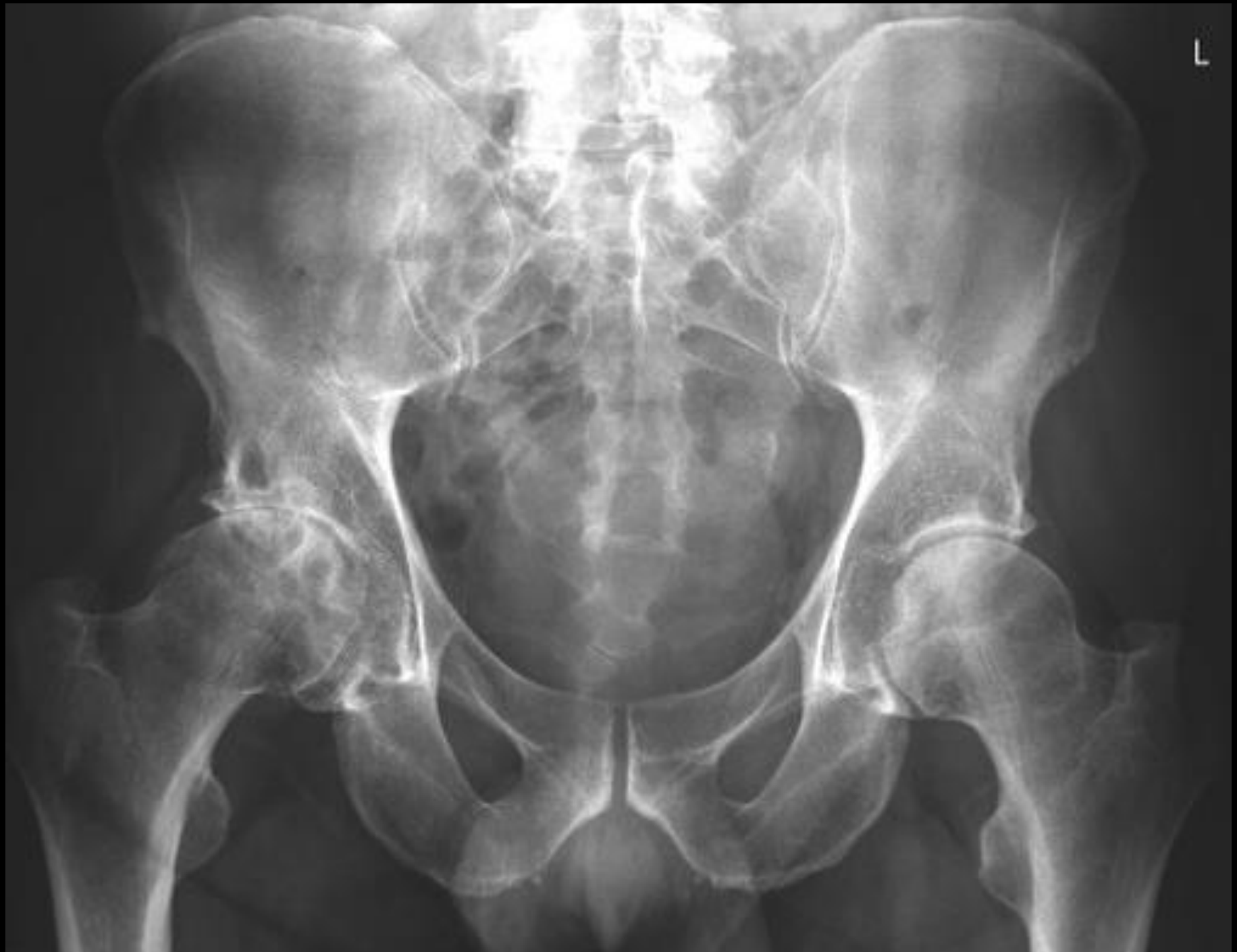
Background

- Most common type of arthritis – affects 1.5 million Australians (~2-3% health expenditure)
- Uncommon before 45 years, significant increase with age – 40% of 65 year olds and >70% of those 75 year
- X-ray changes more prevalent, but limited correlation between X-rays & symptoms
- Moderate correlation between symptoms and certain MRI changes eg bone marrow lesions, cartilage deficits
- Defined as symptoms + structural changes
- Women affected > men except for hip OA (typically unilateral)

Affected Sites

- Knee – greatest disability & most studied as most homogeneous population; males – unilateral & trauma history versus females – bilateral; usually starts in medial compartment
- Hips – superior pole most commonly affected
- Hands – base of thumb, DIP and PIP joints (strongly associated with family history, females, middle age onset)
- Spine (any section) – apophyseal joints
- Mixtures of the above sites
- If ≥4 sites affected, QOL, pain & disability=RA

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Risk factors

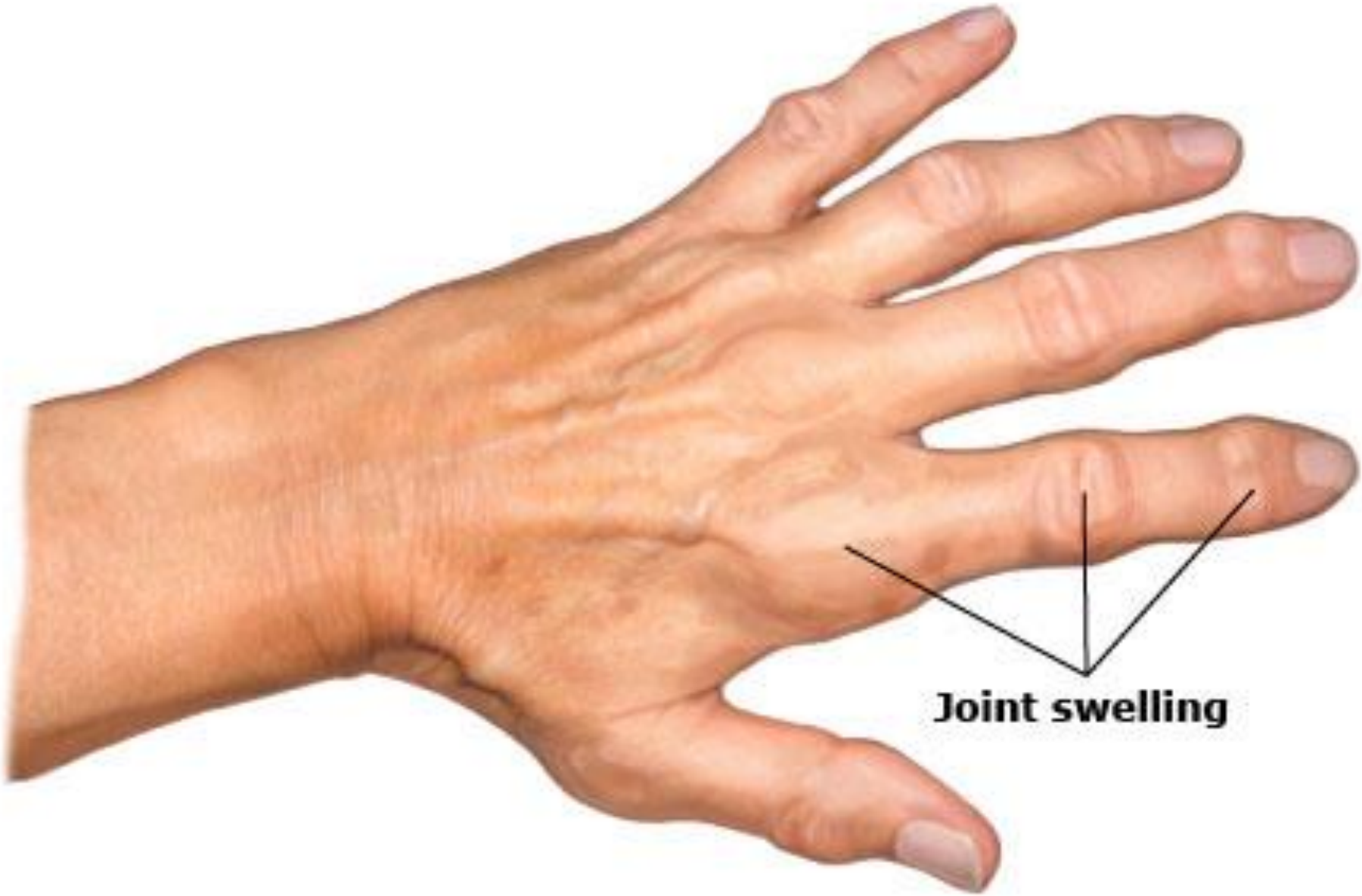
- Secondary to preceding joint problem – major injury, mal-alignment, inflammatory arthritis, prior infection
- Genetic component (family history and female) – generalised pattern
- Increasing age
- Obesity – particularly knee & ? Hip OA
- Repetitive over-use & certain occupations
- ? Joint hypermobility as a risk factor
- Poor thigh muscle strength (knee OA)

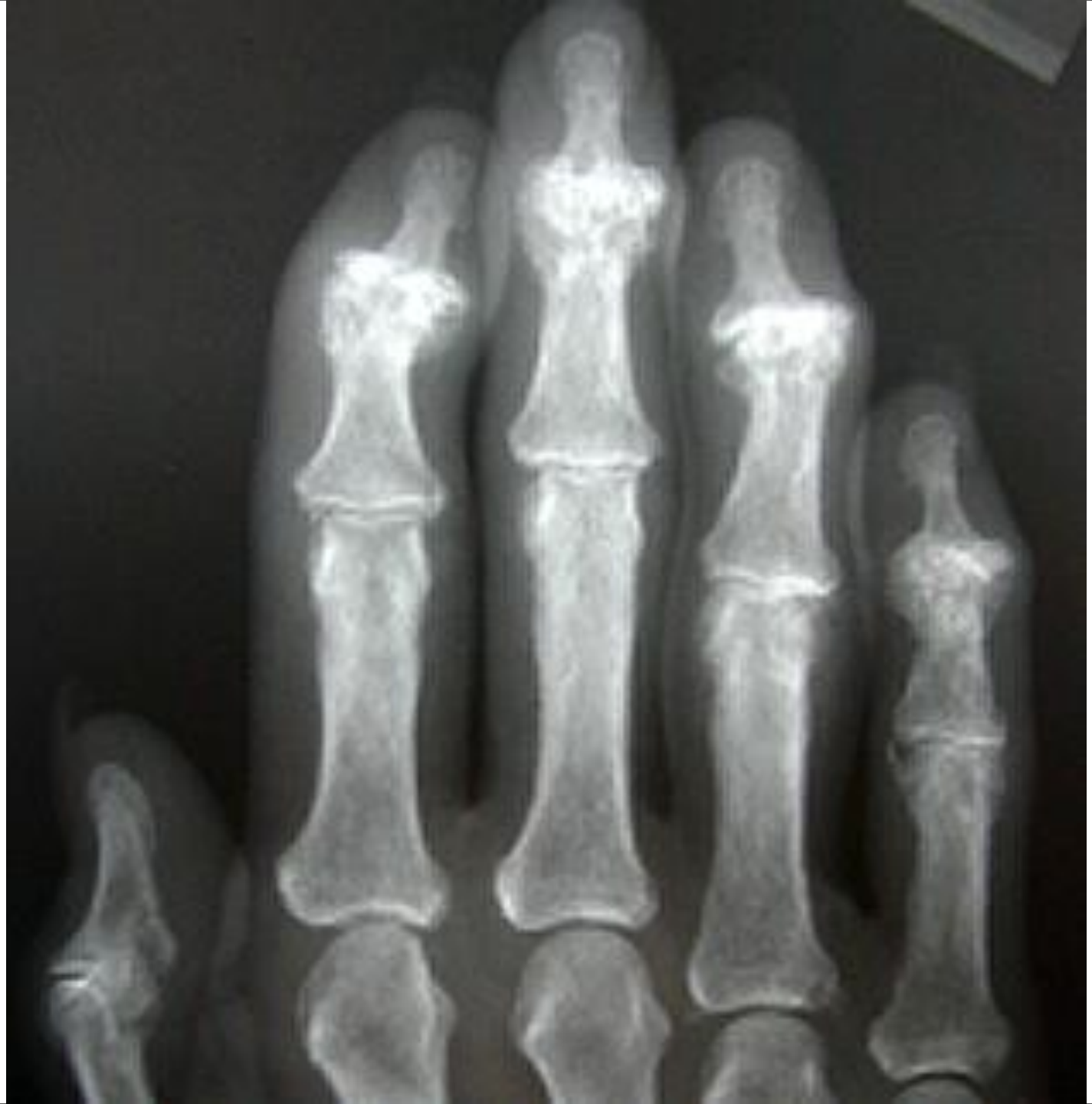
Pathophysiology

- Not just simple “wear & tear” degeneration
- Dynamic cell driven process
- Commonly, inflammatory component – mild-moderate, at least intermittently
- Loss of articular cartilage → hypertrophic reaction at joint margin (osteophytes) & subchondral changes (oedema & cysts)
- Inflamed synovium often seen on MRI
- Loss of meniscal integrity & ligament injury

Clinical Manifestations

- Pain is the predominate symptom – arising from joint itself & peri-articular structures & centrally
- Some evidence that pain may be protective of future joint destruction
- Stiffness
- Limitation of movement & functional restriction
- Local tenderness
- Crepitus
- Joint swelling (sometimes)
- Psychosocial aspects – depressed mood, loss of independence, anxiety


Joint swelling



Management Principles

- Patient education & self-management – WA study published in A&R 2012
- Medications – symptom management +/- disease modifying (? Strontium – Reginster et al, ARD 2013)
- Non-medication strategies - diet & complementary therapies; exercise & physical therapies; weight reduction; aids/modifications
- Need a plan for regular treatment & how to manage a symptom “flare”
- Surgery very effective in selected patients – approx 50,000 arthroplasties/year

DMOAD: Disease Modifying OA Drugs

- None available for clinical practice
- SEKOIA Trial (Strontium 1 or 2 g per day versus placebo) – small, non-clinical x-ray benefit over 3 years with either dose, possible symptom benefit only with 2g/day
- Is it possible to change symptoms as well as structural modification in OA?
- Other drugs – Glucosamine, NOS inhibitors, statins (no consistent effect)

Symptom Relieving Medications

- About 60% use regular paracetamol – reduces pain by 5-9 mm (100 mm scale)
- About 50% use NSAID (mainly, celecoxib and meloxicam in Australia) - reduce pain ~12-15 mm on 100 mm scale
- Combining NSAID and paracetamol – no clear increased analgesia but ? more GIT bleeding (Doherty et al 2011 – ARD)
- All NSAID carry GIT and CVS risk – avoid chronic dosing with diclofenac
- Paracetamol combinations – opioid & tramadol ? their place in therapy

Background to NSAID & CVS Safety Debate

- Patchwork of evidence over last 10 years – mixed messages & difficult data interpretation
- Risk first emerged with VIGOR (NEJM 2000) - >8000 patients with RA: 18 cases of MI with rofecoxib 50 mg/day vs 3 cases treated with Naproxen 1000 mg/day
- ½ of MI patients not taking low dose ASA (exclusion criteria)

General Messages about NSAID & CVS Safety

- All NSAID drugs confer increased risk of serious CVS events & the magnitude of risk is dependent on the patient's CVS risk
- Symptomatic treatment only – mean change of 13 mm on 100 mm VAS
- All studies assess patients taking NSAID for 1-3 years on a continual basis, so ? effect of short term, intermittent or prn use
- Can't forget GIT toxicity when making choice
- Same message as previously – "lowest dose for the shortest possible period"
- Under-utilization of non-drug measures -weight loss, exercise programs (local & general), orthotics

- **Summary of relative risk estimates for cardiovascular events with individual NSAIDs (versus non-use)**

NSAID	Serious Cardiovascular Events; RR (95% CI) Versus Non-use of NSAIDs					
	Observational Studies (Outcomes)				Randomised Studies (Outcomes)	
	Hernandez-Diaz et al., 2006 [4] (AMI)	Singh et al., 2006 [5] (AMI)	McGettigan and Henry, 2006 [6] (CV Events)	McGettigan and Henry, 2011 [9] (CV Events)	Trelle et al., 2011 [7] (APTC Composite Outcomes)	Kearney et al., 2006 [8] (CV Events)
Etoricoxib	nr	nr	nr	2.05 (1.45–2.88)	1.53 (0.74–3.17)	nr
Etodolac	nr	nr	nr	1.55 (1.28–1.87)	nr	nr
Rofecoxib	1.27 (1.12–1.44)	nr	1.35 (1.15–1.59)	1.45 (1.33–1.59)	1.44 (1.00–1.99)	1.42 (1.13–1.78) (with celecoxib)[a]
Diclofenac	1.39 (1.18–1.64)	1.38 (1.22–1.57)	1.40 (1.16–1.70)	1.40 (1.27–1.55)	1.60 (0.85–2.99)	1.63 (1.12–2.37)
Indometacin	nr	nr	1.30 (1.07–1.60)	1.30 (1.19–1.41)	nr	nr
Meloxicam	nr	nr	1.25 (1.00–1.55)	1.20 (1.07–1.33)	nr	nr
Ibuprofen	1.01 (0.89–1.15)	1.11 (1.06–1.17)	1.07 (0.97–1.18)	1.18 (1.11–1.25)	2.26 (1.11–4.89)	1.51 (0.96–2.37)
Celecoxib	0.97 (0.86–1.08)	nr	1.06 (0.91–1.23)	1.17 (1.08–1.27)	1.43 (0.94–2.16)	1.42 (1.13–1.78) (with rofecoxib)[a]
Naproxen	0.98 (0.87–1.11)	0.99 (0.88–1.11)	0.97 (0.87–1.07)	1.09 (1.02–1.16)	1.22 (0.78–1.93)	0.92 (0.67–1.26)
Piroxicam	nr	nr	1.06 (0.70–1.59)	1.08 (0.91–1.30)	nr	nr

[a]celecoxib and rofecoxib analysed together.
AMI, acute myocardial infarction; APTC, Anti-Platelet Trialists Collaboration; CV, cardiovascular; nr, not reported.
doi:10.1371/journal.pmed.1001388.t001

McGettigan P, Henry D (2013) Use of Non-Steroidal Anti-Inflammatory Drugs That Elevate Cardiovascular Risk: An Examination of Sales and Essential Medicines Lists in Low-, Middle-, and High-Income Countries. PLoS Med 10(2): e1001388. doi:10.1371/journal.pmed.1001388
http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.1001388

CVS Risk & individual NSAID

- All NSAID associated with increased risk of CVS events
- Naproxen appears to be the least harmful in terms of various types of CVS events
- Ibuprofen, diclofenac, etoricoxib & lumiracoxib associated with risk increase of at least 30% for several CVS outcomes
- Relationship between risk of CVS harm & COX-2 selectivity not so clear

Other Clinical Considerations for NSAID related CVS Risk

- High CVS risk – 5 year risk of CV event >15% - anyone with established CVD, diabetic nephropathy, age > 65-75 years, & a host of CVS risk factors to consider
- Where does meloxicam fit in? - McGettigan systematic review (JAMA 2006) – relative CV risk was 1.25 (1.0-1.55)
- PRECISION study reported in NEJM 2016 - prospective safety analysis of celecoxib versus ibuprofen or naproxen showed equal with 2.5% having MI over 20 months

NSAID & GIT Risks

- Strategies to significantly reduce GIT risk may change an individual's status – often more amenable to modification than significant CVS risk factors
- Greatest risk factors for significant GIT harm with NSAID – presence of *H.pylori*, age > 65 years, past history of peptic ulcer disease & ? dyspepsia, concomitant medication use (eg prednisolone, SSRI)
- Often GIT relative risk is very different to CVS relative risk for each individual NSAID (eg differing profiles for diclofenac – relatively low GIT risk but high relative CVS risk)

Relative risk of gastrointestinal complications with NSAID, relative to ibuprofen or non-use (shaded)

Drug	Case-control studies	Cohort study	Italian case-control
Non-use			1.0
Ibuprofen	1.0	1.0	2.1 (0.6 to 7.1)
Fenoprofen	1.6 (1.0 to 2.5)	3.1 (0.7 to 13)	
Aspirin	1.6 (1.3 to 2.0)		
Diclofenac	1.8 (1.4 to 2.3)	1.4 (0.7 to 2.6)	2.7 (1.5 to 4.8)
Sulindac	2.1 (1.6 to 2.7)		
Diflusinal	2.2 (1.2 to 4.1)		
Naproxen	2.2 (1.7 to 2.9)	1.4 (0.9 to 2.5)	4.3 (1.6 to 11.2)
Indomethacin	2.4 (1.9 to 3.1)	1.3 (0.7 to 2.3)	5.4 (1.6 to 18.9)
Tolmetin	3.0 (1.8 to 4.9)		
Piroxicam	3.8 (2.7 to 5.2)	2.8 (1.8 to 4.4)	9.5 (6.5 to 13.8)
Ketoprofen	4.2 (2.7 to 6.4)	1.3 (0.7 to 2.6)	3.2 (0.9 to 11.9)
Celebrex	NR	NR	NR
Ketorolac			24.7(9.6 to 63.5)

Note that the Italian case-control study (shaded) compares risk of gastrointestinal event

Clinical Algorithm (Personal)

	Low Cardiovascular Risk	**High Cardiovascular Risk**
Low Gastrointestinal Risk	Broad choice	Naproxen
High Gastrointestinal Risk	Celecoxib	AVOID

Intra-articular Treatment

- Single CS injection may provide rapid relief for up to 4 weeks in knee OA (better result if effusion) - dwindling efficacy with repeat injections
- Hyaluronic acid injection(s) – small pain relieving effect with slower onset but more prolonged (3 months); most effective in mild-moderate knee OA

Complementary Therapies

- Glucosamine – more than 30 studies, mostly short duration (3 months), versus placebo and NSAID, no consistent positive effect on pain relief & retarding structural progression except with 1 brand
- Chondroitin – some symptom relief (9 mm reduction) in a smaller number of studies (knee and hand OA)
- GC + Chondroitin – no better than placebo over 6 months for pain & function (A&R 2017)
- Topical NSAID, comfrey root extract or rubefacients – short term analgesia (up to 10 days)
- Various nutriceuticals with very low level evidence (met-analysis 2016 –IJRD) – curcumin, avocado, etc

Diet and OA

- High dose Omega-3 (supplement &/or diet) improves symptoms (pain) & disability out to 2 years – knee +/- hand OA (Aust study of 202 patients)
- Omega-3 has NSAID sparing effect for most types of arthritis (except gout)
- Adequate Vitamin D important (McAlindon et al, JAMA 2013) – symptoms and structural benefit
- Ayurvedic medicine or diet offers equivalent analgesia to GS and celecoxib (6 month study – published Rheumatology 2013 online by Chopra et al)

Weight Reduction for OA

- Intensive weight loss combined with low-moderate intensity exercise halves knee pain in overweight patients (RNS Study)
- 450 patients aged > 55 years with BMI 27-42 → pain scores fell from 67 to 33 mm; also improved function & walk speed
- At 18 months, lost 11 kg (11%) with diet + exercise, 9 kg with diet & 2 kg with exercise alone
- Exercise – 2 x 15 min walks & 1 x 20 min weight training x 3/week
- Greater benefit in those with mild-moderate OA & weight loss is also good for structure preservation

Physical Therapies and OA

- Patella taping – conflicting evidence about medial patella taping (+ strengthening of vastus medialis quad) for S/T analgesia – may be a vehicle to facilitate activity
- GPs aware of the HANDI project
- Lateral heel wedges for medial knee OA (+ talar taping) → S/T pain relief
- TENS – possible S/T benefit (not strong data for support of needling)
- Walking sticks & orthotics have some evidence in selected cases
- Knee braces, massage, magnets – no benefit

Conclusion

- Most common type of arthritis & is a major cause of pain, disability & reduced QOL
- Individualized care – in particular, assess CVS and GIT risk
- Acute action plan as well as maintenance management plan
- Most risk factors for OA are not preventable except optimal weight & exercise
- Management is multi-modal & frequently multi-disciplinary – non-pharmacological means & medicines to control symptoms