

Osteoporosis: secondary prevention

NICE guidelines were updated in 2008 on the secondary prevention of osteoporotic fractures in postmenopausal women.

Key points include

- treatment is indicated following osteoporotic fragility fractures in postmenopausal women who are confirmed to have osteoporosis (a T-score of - 2.5 SD or below). In women aged 75 years or older, a DEXA scan may not be required 'if the responsible clinician considers it to be clinically inappropriate or unfeasible'
- vitamin D and calcium supplementation should be offered to all women unless the clinician is confident they have adequate calcium intake and are vitamin D replete
- alendronate is first-line
- around 25% of patients cannot tolerate alendronate, usually due to upper gastrointestinal problems. These patients should be offered risedronate or etidronate (see treatment criteria below)
- strontium ranelate and raloxifene are recommended if patients cannot tolerate bisphosphonates (see treatment criteria below)

Treatment criteria for patients not taking alendronate

Unfortunately, a number of complicated treatment cut-off tables have been produced in the latest guidelines for patients who do not tolerate alendronate

Risk factors (for use in the tables below)

- parental history of hip fracture
- alcohol intake of 4 or more units per day
- rheumatoid arthritis

T-scores (SD) at (or below) which risedronate or etidronate is recommended when alendronate cannot be taken

Age (years) No risk factors 1 risk factor 2 risk factors

50-54	Not indicated	- 3.0	- 2.5
55-59	- 3.0	- 3.0	- 2.5
60-64	- 3.0	- 3.0	- 2.5
65-69	- 3.0	- 2.5	- 2.5
70 or older	- 2.5	- 2.5	- 2.5

T-scores (SD) at (or below) which strontium ranelate or raloxifene is recommended when alendronate and either risedronate or etidronate cannot be taken

Age (years) No risk factors 1 risk factor 2 risk factors

50-54	Not indicated	- 3.5	- 3.5
55-59	- 4.0	- 3.5	- 3.5
60-64	- 4.0	- 3.5	- 3.5

65-69	- 4.0	- 3.5	- 3.0
70-74	- 3.0	- 3.0	- 2.5
75 or older	- 3.0	- 2.5	- 2.5

Supplementary notes on treatment

Bisphosphonates

- alendronate, risedronate and etidronate are all licensed for the prevention and treatment of post-menopausal and glucocorticoid-induced osteoporosis
- all three have been shown to reduce the risk of both vertebral and non-vertebral fractures although alendronate, risedronate may be superior to etidronate in preventing hip fractures
- ibandronate is a once-monthly oral bisphosphonate

Vitamin D and calcium

- poor evidence base to suggest reduced fracture rates in the general population at risk of osteoporotic fractures - may reduce rates in frail, housebound patients

Raloxifene - selective oestrogen receptor modulator (SERM)

- has been shown to prevent bone loss and to reduce the risk of vertebral fractures, but has not yet been shown to reduce the risk of non-vertebral fractures
- has been shown to increase bone density in the spine and proximal femur
- may worsen menopausal symptoms
- increased risk of thromboembolic events
- may decrease risk of breast cancer

Strontium ranelate

- 'dual action bone agent' - increases deposition of new bone by osteoblasts and reduces the resorption of bone by osteoclasts
- strong evidence base, may be second-line treatment in near future
- increased risk of thromboembolic events

Teriparatide

- recombinant form of parathyroid hormone
- very effective at increasing bone mineral density but role in the management of osteoporosis yet to be clearly defined

Hormone replacement therapy

- has been shown to reduce the incidence of vertebral fracture and non-vertebral fractures
- due to concerns about increased rates of cardiovascular disease and breast cancer it is no longer recommended for primary or secondary prevention of osteoporosis unless the woman is suffering from vasomotor symptoms

Hip protectors

- evidence to suggest significantly reduce hip fractures in nursing home patients
- compliance is a problem

Falls risk assessment

- no evidence to suggest reduced fracture rates
- however, do reduce rate of falls and should be considered in management of high risk patients

Osteoarthritis: management

NICE published guidelines on the management of osteoarthritis (OA) in 2008

- all patients should be offered help with weight loss, given advice about local muscle strengthening exercises and general aerobic fitness
- paracetamol and topical NSAIDs are first-line analgesics. Topical NSAIDs are indicated only for OA of the knee or hand
- second-line treatment is oral NSAIDs/COX-2 inhibitors, opioids, capsaicin cream and intra-articular corticosteroids. A proton pump inhibitor should be co-prescribed with NSAIDs and COX-2 inhibitors. These drugs should be avoided if the patient takes aspirin
- non-pharmacological treatment options include supports and braces, TENS and shock absorbing insoles or shoes
- if conservative methods fail then refer for consideration of joint replacement

What is the role of glucosamine?

- normal constituent of glycosaminoglycans in cartilage and synovial fluid
- a systematic review of several double blind RCTs of glucosamine in knee osteoarthritis reported significant short-term symptomatic benefits including significantly reduced joint space narrowing and improved pain scores
- more recent studies have however been mixed
- the 2008 NICE guidelines suggest it is not recommended
- a 2008 Drug and Therapeutics Bulletin review advised that whilst glucosamine provides modest pain relief in knee osteoarthritis it should not be prescribed on the NHS due to limited evidence of cost-effectiveness

Methotrexate

Methotrexate is an antimetabolite which inhibits dihydrofolate reductase, an enzyme essential for the synthesis of purines and pyrimidines

Indications

- rheumatoid arthritis
- psoriasis
- acute lymphoblastic leukaemia

Adverse effects

- mucositis
- myelosuppression
- pneumonitis
- liver cirrhosis

Pregnancy

- women should avoid pregnancy for at least 3 months after treatment has stopped
- the BNF also advises that men using methotrexate need to use effective contraception for at least 3 months after treatment

Prescribing methotrexate

- methotrexate is a drug with a high potential for patient harm. It is therefore important that you are familiar with guidelines relating to its use
- methotrexate is taken weekly, rather than daily
- FBC, U&E and LFTs need to be regularly monitored. The Committee on Safety of Medicines recommend 'FBC and renal and LFTs before starting treatment and repeated weekly until therapy stabilised, thereafter patients should be monitored every 2-3 months'
- folic acid 5mg once weekly should be co-prescribed, taken more than 24 hours after methotrexate dose
- the starting dose of methotrexate is 7.5 mg weekly (source: BNF)
- only one strength of methotrexate tablet should be prescribed (usually 2.5 mg)
- avoid prescribing trimethoprim or cotrimoxazole concurrently - increases risk of marrow aplasia

Gout: management

Gout is a form of microcrystal synovitis caused by the deposition of monosodium urate monohydrate in the synovium. It is caused by chronic hyperuricaemia (uric acid > 450 $\mu\text{mol/l}$)

Acute management

- NSAIDs
- intra-articular steroid injection

- colchicine has a slower onset of action. The main side-effect is diarrhoea
- if the patient is already taking allopurinol it should be continued

Allopurinol prophylaxis - see indications below

- allopurinol should not be started until 2 weeks after an acute attack has settled as it may precipitate a further attack if started too early
- initial dose of 100 mg od, with the dose titrated every few weeks to aim for a serum uric acid of $< 300 \mu\text{mol/l}$
- NSAID or colchicine cover should be used when starting allopurinol

Indications for allopurinol*

- recurrent attacks - the British Society for Rheumatology recommend 'In uncomplicated gout uric acid lowering drug therapy should be started if a second attack, or further attacks occur within 1 year'
- tophi
- renal disease
- uric acid renal stones
- prophylaxis if on cytotoxics or diuretics

Lifestyle modifications

- reduce alcohol intake and avoid during an acute attack
- lose weight if obese
- avoid food high in purines e.g. Liver, kidneys, seafood, oily fish (mackerel, sardines) and yeast products

*patients with Lesch-Nyhan syndrome often take allopurinol for life

Temporal arteritis

Temporal arteritis is large vessel vasculitis which overlaps with polymyalgia rheumatica (PMR). Histology shows changes which characteristically 'skips' certain sections of affected artery whilst damaging others.

Features

- typically patient > 60 years old
- usually rapid onset (e.g. < 1 month)
- headache (found in 85%)
- jaw claudication (65%)

- visual disturbances secondary to anterior ischemic optic neuropathy
- tender, palpable temporal artery
- features of PMR: aching, morning stiffness in proximal limb muscles (not weakness)
- also lethargy, depression, low-grade fever, anorexia, night sweats

Investigations

- raised inflammatory markers: ESR > 50 mm/hr (note ESR < 30 in 10% of patients). CRP may also be elevated
- temporal artery biopsy: skip lesions may be present
- note creatine kinase and EMG normal

Treatment

- high-dose prednisolone - there should be a dramatic response, if not the diagnosis should be reconsidered
- urgent ophthalmology review. Patients with visual symptoms should be seen the same-day by an ophthalmologist. Visual damage is often irreversible

Systemic sclerosis

Systemic sclerosis is a condition of unknown aetiology characterised by hardened, sclerotic skin and other connective tissues. It is four times more common in females

There are three patterns of disease:

Limited cutaneous systemic sclerosis

- Raynaud's may be first sign
- scleroderma affects face and distal limbs predominately
- associated with anti-centromere antibodies
- a subtype of limited systemic sclerosis is CREST syndrome: Calcinosis, Raynaud's phenomenon, oEsophageal dysmotility, Sclerodactyly, Telangiectasia

Diffuse cutaneous systemic sclerosis

- scleroderma affects trunk and proximal limbs predominately
- associated with scl-70 antibodies
- hypertension, lung fibrosis and renal involvement seen
- poor prognosis

Scleroderma (without internal organ involvement)

- tightening and fibrosis of skin

- may be manifest as plaques (morphoea) or linear

Antibodies

- ANA positive in 90%
- RF positive in 30%
- anti-scl-70 antibodies associated with diffuse cutaneous systemic sclerosis
- anti-centromere antibodies associated with limited cutaneous systemic sclerosis

Ankylosing spondylitis: investigation and management

Ankylosing spondylitis is a HLA-B27 associated spondyloarthropathy. It typically presents in males (sex ratio 5:1) aged 20-30 years old.

Inflammatory markers (ESR, CRP) are typically raised although normal levels do not exclude ankylosing spondylitis.

HLA-B27 is of little use in making the diagnosis as it is positive in:

- 90% of patients with ankylosing spondylitis
- 10% of normal patients

Plain x-ray of the sacroiliac joints is the most useful investigation in establishing the diagnosis. Radiographs may be normal early in disease, later changes include:

- sacroilitis: subchondral erosions, sclerosis
- squaring of lumbar vertebrae
- 'bamboo spine' (late & uncommon)
- chest x-ray: apical fibrosis

Spirometry may show a restrictive defect due to a combination of pulmonary fibrosis, kyphosis and ankylosis of the costovertebral joints.

Management

Early diagnosis is now more important following the advent of anti-TNF therapy

- encourage regular exercise such as swimming
- NSAIDs
- physiotherapy
- the disease-modifying drugs which are used to treat rheumatoid arthritis (such as sulphasalazine) are only really useful if there is peripheral joint involvement
- TNF-alpha blockers such as etanercept and adalimumab are increasingly used. This approach for severe ankylosing spondylitis was supported by NICE in 2008

Fibromyalgia

Fibromyalgia is a syndrome characterised by widespread pain throughout the body with tender points at specific anatomical sites. The cause of fibromyalgia is unknown.

Epidemiology

- women are 10 times more likely to be affected
- typically presents between 30-50 years old

Features

- pain: at multiple site, sometimes 'pain all over'
- lethargy
- sleep disturbance, headaches, dizziness are common

Diagnosis is clinical and sometimes refers to the American College of Rheumatology classification criteria which lists 9 pairs of tender points on the body. If a patient is tender in at least 11 of these 18 points it makes a diagnosis of fibromyalgia more likely

The management of fibromyalgia is often difficult and needs to be tailored to the individual patient. A psychosocial and multidisciplinary approach is helpful. Unfortunately there is currently a paucity of evidence and guidelines to guide practice. The following is partly based on consensus guidelines from the European League against Rheumatism (EULAR) published in 2007.

- explanation
- exercise programme
- cognitive behavioural therapy
- anti-depressants: amitriptyline

Rheumatoid arthritis: drug side-effects

The table below lists some of the characteristic (if not common) side-effects of drugs used to treat rheumatoid arthritis:

Drug	Side-effects
Methotrexate	Myelosuppression Liver cirrhosis Pneumonitis
Sulfasalazine	Rashes Oligospermia Heinz body anaemia
Leflunomide	Liver impairment

Hydroxychloroquine	Interstitial lung disease Hypertension Retinopathy Corneal deposits
Prednisolone	Cushingoid features Osteoporosis Impaired glucose tolerance Hypertension Cataracts
Gold	Proteinuria
Penicillamine	Proteinuria Exacerbation of myasthenia gravis
Etanercept	Demyelination Reactivation of tuberculosis
Infliximab	Reactivation of tuberculosis
Adalimumab	Reactivation of tuberculosis
Rituximab	Infusion reactions are common

Polymyalgia rheumatica

Pathophysiology

- overlaps with temporal arteritis
- histology shows vasculitis with giant cells, characteristically 'skips' certain sections of affected artery whilst damaging others
- muscle bed arteries affected most in polymyalgia rheumatica

Features

- typically patient > 60 years old
- usually rapid onset (e.g. < 1 month)
- aching, morning stiffness in proximal limb muscles (not weakness)
- also mild polyarthralgia, lethargy, depression, low-grade fever, anorexia, night sweats

Investigations

- ESR > 40 mm/hr
- note CK and EMG normal

- reduced CD8+ T cells

Treatment

- prednisolone e.g. 15mg/od - dramatic response

Rheumatoid arthritis: diagnosis

NICE have stated that clinical diagnosis is more important than criteria such as those defined by the American College of Rheumatology.

2010 American College of Rheumatology criteria

Target population. Patients who

- 1) have at least 1 joint with definite clinical synovitis
- 2) with the synovitis not better explained by another disease

Classification criteria for rheumatoid arthritis (add score of categories A-D; a score of 6/10 is needed definite rheumatoid arthritis)

Key

- RF = rheumatoid factor
- ACPA = anti-cyclic citrullinated peptide antibody

A. Joint involvement

1 large joint	0
2 - 10 large joints	1
1 - 3 small joints (with or without involvement of large joints)	2
4 - 10 small joints (with or without involvement of large joints)	3
10 joints (at least 1 small joint)	5

B. Serology (at least 1 test result is needed for classification)

Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3

C. Acute-phase reactants (at least 1 test result is needed for classification)

Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1

D. Duration of symptoms

< 6 weeks	0
> 6 weeks	1