RHEUMATOLOGY

This page intentionally left blank

14

GENERALIZED MUSCULOSKELETAL PROBLEMS

Anthony K. Clarke, Julia L. Newton and Raashid Luqmani

Cases relevant to this chapter

21, 60, 69, 73, 83, 98, 99

Essential facts

1. Non-specific musculoskeletal pains, especially back or neck related, are common and become more prevalent with age.
2. Pain is a neuropsychological phenomenon.
3. Fibromyalgia is a syndrome characterized by widespread body pain and sleep disturbance.
4. Chronic fatigue syndromes are common and disabling.
5. Pacing, psychological and physical support, provided by a dedicated multi-disciplinary team, offer a significant opportunity for recovery.
6. Musculoskeletal manifestations of endocrine disease are dependent on age and underlying disease duration.

CHRONIC PAIN

Aches and pains are an everyday accompaniment of the human condition. Children run about and fall over. Young men play contact sports. Pregnant women get back pain. Digging the garden leads to muscular pain. Osteoarthritis affects the majority of the population. For a small minority of the population, musculoskeletal symptoms are due to serious, progressive disorders, such as rheumatoid arthritis. One of the major challenges of modern medicine is that group of patients who do not have a rheumatic disorder, but whose symptoms are in excess of what can be described as 'the aches and pains of everyday life'. It can be argued that in our modern consumerist society there is a basic intolerance of *any* symptoms. This does not explain the large number of people who regularly attend their general practitioners (GPs) and rheumatology departments complaining of disabling symptoms that interfere with work, household duties and leisure activities. At least 10% of people in Britain suffer from chronic pain.

In this chapter the features of the commonly seen conditions and their management are described, using an evidence-based approach. There are a number of recognized chronic pain syndromes, including:

- Fibromyalgia
- Complex regional pain syndrome (CRPS type I) (previously algodystrophy, Sudek's atrophy or sympathetic dystrophy)
- Chronic fatigue syndrome (CFS)
- Causalgia (CRPS type II)
- Phantom limb pain
- Post-herpetic neuralgia
- Inappropriate pain (otherwise pain augmentation).

IMPORTANCE OF A POSITIVE DIAGNOSIS

Many diseases present with aches and pains, general malaise and fatigue. Common ones include hypothyroidism, low vitamin D levels, diabetes mellitus, malignant disease, inflammatory joint disease and, less commonly, other autoimmune rheumatic disorders, such as systemic lupus erythematosus (SLE). It is essential when confronted by a patient with such symptoms to take a full history, paying particular attention to such factors as weight loss, change in bowel habit and the red flags associated with serious back pain (see Chapter 22).

A careful history and clinical examination will ensure that inflammatory arthritis and other autoimmune rheumatic disorders are excluded and that the typical signs of fibromyalgia, for instance, are present. Appropriate investigations may be necessary, such as autoantibody testing for indicative features (not as a blanket screening test), thyroid function, glucose, muscle enzymes (particularly in case of muscle weakness). It is particularly important that in suspected inappropriate pain and chronic fatigue syndromes a full medical screening is undertaken.

FIBROMYALGIA

Fibromyalgia is a relatively new condition. Although rheumatism, fibrositis and lumbago are terms of some antiquity, fibromyalgia became a recognized rheumatological diagnosis only in the early 1980s. It is important to emphasize that fibromyalgia is not a disease, and that some rheumatologists refuse to recognize its existence as a distinct entity. It can be precipitated by any condition that causes sleep disturbance, and can be induced by deliberate sleep deprivation. The diagnosis depends upon the presence of two main criteria: (1) widespread pain; and (2) associated symptoms of fatigue, unrefreshing sleep, cognitive features, plus a wide variety of possible somatic symptoms such as irritable bowel syndrome, dry mouth or eyes.

Typically, the patient reports that they wake feeling unrefreshed. Patients may report that on some days they feel good and full of energy, whereas on others they are very achy and feel exhausted. The response to this is to cram as much into the good days as possible, resulting in worsening of their symptoms over the course of the next few days.

Management includes improvement in the sleep pattern, attention to the underlying precipitating cause, and pacing. Typically, the sleep is improved by the use of small doses of a tricyclic antidepressant. The most popular is amitriptyline. Usually this is started in a very low dose, 10 mg, given 2–3 hours before retiring for the night. The dose is then slowly increased (i.e. every 7–10 days) by 10 mg until a dose is found that produces a good, refreshing, sleep pattern. However, the evidence base for its use is limited. By contrast, there is good evidence for benefit using serotonin- and norepinephrine-reuptake inhibitors duloxetine and milnacipran (the latter is licensed for use only in the USA) and the $\alpha_2\delta$ ligand pregabalin.

Pacing can be a useful strategy for some patients. Because of the typical peaks and troughs of the condition, it is important that on the good days only normal activities are pursued, i.e. the amount that the individual can cope with on a bad day. This allows for a steady improvement in the physical capacity.

Unfortunately, the outcome for most patients remains unsatisfactory. Most studies show between 20% and 30% improvement in pain and quality of life respectively from pharmacological treatment. The effect of non-pharmacological treatment remains less certain. It is likely to be of most benefit in selected patients, such as those with significant psychological distress.

COMPLEX REGIONAL PAIN SYNDROME

Although the physical signs may vary, the main feature is unremitting pain that interferes with normal activities. The pain is often described by the sufferer as burning or crushing. The pain may be modified by analgesics, but is rarely abolished and is often more sensitive to drugs aimed at neurogenic pain, such as carbamazepine, pregabalin or duloxetine. Another drug, milnacipran is available in the USA but not approved for use in the UK or Europe. Type I complex regional pain syndrome is idiopathic and was formerly known as reflex sympathetic dystrophy, Sudek's atrophy or algodystrophy.

Type II complex regional pain syndrome follows a nerve injury and was formerly referred to as causalgia. CRPS type I is characterized clinically by severe prolonged pain out of proportion to

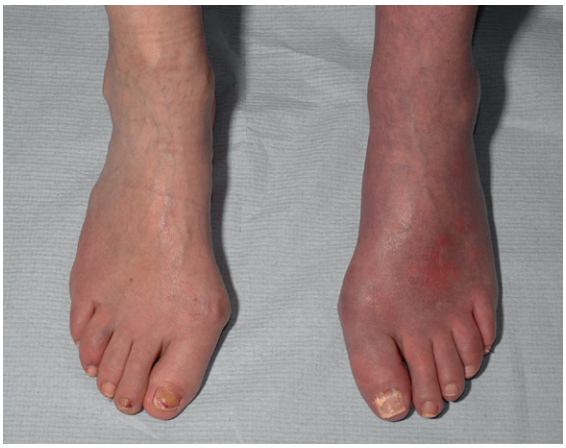


FIGURE 14.1 Complex regional pain syndrome affecting the left lower limb. Note the dusky discoloration of the left foot

any injury, allodynia (pain on light touch to the skin), cold, clammy skin and loss of function (Fig. 14.1). Typically the skin is red and has a shiny appearance, with hypersensitivity. The exact cause of the condition is unknown. A variety of physiological abnormalities have been described including autonomic dysfunction, microcirculation abnormalities and muscle mitochondrial changes, amongst others. Radiographs taken in established cases may demonstrate osteoporosis, which is frequently patchy. Magnetic resonance imaging (MRI) shows patchy or diffuse bone marrow oedema, on T2 images. Levels of inflammatory markers are not normally raised.

CRPS type II is very similar to CRPS type I in the intensity of the pain, but usually without the obvious physical signs. Most cases of CRPS are treated by intensive physiotherapy and usually resolve slowly over a period of months. For many patients, the best approach is to help them adapt to and cope with the pain, using a combination of cognitive behavioural therapy, physiotherapy (specifically as graded exercise), analgesia and pain modifiers.

CHRONIC FATIGUE SYNDROME (CFS)

There is significant controversy surrounding the nature of CFS. Significant and strongly voiced differences of opinion exist between patients and health-care professionals regarding several aspects of management. These issues have hampered attempts to produce a sound evidence-based strategy for these conditions. There are likely to be several causes of CFS. CFS can be a complication of some viral illnesses, such as influenza or glandular fever. Similarly, severe, longstanding fibromyalgia can develop into CFS. Other precipitants appear to include surgical operations and debilitation associated with severe medical illnesses. Some cases appear to arise spontaneously. The condition is much commoner in women and there is a significant subgroup of adolescent sufferers.

Fatigue is the primary symptom. This is not just tiredness, nor the type of almost pleasant fatigue felt after heavy physical activity, but an overwhelming sensation that makes the sufferer feel physically ill. It is not relieved by sleep and, indeed, many patients complain that even when they do sleep properly (sleep is often disturbed, with early morning waking) it is not refreshing. Other symptoms include arthralgia and myalgia (which is why many patients are referred for rheumatological opinions), low-grade fever, irritable bowel syndrome, visual disturbance, and poor concentration and memory. There are usually good days and bad days and, as with fibromyalgia, there is a very strong temptation to overdo things on the good days. There are no specific clinical signs.

Wherever possible a positive diagnosis of CFS should be made, rather than seeing it as a diagnosis of exclusion. Other causes of fatigue, such as hypothyroidism and severe anaemia, do need to be considered in the differential diagnosis, but it is unusual for a good history and examination not to spot these types of problem, and simple screening tests, such as thyroid function and a full blood count, should be undertaken.

There is no clear evidence base for any benefit from any specific pharmacological intervention. Treatment consists of reassurance that the diagnosis has been positively made, that the condition is treatable, and that a programme is available. That programme should include carefully paced activity, help with sleep disturbance and cognitive behavioural therapy. There are a number of support organizations in the UK and elsewhere; an initiative by the Department of Health has produced a network of cooperative centres for the management of CFS.

HYPERMOBILITY SYNDROME

Between 10% and 25% of the population have joint laxity, but the majority of these individuals do not suffer pain from their hypermobile joints,

and indeed can make use of their flexibility in sports and dance. Generalized hypermobility is most common in children, followed by young, white caucasian females. Patients with hypermobility and musculoskeletal injuries may present to their GP with non-specific pain, especially myalgia and arthralgia. Hypermobility syndrome is a term used to describe this group of musculoskeletal complaints, which appear to be associated with non-pathological excessive joint mobility. The most common form is termed 'benign joint hypermobility syndrome'. Less common causes of joint laxity include Marfan syndrome, Ehlers–Danlos syndrome and osteogenesis imperfecta, which are beyond the scope of this book. Management of hypermobility syndrome includes reassurance (that they do not have arthritis), patient education, stretching and strengthening exercises for the affected joint or joints.

RHEUMATIC MANIFESTATIONS OF METABOLIC AND ENDOCRINE DISEASES

Many endocrine disorders have musculoskeletal manifestations. A rheumatological complaint may, therefore, be indicative of an undiagnosed endocrinopathy. An endocrine history will uncover common symptoms that suggest an endocrine cause (Box 14.1). Because endocrine and rheumatic diseases often coexist, it is important to ask about endocrine symptoms in a patient with an established rheumatological diagnosis.

In this section the common rheumatic manifestations of metabolic and endocrine disease will be discussed (Table 14.1). The more common diseases are concentrated upon, but some rarer disorders have been included if musculoskeletal symptoms are particularly prominent.

Box 14.1
Endocrine history questions

- Weight change
- Hair loss/dryness
- Infertility
- Reduced libido
- Mood changes
- Fatigue
- Heat/cold intolerance
- Constipation/diarrhoea
- Family history of endocrine disease
- History of other endocrine problems

DIABETES MELLITUS

Both type 1 and 2 diabetes mellitus (DM) are associated with rheumatological complaints (Table 14.2). These disorders are either unique to diabetic patients or are known to occur in the general

Table 14.1 Endocrine and metabolic diseases with musculoskeletal manifestations

Endocrine Disorders	Metabolic Disorders
Diabetes mellitus	Hyperlipidaemia
Hyperthyroidism	Renal failure
Hypothyroidism	Ochronosis
Hyperparathyroidism	Haemochromatosis
Acromegaly	Lysosomal storage disorders Glycogen storage metabolic myopathies

Table 14.2 Musculoskeletal manifestations of diabetes mellitus

Specific to Diabetes Mellitus	Increased Prevalence in Diabetes Mellitus	Possible Association with Diabetes Mellitus
Limited joint mobility	Dupuytren's contracture	Osteoarthritis
Diabetic amyotrophy	Palmar flexor tenosynovitis	
Diabetic muscle infarction	Carpal tunnel syndrome	
	Adhesive capsulitis	
	DISH	
	Scleroedema	
	Neuropathic arthropathy	
	Bone and joint infection	

DISH, diffuse idiopathic skeletal hyperostosis.

population, but have an increased incidence in patients with DM. Musculoskeletal problems in DM are becoming increasingly common owing to the increased life expectancy of diabetic patients. The pathophysiology of these disorders in DM is poorly understood.

The presence of one musculoskeletal problem in DM increases the likelihood of developing other musculoskeletal complications; there is an increased incidence of adhesive capsulitis (AC), Dupuytren's contracture and limited joint mobility occurring together in the same individual than would be expected. Treatment may include corticosteroid injection, which in DM should be used with caution because hyperglycaemia may follow.

LIMITED JOINT MOBILITY (DIABETIC CHEIROARTHROPATHY, DIABETIC HAND SYNDROME)

This condition produces a generalized non-painful stiffness and puffiness of the hands with flexion contractures of all the fingers so that the patient is unable to place the palmar surfaces of the hands and fingers flatly together ('prayer sign'). It begins with the little finger and progresses laterally. Some 8–50% of patients with DM develop limited joint mobility; it occurs in both types 1 and 2 DM. On biopsy there is a loss of elastic fibres in the skin. There is an association between the presence of limited joint mobility and microvascular and macrovascular complications in DM. There is no effective therapy, but good diabetic control and exercises concentrating on finger extension may help to prevent further deterioration of the condition.

DUPUYTREN'S CONTRACTURE

Dupuytren's contracture is due to thickening and tethering of the palmar fascia resulting in digital contracture (see p. 281). This condition occurs more commonly in diabetic patients, but is also common in the general population; it affects 5–13% of the general population and 12–63% of diabetic patients. It initially affects the ring and little fingers in the general population, but the ring and middle fingers in diabetics. Sixty-five per cent are bilateral and men are affected more than women overall, but there is an equal sex incidence when present in association with DM. It is usually less progressive in the diabetic population and there is less need for surgery. Although often idiopathic, there are other known associations in addition to diabetes (Table 14.3).

Table 14.3 Associations of Dupuytren's contracture

Association	Frequency
Familial	27–68%
Diabetes	20–63%
Prior hand trauma	13%
Alcohol	10%
Epilepsy	2%
Smoking	Unknown
Manual labour	Unknown
Ischaemic heart disease	Unknown
HIV infection	Unknown

Treatment includes occupational therapy, physiotherapy, steroid injections and surgical fasciectomy, but the latter is the only treatment supported by evidence.

PALMAR FLEXOR TENOSYNOVITIS

This common condition is due to fibrous proliferation of the tendon sheath preventing the normal smooth movement of the tendon. There is often an associated 'trigger finger'. It affects less than 1% of the general population, compared with 11% of diabetic patients. The underlying reason for this increased prevalence is not known. Treatment includes good glycaemic control, hand exercises, local corticosteroid injections and surgery, if these conservative measures fail.

ADHESIVE CAPSULITIS (FROZEN SHOULDER)

This normally common condition (see p. 280) has a significantly increased prevalence in the diabetic population of 11–30%. It is characterized by progressive painful restriction of gleno-humeral movement. The pathology involves inflammation and then fibrosis resulting in adherence of the joint capsule to the humeral head. There are three stages to adhesive capsulitis: painful, adhesive and resolution. The process takes up to 2 years. Although physiotherapy, non-steroidal anti-inflammatory drugs (NSAIDs) and local corticosteroid injections can reduce pain and improve the range of motion to a degree, no treatment appears to shorten the cycle. In diabetics, adhesive capsulitis tends to occur at a younger age and is often less painful, but the cycle to resolution often takes longer.

OSTEOPENIA

Osteopenia and osteoporosis occur in type 1 DM. The longer standing the DM, the greater the bone loss and increased fracture risk. Insulin and insulin-like growth factor 1 (IGF-1) have anabolic effects, including the promotion of osteoblastic activity. The lack of these proteins in type 1 DM, but the excess presence in type 2 DM, helps to explain the normal bone density of type 2 diabetic patients. Type 2 DM is also associated with obesity, which again is associated with a lower incidence of osteopenia/osteoporosis. Despite the reassuring nature of dual-energy X-ray absorptiometry (DEXA) results in type 2 DM, there is an increased risk of fracture, suggesting that there is an effect on bone quality compared with bone density. There is likely to be a role for osteocalcin and adiponectin in explaining the association between fracture risk and diabetes.

CARPAL TUNNEL SYNDROME

This is a common entrapment neuropathy affecting the median nerve as it passes through the carpal tunnel at the wrist under flexor retinaculum, the transverse carpal ligament (see (Fig. 14.2) and p. 282). Some 11–16% of patients with DM develop carpal tunnel syndrome (CTS). Characteristically, the patient develops pain and paraesthesia in a median nerve distribution: the palmar and dorsal aspects of the thumb, index and middle fingers, and the radial half of the ring finger. The exact distribution may vary from person to person and the pain may radiate to the forearm. The pain and paraesthesia are typically worse at night. Weakness may develop affecting the muscles supplied by the median nerve, such as the thenar eminence of the thumb. The ideal muscles to test are abductor pollicis brevis and opponens pollicis. There may be muscle atrophy of the thenar eminence. Tinel's test, tapping over the median nerve at the wrist, and Phalen's test, prolonged palmar flexion of the wrist for 60 seconds, may reproduce the symptoms. Diagnosis is based on history, examination and electrophysiology studies. Treatment includes splinting, corticosteroid injection or surgical release but, where it is a secondary phenomenon, treatment of the underlying disorder is most important. Some 5–8% of patients with CTS have diabetes, highlighting the importance of a high index of suspicion at the patient's first presentation.

DIFFUSE IDIOPATHIC SKELETAL HYPEROSTOSIS (FORESTIER DISEASE)

Diffuse idiopathic skeletal hyperostosis (DISH) is a condition where calcification of the anterior longitudinal ligament of the spine occurs with heterotopic ossification of joint capsules, tendon entheses and ligaments (Fig. 14.3). It is often asymptomatic or may present with spinal pain and stiffness. In the normal population DISH is a disease of the elderly and has a prevalence of 2–13%. In diabetics it typically occurs at a younger average age and the prevalence is increased to 13–49%. It is more common in type 2 DM. It is hypothesized that the increase in IGF-1 in type 2 DM promotes osteoblast proliferation and ossification.

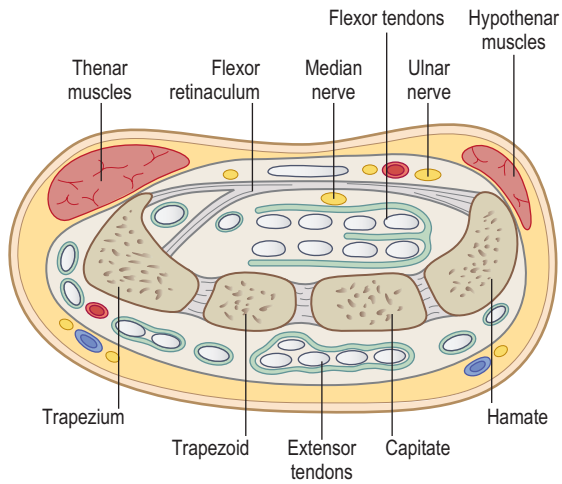


FIGURE 14.2 Cross-section through the wrist to demonstrate the structures surrounding the median nerve as it traverses the carpal tunnel. Increased volume of any of these structures can increase the pressure on the median nerve, resulting in neurological features of dysaesthesia and weakness

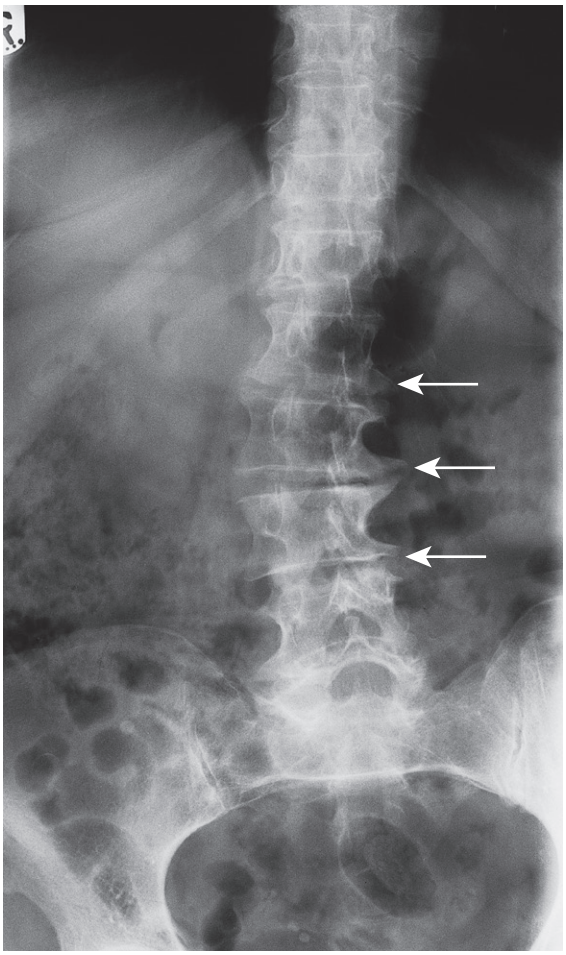


FIGURE 14.3 Radiograph of the lumbar spine showing flowing osteophytes in a patient with diffuse idiopathic skeletal hyperostosis

DIABETIC AMYOTROPHY

Diabetic amyotrophy is characterized by painful severe muscle wasting and weakness, typically affecting the proximal lower limbs. It is a subset of diabetic neuropathy, and reflexes are absent. It usually affects older men with type 2 DM. The aetiology is unknown and, although there is usually spontaneous improvement, this is often incomplete.

SCLEROEDEMA

This is a rare condition that has an association with DM, usually longstanding type 1 disease, but it does occur with type 2 DM. Other associations include blood dyscrasias and post-infection. It is of unknown cause and characterized by non-pitting induration of the skin. In diabetic patients it classically affects the upper back and tends to spare the extremities, but it may contribute to the development of limited joint mobility. Generally, it is a benign, self-limiting skin disease. On histological examination there is excess mucopolysaccharide deposition in the dermis and the condition is clearly distinguishable from scleroderma (see Chapter 17: Systemic diseases). There is no proven effective treatment.

Box 14.2
Differential diagnosis of neuropathic osteoarthropathy

- Osteomyelitis
- Erosive inflammatory arthritis
- Osteoarthritis
- Tumour

NEUROPATHIC ARTHROPATHY (CHARCOT'S JOINT)

This is a destructive arthropathy that affects the tarsal and metatarsal joints in the foot. The exact mechanism of neuropathic arthropathy is not fully understood. There is increased osteoclastogenesis and osteopenia, and hypervascularity of bone. The bone is weakened and susceptible to fracture and collapse. The universal presence of a sensory neuropathy combined with arterial disease, trauma and infection is thought to predispose to the characteristic painless chronic deformity of a 'Charcot joint'. The affected limb may become swollen, warm and red, often without a history of trauma. There may be associated skin ulceration and infection, sometimes requiring amputation. The main differential diagnoses are shown in Box 14.2.

Good diabetic control and foot care are of prime importance in all diabetic patients, and prevention is the main aim of management. Instability or deformity may limit the use of standard footwear. The foot should be kept plantigrade with orthoses to maintain a normal gait pattern. Early diagnosis of neuropathic arthropathy will help to prevent further deterioration. Bisphosphonates have been used to halt the aggressive osteoclast activity. In advanced cases surgery may be required.

BONE AND JOINT INFECTION

The prevalence of both septic arthritis and osteomyelitis is increased in DM. There is an increased incidence of soft-tissue infection and ulceration, particularly in association with neuropathic

arthropathy. This provides a route from which bone and joint infection could develop by direct invasion from an overlying soft-tissue infection or haematogenous spread to a distant joint.

Investigation of a suspected septic arthritis must include synovial fluid aspiration. MRI is very useful in differentiating neuropathic arthropathy from osteomyelitis in the diabetic foot, but bone biopsy may be required. Treatment is with appropriate antibiotics and washout of the affected septic joint. For more details on bone and joint infection see Chapter 6.

DIABETIC MUSCLE INFARCTION

This is a rare phenomenon and usually occurs in the thigh. Diagnosis is by MRI, and biopsy demonstrates muscle necrosis and an associated microvasculopathy.

OSTEOARTHRITIS

There is an increased rate of osteoarthritis (OA) in diabetic patients, but this is not well characterized and may be due to the increased level of obesity rather than the diabetes. For more details on OA see Chapter 15.

THYROID DISEASE

Both hypothyroidism and hyperthyroidism have rheumatological associations (Table 14.4).

Congenital absence of thyroid hormone occurs as an autosomal recessive trait in 1 in 4000 births. The phenotypic picture includes growth retardation, delayed dental development and delayed skeletal maturation. A well described skeletal abnormality is deformity of the 12th thoracic and the 1st lumbar vertebrae, known as a gibbus deformity. In developed countries this condition is routinely tested for at birth, but in cases of delayed epiphyseal closure or growth retardation, thyroid function tests should be carried out. Acquired hypothyroidism, most commonly due to the autoimmune condition Hashimoto's thyroiditis, is most prevalent in middle-aged women and is often subclinical.

The effects on the musculoskeletal system in hyperthyroidism may be due to excess thyroid hormone, either from primary hyperthyroidism or from excess replacement therapy.

OSTEOPOROSIS

The highly organized process of bone remodelling is explained in Chapter 2. Thyroid hormone is known to be a stimulator of bone remodelling and increased bone turnover. Excess thyroid hormone causes a decrease in cancellous bone. There is a direct relationship between the duration of the excess thyroid hormone production and the severity of the osteoporosis.

Table 14.4 Musculoskeletal manifestations in thyroid disease

Manifestation	Type of Thyroid Disease
Arthralgia	Hypothyroidism and hyperthyroidism
Myalgia	Hypothyroidism and hyperthyroidism
Raised creatine kinase	Hypothyroidism
Proximal painless myopathy	Hypothyroidism and hyperthyroidism
Carpal tunnel syndrome	Hypothyroidism
Chondrocalcinosis	Hypothyroidism
Osteoporosis	Hyperthyroidism
Increased fracture risk	Hypothyroidism and hyperthyroidism
Osteonecrosis	Hypothyroidism and hyperthyroidism
Thyroid acropachy	Hyperthyroidism (specifically Grave's disease)

THYROID ACROPACHY

Thyroid acropachy is a rare condition characterized by the development of painless soft-tissue swelling of the fingers and toes in association with clubbing and periostitis. This condition is unique to longstanding Grave's disease; an autoimmune condition characterized by the presence of thyroid autoantibodies.

EFFECTS OF TREATING THYROID DISEASE ON THE MUSCULOSKELETAL PROBLEMS

With treatment of the underlying thyroid disease, the arthralgia, muscle disorders and carpal tunnel syndrome resolve. Thyroid acropachy is due to the circulating antibodies and is, therefore, unresponsive. Osteoporosis and osteonecrosis are not reversible with treatment of the underlying thyroid disorder.

HYPERPARATHYROIDISM

Primary hyperparathyroidism is due to an excess production of parathyroid hormone (PTH) by the parathyroid glands. Secondary hyperparathyroidism occurs when there has been prolonged stimulation of the parathyroid glands due to a low serum calcium. Secondary hyperparathyroidism is most commonly seen in renal failure and in malabsorption syndromes. The main consequences of hyperparathyroidism are hypercalcaemia and osteopenia/osteoporosis. Primary hyperparathyroidism is the commonest cause of hypercalcaemia and 80–90% of cases are due to an adenoma. Rheumatic manifestations of hyperparathyroidism are shown in Box 14.3.

Classical parathyroid bone disease occurs in both primary and secondary subtypes and is called osteitis fibrosa cystica (OFC). OFC is characterized by osteopenia, subperiosteal bone resorption and cyst formation; the commonest areas to be involved are the distal phalanges, the distal clavicle and the skull. A cyst-like area with associated swelling is known as a Brown tumour. Due to early diagnosis, OFC is now a rare phenomenon.

An increased or inappropriately normal PTH level in the presence of a raised serum calcium concentration confirms hyperparathyroidism. This is in contrast to the hypercalcaemia of malignancy, the second commonest cause of a raised calcium level, where the PTH will be suppressed. Phosphate levels will be in the low normal or low range, and bone alkaline phosphatase levels will be raised.

Box 14.3
Rheumatoid manifestations of hyperparathyroidism

- Bone pain
- Arthralgia
- Osteopenia/osteoporosis
- Insufficiency fractures
- Calcium pyrophosphate deposition disease/chondrocalcinosis
- Metastatic calcification
- Renal failure
- Proximal myopathy with normal creatine kinase
- Osteitis fibrosa cystica

HYPERADRENOCORTISOLISM

This can either be congenital, acquired or iatrogenic from corticosteroid treatment. Before epiphyseal closure, hypercortisolism leads to growth retardation and a reduction in peak bone mass. The clinical picture in adults is called Cushing syndrome (CS). The most important musculoskeletal manifestation in CS is bone loss and increased fracture risk. Myopathy with a normal creatine kinase level is common in CS, and may be severe. With treatment, the majority of the musculoskeletal manifestations are reversible. The bone mass may take up to 10 years to recover, during which fracture risk remains increased, and recovery may be incomplete.

ACROMEGALY

The clinical syndrome associated with acromegaly is due to an excess of growth hormone (GH). This is usually secondary to a pituitary tumour. GH, via stimulation of insulin-like growth factor 1 (IGF-1), stimulates protein synthesis and, therefore, growth of all tissues, producing characteristic changes in the bone and soft tissue of the musculoskeletal system. The overall impact on bone depends upon what other hormone deficiencies may be present. The musculoskeletal manifestations of acromegaly are shown in Box 14.4.

The arthritis in acromegaly is a bi-phasic process. Initially, there is joint pain in association

Box 14.4
Musculoskeletal manifestations of acromegaly

- Enlargement of the hands and feet
- Arthralgia
- Ligament laxity
- Cartilage overgrowth
- Osteoarthritis
- Myalgia
- Carpal tunnel syndrome
- Chondrocalcinosis
- Diffuse idiopathic skeletal hyperostosis
- Spinal cord compression, nerve root compression and cauda equina syndrome
- Kyphosis
- Proximal myopathy with normal creatine kinase

with ligament laxity and cartilage overgrowth. This produces widened joint spaces on X-ray. The second stage is the development of premature and severe OA. Early OA in acromegaly gives the unusual pathognomonic X-ray appearance of osteophytes and a widened joint space, compared with the narrow joint space usually associated with OA. Advanced acromegalic arthropathy is typical of advanced OA, but the distribution is unusual with frequent involvement of the non-weight-bearing joints. The most commonly affected joint is the hip.

An increased bone mineral density is recognized in acromegaly. Osteoporosis and insufficiency fractures also occur at an increased rate, but the osteoporosis occurs late in the disease and is secondary to hypogonadism, which is caused by the pituitary tumour.

ALKAPTONURIA (OCHRONOSIS)

Alkaptonuria is a rare autosomal recessive disease affecting 1 in 200 000 of the population and causing a deficiency of homogentisic acid oxidase. The disease manifests itself in the second and third decades. A classical sign is the oxidation of urine to a dark colour on standing. The main musculoskeletal features of alkaptonuria are shown in Box 14.5.

The main differential diagnoses are OA, ankylosing spondylitis (AS) and calcium pyrophosphate dihydrate (CPPD) deposition disease, which may coexist. The lack of osteophytes and small-joint involvement in combination with major involvement of the non-weight-bearing joints helps to differentiate ochronotic arthropathy from OA. The absence of the classical syndesmophytes and sacroiliitis of AS helps to differentiate ochronotic arthropathy from AS. There is no specific treatment for the arthritis.

OSTEOARTICULAR DISORDERS OF RENAL ORIGIN

Patients with renal failure and on long-term dialysis are surviving for longer and musculoskeletal conditions (Table 14.5) are an important cause of morbidity and reduced quality of life.

Box 14.5
Main musculoskeletal features of alkaptonuria

- Connective tissue pigmentation, 'ochre' in colour, visible in the sclera and pinna
- Degenerative arthritis of spine and large joints
- Acute inflammatory exacerbations of arthritis
- Dense calcification of intervertebral discs

Table 14.5 Musculoskeletal manifestations in renal failure

Manifestation	Description
β_2-Microglobulin amyloidosis	Carpal tunnel syndrome (CTS), adhesive capsulitis (AC), symmetrical erosive arthropathy of small and large joints, erosive spondylo-arthropathy (often with cervical spine involvement), flexion contractures, bone cysts, pathological fractures within amyloid deposits in bone
Crystal arthropathies	Calcium phosphate, calcium pyrophosphate dihydrate (pseudo-gout), calcium oxalate, monosodium urate (gout)
Bone and joint infection	Septic arthritis, osteomyelitis, discitis
Erosive arthropathy	Painless erosive arthritis in dialysis patients without amyloidosis – a separate entity to osteoarthritis and rheumatoid arthritis
Carpal tunnel syndrome	37% of patients with renal failure and CTS do not have amyloidosis. The underlying cause for the increased incidence is not known
Osteonecrosis	Small increase in osteonecrosis in patients on dialysis. A large increase after transplantation due to the high-dose corticosteroids
Secondary hyperparathyroidism	See section on hyperparathyroidism

β_2-MICROGLOBIN AMYLOIDOSIS

This is a consequence of chronic renal failure, not just long-term haemodialysis or peritoneal dialysis. β_2-Microglobulin amyloid is deposited in and around joints and tendons, causing a spectrum of problems.

Diagnosis is by history and examination in combination with typical radiological findings and the classical Congo red staining of amyloid tissue on biopsy. A non-invasive test using ^{123}I-labelled serum amyloid P component (^{123}I-SAP) demonstrates increased radio-tracer uptake in the presence of amyloid deposition.

Treatment is mainly symptomatic. Successful renal transplantation can lead to an improvement in symptoms and a degree of regression of amyloid deposits. There is return with graft failure and recommencement of dialysis.

CRYSTAL ARTHROPATHIES

A variety of crystal deposition may occur in renal disease. The commonest crystal is calcium phosphate and, as well as producing an acute arthritis, periarticular deposition is frequent and usually asymptomatic. The incidence of CPPD is only slightly higher in patients with renal failure than in the general population. The X-ray appearance of chondrocalcinosis in renal failure may be produced by both CPPD and calcium oxalate deposition. Gout is common in patients with renal failure, but this risk returns to normal once dialysis is commenced.

BONE AND JOINT INFECTIONS

Renal failure, dialysis and immunosuppressive treatment for transplants all increase the risk of infection. The presence of pre-existing joint disease further increases the risk; patients with amyloid arthropathy are particularly susceptible. Septic arthritis is more often polyarticular in DM.

PRIMARY HYPERLIPIDAEMIA

The primary hyperlipidaemias are a common collection of disorders, affecting 1 in 500 people. Musculoskeletal problems, although benign, are often the initial or an early complaint of familial hypercholesterolaemia. Early diagnosis has obvious cardiovascular benefits for the future.

The main musculoskeletal problem is tendon xanthomas, typically of the Achilles tendon. In homozygotes these appear in childhood, and in heterozygotes in early adulthood. An oligoarthritis and a non-deforming polyarthritis, often flitting in nature, may also occur.

Treatment is symptomatic; NSAIDs should be used as required, but in the minimum dose and for the shortest duration possible to control the symptoms. This is to minimize the potential increase in a population that already has a significant risk of cardiovascular events. Rarely, excision is necessary. Aggressive treatment with lipid-lowering drugs can lead to regression in xanthoma size.

LYSOSOMAL STORAGE DISORDERS

The lysosomal storage disorders include the glycosphingolipidoses and the mucopolysaccharidoses. The commonest type within each of the two groups is Gaucher disease and Hurler syndrome respectively (Table 14.6). These are a rare collection of genetic disorders, but have been included because the musculoskeletal manifestations are important causes of extra-neurological morbidity. These disorders have a combined prevalence of 8–14 per 100 000 live births.

Recent developments in enzyme replacement therapy have altered the course of the diseases and the musculoskeletal complications.

Table 14.6 Musculoskeletal manifestations of the common lysosomal storage disorders

Disorder	Enzyme Deficiency	Manifestation
Gaucher disease	β-glucosidase	Osteopenia, increased fracture risk, focal lytic/sclerotic lesions, osteonecrosis
Hurler syndrome	α-L-iduronidase	Short stature, dysostosis multiplex*, craniofacial abnormalities, entrapment neuropathies, spondylolisthesis, degenerative arthritis

*Encompasses the radiological findings of large skull, hypoplastic vertebrae, gibbus deformity of the vertebrae, paddle-shaped ribs.

Table 14.7 Glycogen storage disease types with prominent muscle symptoms

Glycogen Storage Disease Type	Name	Enzyme Deficiency	Manifestation
II (adult-onset subset)	Pompe disease (acid maltase deficiency)	α-1,4-glucosidase	Proximal myopathy and respiratory muscle weakness
V	McArdle disease	Myophosphorylase	Muscle fatigue, muscle cramp, weakness and rhabdomyolysis
VII	Tauri disease	Phosphofructokinase	

GLYCOGEN STORAGE DISEASE

These are a rare collection of genetic diseases, glycogen storage disease (GSD) I–VII with an overall incidence of 1 in 25 000 live births. Although the involvement of muscle is present in all types, the clinical picture is often dominated by other features including liver failure and severe hypoglycaemia. The only types likely to present to a rheumatologist are patients with GSD II (adult-onset subset), V and VII (Table 14.7). In these types the involvement of skeletal muscle dominates the clinical picture.

HAEMOCHROMATOSIS

Haemochromatosis is an autosomal recessive disease with an approximate incidence of 1 in 300.

PATHOGENESIS

There is increased iron absorption leading to iron deposition in the tissues and viscera. Chronic iron overload leads to tissue damage and subsequent fibrosis.

CLINICAL FEATURES

The condition has an equal sex incidence with onset in middle age in men, but is delayed to postmenopausal age in women. The symptoms and signs of the organ systems involved are listed in Box 14.6. The arthropathy is one of the commonest manifestations of haemochromatosis and is present in 40–60% of patients. It typically involves the metacarpophalangeal (MCP) joints of the index and middle fingers. Some 15–30% of patients suffer acute inflammatory episodes of arthritis secondary to CPPD deposition, usually affecting the wrist and knees. The associated chondrocalcinosis can also be seen in the intevertebral discs and the symphysis pubis. One of the common mutations to cause haemochromatosis is also associated with porphyria cutanea tarda.

Box 14.6
Clinical manifestations of haemochromatosis

- Porphyria cutanea tarda
- Skin pigmentation
- Chronic arthropathy
- Chondrocalcinosis
- Cardiomyopathy
- Hepatic cirrhosis
- Hepatocellular carcinoma
- Diabetes
- Hypogonadism

INVESTIGATIONS

Abnormal liver function test (LFT) results support the diagnosis, which is confirmed by demonstrating iron overload with a high serum ferritin concentration. Patients often have increased glucose levels or are frankly diabetic. Liver biopsy also shows excess iron in the parenchymal cells. Plain X-ray demonstrates typical changes of OA with joint space narrowing, osteophytes and sclerosis.

DIFFERENTIAL DIAGNOSIS

This includes secondary iron overload from repeated transfusions, for example in thalassaemia. Alcoholic liver disease can cause abnormal LFT results and a raised ferritin level.

TREATMENT

Excess iron is removed by regular venesection. Menstrual blood loss explains why presentation is delayed in women. Iron-chelating agents may be used. The arthropathy does not respond to venesection and is managed symptomatically with analgesia and NSAIDs. The latter should be used with

caution in liver disease. Diagnostic awareness of the arthropathy associated with haemochromatosis may allow early diagnosis and instigation of effective treatment in the pre-cirrhotic stage, which then has a good prognosis. Once cirrhosis has developed there is a 200-fold increased risk of hepatocellular carcinoma.

FURTHER READING

Ardic F, Soyupek F, Kahraman Y et al. The musculoskeletal complications seen in type II diabetics: predominance of hand involvement. Clin Rheumatol 2003; 22:229–233.

Birklein F. Complex regional pain syndrome. J Neurol 2005; 252:131–138.

Carnevale V, Romagnoli E, D'Erasmo E. Skeletal involvement in patients with diabetes mellitus. Diabetes Metab Res Rev 2004; 20:196–204.

Guzman J, Esmail R, Karjalalainen K et al. Multidisciplinary rehabilitation for chronic low back pain: systematic review. BMJ 2001; 322:1511–1516.

Jacobs-Kosmin D, DeHoratius RJ. Musculoskeletal manifestations of endocrine disorders. Curr Opin Rheumatol 2005; 17:64–69.

Kay J, Bardin T. Osteoarticular disorders of renal origin: disease-related and iatrogenic Baillieres Clin Rheumatol 2000; 14:285–305.

Lemstra M, Olszynski WP. The effectiveness of multidisciplinary rehabilitation in the treatment of fibromyalgia: a randomized controlled trial. Clin J Pain 2005; 21:166–174.

Mannerkorpi K. Exercise in fibromyalgia. Curr Opin Rheumatol 2005; 17:190–194.

Ong BN, Evans D, Bartlam A. A patient's journey with myalgic encephalomyelitis. BMJ 2005; 330:648–650.

Roberts CGP, Ladenson PW. Skeletal involvement in patients with diabetes mellitus. Lancet 2004; 363:793–803.

Sandstrom MJ, Keefe FJ. Self-management of fibromyalgia: the role of formal coping skills training and physical exercise training programs. Arthritis Care Res 1998; 11:432–447.

Wolfe F, Clauw DJ, Fitzcharles MA et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken) 2010; 62:600–610.

15

OSTEOARTHRITIS AND CRYSTAL ARTHROPATHIES

George Nuki, Daniel Porter and Raashid Luqmani

Cases relevant to this chapter

16, 68, 70–71, 76, 86, 92

Essential facts

1. Osteoarthritis (OA) is the clinical and pathological outcome of a range of factors that lead to pain, disability and structural failure in synovial joints.
2. By the age of 65 years, 80% of people have radiographic evidence of OA affecting the spine, hips, knees, hands and feet, but only one in four are symptomatic.
3. OA is a dynamic process of remodelling and proliferation of new bone, cartilage and connective tissues, as well as focal degeneration of articular cartilage.
4. Insidious pain occurs as a result of increased pressure or microfractures in the subchondral bone, low-grade synovitis, inflammatory effusions, capsular distension, enthesitis or muscle spasm, and nocturnal aching may be associated with hyperaemia in the subchondral bone.
5. Consider a predisposing underlying condition in patients with OA before the age of 40 years or if OA develops in unusual sites.
6. Medical treatment of OA is to relieve symptoms, maintain and improve joint function, and minimize disability and handicap; optimal management requires a combination of non-pharmacological and pharmacological modalities.
7. Surgical management of OA is indicated where medical therapy has failed; joint replacement is effective and cost-effective, irrespective of age.
8. Calcium pyrophosphate dihydrate crystals are deposited at entheses, in hyaline cartilage and in fibrocartilage, and are associated with chondrocalcinosis and degenerative changes; shedding of crystals into joints can provoke acute synovitis (pseudogout) or chronic pyrophosphate arthropathy.
9. Acute gout usually presents as monoarthritis in a distal joint of the foot or hand.
10. Recurrent attacks of gout cause progressive cartilage and bone erosion, deposition of palpable masses of urate crystals ('tophi'), and an asymmetrical erosive inflammatory polyarthritis. Gout is now the commonest type of chronic inflammatory arthritis.

OSTEOARTHRITIS

Osteoarthritis (OA), also sometimes called osteoarthrosis or degenerative joint disease, is not a single disease, but rather the clinical and pathological outcome of a range of disorders and conditions that lead to pain, disability and structural failure in synovial joints. OA is classified as being *primary* (idiopathic) or *secondary,* when it follows some clearly defined predisposing disorder or disease (Table 15.1), but the development of all types of OA is associated with multiple aetiological factors.

EPIDEMIOLOGY

OA is the commonest type of arthritis. Radiographic and autopsy surveys show a steady age-related increase in prevalence from the age of 30 years. By the age of 65 years, 80% of people have some radiographic evidence of OA, although only one in four is symptomatic. The joints most frequently affected are the spine, hips, knees, and some of the small joints of the hands and feet (Fig. 15.1). Community-based studies in the UK have shown that 10% of the population over the age of 55 years have troublesome knee pain and, of those, 25% are severely disabled. OA is the leading cause of physical disability in people age over 65 years. The prevalence of both radiographically defined OA and OA-related disability is greater in women than in men. Although disability associated with OA also increases steadily with age, the majority of people with OA-related disability in the community are between the ages of 55 and 75 years.

Risk factors for OA include constitutional factors such as age, sex, the shape and alignment of joints, obesity and some genetic determinants, but there are also important environmental triggers, such as previous injury or the repetitive trauma associated with certain recreational activities, such as weightlifting or long-distance running, and with some occupations, such as mining and farming.

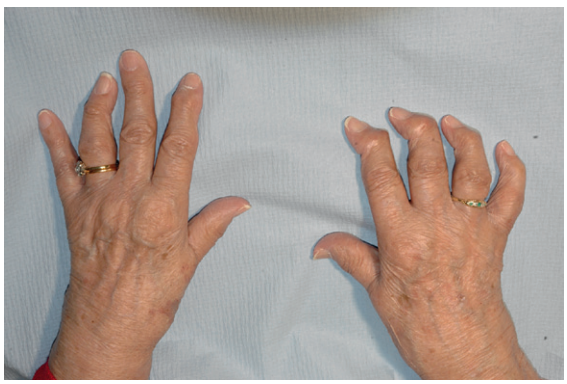


FIGURE 15.1 Hand osteoarthritis

Table 15.1 Subsets of osteoarthritis

Primary (Idiopathic)	Secondary
Localized • Hands and feet • Knee • Hip • Spine	Localized • Hip disease, e.g. Perthes' • Mechanical and local factors, e.g. obesity, post-traumatic, hypermobility, varus–valgus
Generalized • three or more joint areas	Generalized • Bone dysplasia • Metabolic Calcium deposition disease • Calcium pyrophosphate deposition disease • Hydroxyapatite arthropathy • Destructive arthropathies Other bone and joint disorders • Avascular necrosis • Rheumatoid arthritis • Paget's disease Miscellaneous other diseases • Endocrine, e.g. acromegaly, neuropathic

Mechanical factors play a role in the pathogenesis of all types of primary, as well as secondary, OA. Joint failure occurs when mechanical stresses overwhelm the capacity of articular tissues to resist and repair the damage. Structural failure of the *articular* cartilage, bone and periarticular tissues can result from abnormal mechanical stresses damaging previously normal tissues, or from the failure of pathologically impaired joint tissues in response to physiologically normal mechanical forces (Fig. 15.2). Obesity, joint mal-alignment, occupational trauma and muscle weakness are all important, potentially modifiable, biomechanical risk factors that determine the site and severity of the disease. *Race and ethnicity* have some influence on the probability of developing OA at different sites. Although OA of the knee is prevalent in all ethnic groups (particularly frequent in black women), hip, hand and generalized OA are seen predominantly in Caucasians. *Genetic factors* are known to be important determinants. Twin studies suggest heritability of up to 65% in primary OA of the hand and knee, but the susceptibility genes themselves still remain largely undefined.

Progress has been made in identifying mutations in collagen genes that are associated with different types of bone and cartilage dysplasia where OA is part of a more complex phenotype, but none of these single gene mutations in genes that code for structural matrix proteins appears to be important in determining susceptibility to the common types of OA. Recently, however, there has been some progress in identifying a promoter polymorphism in a bone morphogenetic protein (growth differentiation factor 5) that is associated with both hip and knee OA, as well as other polymorphisms in genes that code for signalling proteins involved in the development and maintenance of articular cartilage, which appear to be associated with susceptibility to hip OA in certain ethnic groups (see Chapter 3).

PATHOLOGY AND PATHOGENESIS

OA involves all tissues of the joint (subchondral bone, ligaments, capsule and synovial membrane) as well as the articular cartilage, but inflammatory changes in the synovium are usually minor and secondary. To a variable extent OA is a dynamic process characterized by remodelling of the anatomy of the joint and *proliferation* of new bone in the form of *osteophytes*, as well as by focal *degeneration* of articular cartilage. In many cases these processes reach a state of non-progressive equilibrium, but in others there is symptomatic failure of the joint characterized by progressive degeneration of the articular cartilage with fibrillation, fissuring, ulceration and, eventually, full-thickness focal loss of cartilage at sites of joint loading. In addition, with wear, there is compaction and sclerosis (‘*eburnation*’) of the adjacent

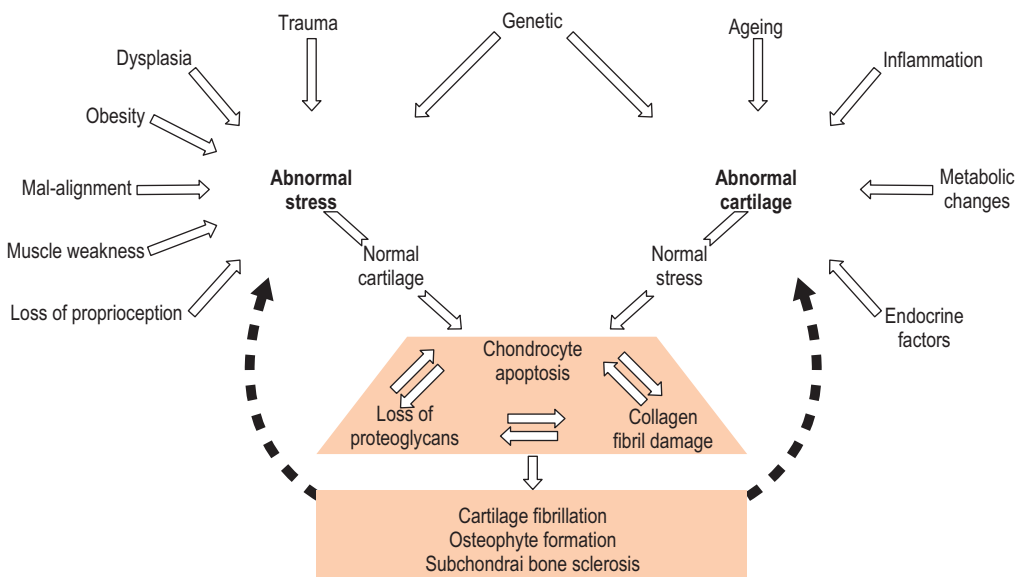


FIGURE 15.2 Factors leading to osteoarthritis

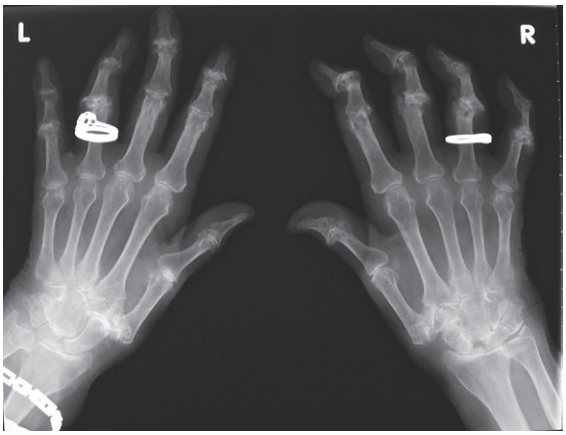


FIGURE 15.3 Radiographic appearances of osteoarthritis, showing loss of joint space and sclerosis in both hands, especially at the first carpometacarpal joint

subchondral bone and the formation of bone cysts (Fig. 15.3). The biomechanical properties of the cortical and subchondral bone play an important role in protecting articular cartilage following impact loading. It is suggested that the pathogenesis of OA in some cases may be initiated by an increase in the density and stiffness of the subchondral bone following the healing of microfractures caused by unprotected loading of joints. The consequent loss of bone viscoelasticity results in steep stiffness gradients in the bone. This in turn results in stretching and fibrillation of the overlying articular cartilage, as well as focal osteonecrosis and the formation of bone cysts. In support of this hypothesis, patients with hip and knee OA have higher than normal bone mass and there is evidence that focal increases in subchondral bone density can precede and predict future cartilage loss in patients with OA of the knee. The sequence of pathological and biochemical changes in the articular cartilage in OA follows a characteristic pattern (Table 15.2), whether primary or secondary to changes in the subchondral bone. Early increases in matrix hydration and articular cartilage thickness follow disruption of the collagen fibre network, loss of tensile strength in the superficial zone of the articular cartilage and swelling of the negatively charged, high-molecular-weight proteoglycan, aggrecan. Initially, chondrocyte activation and proliferation of clusters of chondrocytes are associated with an *anabolic* response with increased synthesis and turnover of matrix collagens and proteoglycans, but in the later

Table 15.2 Structural, cellular and biochemical changes in articular cartilage in osteoarthritis

Structural Change	Cellular Change	Biochemical Change
Early Changes		
↑Cartilage thickness	Collagen fibre network disrupted, leading to: ↓Collagen fibrillogenesis ↑Chondrocyte activation ↑Chondrocyte proliferation	↑PG synthesis and content ↑Chondroitin sulphate ↓Keratan sulphate ↑Water content ↑Cartilage oligomeric protein ↓Aggrecan size ↑Collagen synthesis Chondroitin sulphate neo-epitopes re-expressed
Later Changes		
↓Cartilage thickness Fibrillation	Chondrocyte apoptosis	↓PG synthesis and content ↓Aggrecan ↓Chon.droitin sulphate ↓Collagen synthesis

PG, prostaglandin

stages of OA, *catabolism* of cartilage matrix proteins outstrips the capacity for cartilage repair. Anabolic mediators include growth factors, such as the insulin-like growth factor (IGF-1), fibroblast growth factor (FGF), transforming growth factor β (TGFβ) and the bone morphogenetic proteins (BMPs): the anti-inflammatory cytokine interleukin (IL)-4 and proteinase inhibitors, such as tissue inhibitors of metalloproteinases (TIMPs) and plasminogen activator inhibitor (PAI). Catabolic mediators include nitric oxide, prostaglandins and the pro-inflammatory cytokines IL-1β, tumour necrosis factor (TNFα), IL-6 and IL-17, as well as metalloproteinases (MMP-1, -8, and -13) and aggrecanases (ADAM-TS-4 and -5).

CLINICAL FEATURES

Pain is the presenting symptom in the majority of patients. Usually insidious in onset and

intermittent at first, the pain is typically aching in character. Initially, it is provoked by weight-bearing or movement of the joint, and relieved by rest, but as the disease progresses the pain may be more prolonged and experienced at rest, and may become severe enough to wake the patient at night. Prolonged early morning stiffness is not a feature as it is in rheumatoid arthritis and other predominantly inflammatory joint diseases, but a few minutes of early morning stiffness and transient stiffness (gelling) after rest are common. Pain in OA can emanate from all the tissues of the joint, except the articular cartilage, which is aneural. Pain may result from increased pressure or microfractures in the subchondral bone, from low-grade synovitis, inflammatory effusions, capsular distension, enthesitis or muscle spasm, and nocturnal aching may be associated with hyperaemia in the subchondral bone. Associated anxiety and depression are not uncommon, and these can amplify pain and disability. There is only a weak relationship between symptoms and radiographic evidence of structural changes of OA at all joint sites, although the correlation between pain and structural changes is somewhat stronger in the weight-bearing joints (hip > knee) than in the small joints of the hands. Patients may develop painless functional impairment due to restricted movement in the hands, hips or knees. Physical signs associated with OA include: restriction of movement of joints as a result of capsular fibrosis or blocking by osteophytes, palpable bony swelling, periarticular or joint-line tenderness, deformities with or without joint instability, muscle weakness and wasting in addition to occasional joint effusions, and palpable or even audible joint crepitus.

COMMON CLINICAL PRESENTATIONS

The salient features of the common types of hip, knee, hand and nodal generalized OA are summarized in Table 15.3.

Hip OA commonly affects the superior pole of the joint. Typically, patients present with pain in the groin on exercise, but referred pain in the buttock, anterior thigh, knee and even the lower leg are not uncommon. With increasing severity it radiates down to the knee, is constant on exercise, and begins to cause stiffness and inability to reach down to tie shoe-laces. Pain begins to disturb sleep. Enjoyment of active hobbies is curtailed, and progression to joint destruction and fixed flexion contracture can be the end result in some patients. Characteristically, examination reveals an antalgic

Table 15.3 Common clinical types/patterns of osteoarthritis

Knee Osteoarthritis	Hip Osteoarthritis	Hand Osteoarthritis
Patello-femoral and medial joint compartments	Supero-lateral or central (medial or polar)	Distal interphalangeal and proximal interphalangeal joints, carpometacarpal (CMC) joints of the thumbs
Knee pain Pain on walking ↑uneven ground ↑stairs Antalgic gait Difficulty rising from chairs	Groin pain → thigh/medial side of the knee → buttock Antalgic gait Difficulty with socks and toenails	Pain/swelling/stiffness + Restricted movements Symptoms often settle Hand function preserved Frequent family history
Bilateral > unilateral	Unilateral > bilateral	Usually bilateral
Women > men	Women > men	Women > men Perimenopausal onset
Varus > valgus or Fixed flexion deformities Joint-line tenderness Joint-line bony swelling Crepitus Quads muscle wasting	Pain/restricted movements: internal rotation (early), external rotation/abduction (later) Fixed flexion/ext. rotation Limb shortening Quads/gluteal muscle weakness and/or wasting	Heberden nodes ± Bouchard nodes Subluxation 1st CMC Squaring of hand Associated with OA in other joints (especially knees and medial OA of the hips)

gait with painful restriction of internal rotation with the hip in flexion. Medial pole OA is less common. It occurs more frequently in women, is more frequently bilateral, and less frequently progresses. In patients with generalized nodal OA, the pattern of hip involvement is usually also medial or concentric. Bony destruction of the acetabulum or femoral head may lead to a 'bobbing' short-leg gait. A Trendelenburg gait is rare, but a coxalgic (Duchenne) gait is more common due to a desire to off-load the hip abductor muscles and hence reduce the joint reaction force, which is often three times body weight in single-leg stance. There is little to see apart from thigh wasting and, perhaps, fixed flexion. Tenderness is rare. Range of movement reveals a global deficit and fixed flexion; reduced adduction and internal rotation are often seen. Rotation is often the most 'irritable' of the movements.

Antero-posterior radiographs of the hip and pelvis should be inspected carefully to detect cardinal features of OA. Destructive arthropathy and avascular necrosis may be associated with non-steroidal anti-inflammatory drug (NSAID) therapy.

Knee OA commonly affects the medial and patello-femoral compartments of the joint, but may affect any of the three compartments. The medial compartment is most frequently affected, and leads to a varus deformity. Forces that occur on weight-bearing will pass medial to the knee and this increases point-loading in the medial compartment. Typically, patients present with anterior or medial knee pain aggravated by walking on uneven ground and by ascending or descending stairs. On examination they frequently have a characteristic antalgic gait and bilateral, symmetrical varus deformities. In some patients, knee OA is associated with generalized nodal OA. Unilateral knee OA, especially in men, may be a consequence of a previous injury, meniscus tear or complete meniscal resection.

Nodal OA is a clinically distinct form of primary generalized OA, with a strong genetic component. It is much more common in women than in men and characteristically affects the interphalangeal (IP) joints of the fingers (DIPJs > PIPJs) and the carpometacarpal joints of the thumbs. The onset, which is sometimes subacute with considerable pain, swelling and local inflammation, is often in the perimenopausal period, and may be triggered by oestrogen withdrawal and other endocrine changes at this time. Although multiple joints in both hands are frequently affected, the onset is typically episodic and additive in pattern, with each joint going through a sequence of changes over a number of months. Pain, soft-tissue swelling and tenderness are followed by the gradual development of hard, bony swellings on either side of the extensor tendons on the dorsal aspect of the fingers in relationship to the IP joints. Heberden nodes at the DIPJs are more frequent than Bouchard nodes at the PIPJs. Once the inflammation has settled, patients are left with relatively pain-free, knobbly fingers. Although the lesions can be associated with considerable deformity and subluxation, serious disability is unusual. In generalized nodal OA, osteophyte formation and subluxation of the first carpometacarpal joints results in characteristic 'squaring' of the hands, and the knees and other joints may be also affected. Rarely, in cases with a more acute onset ('hot Heberden nodes'), the initial soft-tissue inflammation is associated with the development of cysts containing hyaluronate. *Erosive OA* is the name sometimes given to describe a rarer variant of nodal osteoarthritis, which is characterized by similar episodic symptoms and signs of local inflammation followed by the development of more destructive subchondral erosions associated with florid proliferation of bone, instability, and subluxation in the PIPJs and DIPJs.

ATYPICAL AND 'SECONDARY' OSTEOARTHRITIS

The possibility of some defined predisposing underlying condition (see Table 15.1) needs to be considered, particularly in patients who develop typical symptoms and signs of OA before the age of 40 years, in those who develop OA in joints that are usually not affected, and in those with certain characteristic patterns of joint involvement. A history of major preceding trauma, such as a fracture that resulted in articular cartilage damage or subsequent mal-alignment, is often found to be the cause of monoarticular OA developing at an early age or in a joint, such as the ankle, that is seldom otherwise affected. Nearly 50% of patients have knee OA 21 years after open meniscectomy, and the average time to develop hip OA following a fracture dislocation is 7 years. Early-onset OA with prominent involvement of the second and third metacarpophalangeal (MCP) joints is very

characteristic in patients with haemochromatosis and may be an early clinical clue that leads to establishment of the diagnosis (for more details see Chapter 14). Although deposition of calcium pyrophosphate dihydrate (CPPD) and basic calcium phosphate (BCP or apatite) crystals is common in articular cartilage in OA, the possibility of familial CPPD disease should be considered in patients presenting with premature knee OA. This is especially important when the knee OA is accompanied by frequent inflammatory episodes or prominent hypertrophic radiographic features, and in patients presenting with OA in relatively atypical joints, such as the shoulder, elbow or radiocarpal joints in the wrists.

INVESTIGATIONS

Plain radiographs are used to assess the severity of the structural changes in patients with OA. Because radiographic evidence of OA is so frequent in asymptomatic middle-aged and elderly persons, it is important to consider the clinical features (symptoms and signs) when interpreting the results. Focal, rather than uniform, joint space narrowing and the presence of osteophytes are the main radiographic features, with subchondral bone sclerosis and cysts in more advanced cases. Ossified synovial loose bodies and chondrocalcinosis can also sometimes be detected on plain radiography. Standing radiographs are required to assess the extent to which joint space narrowing reflects loss of articular cartilage in the tibio-femoral joints.

Magnetic resonance imaging (MRI) is being developed for the earlier and more quantitative detection of articular cartilage changes, including changes in hydration and proteoglycan composition, but has yet to be refined and validated sufficiently to make it useful in clinical practice. This is also true of isotope scans with ^{99}Tc-labelled bisphosphonate, which in research studies have shown increased uptake of isotope in OA joints that subsequently go on to develop progressive structural changes. MRI is, however, useful for detecting intra-articular soft-tissue lesions, such as meniscus tears, and for the diagnosis of osteonecrosis. Bone scintigraphy is occasionally used for the detection of osteonecrosis, stress fractures and bone metastases but is increasingly being replaced by MRI.

Blood tests are not helpful in the diagnosis or management of OA and are used largely to exclude other diseases associated with systemic inflammation or metabolic abnormalities. For example, measurements of serum calcium and alkaline phosphatase are critical for the diagnosis of primary hyperparathyroidism and hypophosphatasia; measurement of serum ferritin is required for the diagnosis of haemochromatosis; and detection of homogentisic acid in the urine will confirm a diagnosis of ochronosis.

Although cartilage degradation products, such as hyaluronan, keratan sulphate and cartilage oligomeric protein, and cartilage synthesis markers, such as Type II collagen c-pro-peptide, have been shown to be increased in the plasma, synovial fluid or urine of patients with OA, there are currently no biochemical or molecular markers that have clinical utility for diagnosis, monitoring the progress of structural changes, or assessing the prognosis of OA in clinical practice.

Synovial fluid analysis in OA is really indicated only to exclude bacterial joint infection or gout. The fluid is usually clear and viscous with a low cell count. Detection of crystals by polarizing light microscopy is not helpful in distinguishing OA from primary calcium crystal deposition disorders, because crystals of CPPD and BCP are each detected in up to half of all effusions from patients with knee OA.

MANAGEMENT

Treatment is directed predominantly at relieving symptoms, maintaining and improving joint function, and minimizing disability and handicap. Optimal management of patients with all types of OA requires a combination of non-pharmacological and pharmacological modalities.

NON-PHARMACOLOGICAL MODALITIES OF THERAPY

- All patients should be provided with information and education about the objectives of treatment and the importance of changes in lifestyle, exercise, weight reduction, and other measures to unload the damaged joint. The initial focus should be on self-help and patient-driven treatments, rather than on passive therapies delivered by health professionals.
- All patients with lower-limb OA should be given advice about appropriate footwear with thick, soft soles. Laterally wedged insoles can

give symptomatic relief to some patients with medial tibio-femoral compartment knee OA.
- Patients with symptomatic OA of the hip or knee can benefit from referral to a physiotherapist for: (a) assessment and instruction in appropriate exercises to reduce pain and improve functional capacity, and (b) assessment and provision and instruction in the use of a stick or walker in appropriate circumstances.
- Patients with hip and knee OA should be encouraged to undertake and continue with regular aerobic, muscle-strengthening and range-of-movement exercises. Pool exercises can be effective in patients with symptomatic hip OA associated with muscle spasm.
- Patellar taping can provide short-term symptom relief in some patients with patello-femoral OA.
- A knee brace can reduce pain, improve stability and reduce the risk of falls in patients with knee OA associated with mild/moderate varus or vagus instability.
- Heat packs, ice packs, acupuncture and transcutaneous electrical nerve stimulation have all been shown to be effective for helping with short-term pain control in some patients with knee OA in controlled trials.

PHARMACOLOGICAL MODALITIES OF THERAPY

- Paracetamol (up to 3 g daily) should be the analgesic of first choice for patients with symptomatic OA.
- In patients who do not respond adequately to a trial of paracetamol, the choice of alternative or additional analgesics needs to take into account both the relative efficacy and safety of the drug or drug combination being considered as well as concomitant medication and co-morbidities.
- In some patients who do not respond adequately to paracetamol, NSAIDs at the lowest effective doses can be added or substituted, but long-term use of NSAIDs should be avoided if possible. In patients with increased gastrointestinal risk, a cyclo-oxygenase (COX) 2 selective agent or a non-selective NSAID with co-prescription of a proton pump inhibitor or misoprostol for gastroprotection can be considered.
- All NSAIDs (including COX2-selective agents) should be used with caution in patients with cardiovascular risk factors.
- Topical NSAIDs or topical capsaicin can be effective as adjuncts or alternatives to oral analgesics in some patients with symptomatic knee OA.
- Intra-articular injections with corticosteroids can be considered in patients with moderate to severe pain who are not responding adequately to oral analgesic/anti-inflammatory agents, and in patients with symptomatic knee OA with effusions or other physical signs of local inflammation.
- Intra-articular injections of hyaluronate can be helpful in some patients with knee OA who are unresponsive to, or intolerant of, repeated injections of intra-articular corticosteroids.
- Treatment with glucosamine and/or chondroitin sulphate may provide symptomatic benefit in patients with knee OA. If no response is apparent within 6 months, treatment should be discontinued. The evidence that these agents may also have structure-modifying effects in slowing the progression of articular cartilage loss remains inconclusive.
- The use of opioids and narcotic analgesics can be considered in exceptional circumstances for the treatment of severe, refractory pain where other pharmacological agents have been ineffective or are contraindicated. Non-pharmacological therapies should be continued in such patients and surgical treatments should be considered.

SURGERY

Patients with hip or knee OA, who are not obtaining adequate pain relief and functional improvement from a combination of non-pharmacological and pharmacological treatment, should be considered for joint replacement surgery. Replacement arthroplasties are effective and cost-effective interventions for patients with significant symptoms and/or functional limitations associated with a reduced health-related quality of life, despite conservative therapy, irrespective of age. Patients unfit for general anaesthesia can often be considered for surgery using regional anaesthesia, but severe dementia, active sepsis, leg ulcers and significant peripheral vascular disease are important contraindications.

By far the commonest surgical procedure for hip OA is total hip replacement (arthroplasty). More than 50 000 are performed annually in the UK. Patient-derived outcome measures for locomotor disease (e.g. the Oxford Hip Score or the Short Form (SF) 12 questionnaire) reveal that the quality of life improves dramatically after a successful total hip arthroplasty. The first durable hip replacement, the Charnley low-friction arthroplasty, was

developed by Sir John Charnley in the early 1960s, and some of his patients still have their implants to this day. His solution to the difficult problem of developing a durable surface with little wear-debris and a low coefficient of friction was to articulate a metal ball within a polyethylene (plastic) socket. Most hip replacements in the UK are cemented into the bone (Fig. 15.4), although uncemented components, which rely on a strong bond between elastic bone and a tightly fitting metal surface, are frequently used in Europe and the USA. In recent years younger patients have been deemed suitable for metal-on-metal hip replacements, which simply resurface the joint (Fig. 15.5). Currently there is interest in the potential effects of metal ions on tissues in patients who have received a metal-on-metal joint replacement.

For a new type of hip replacement to be introduced in the UK it has to be shown to have a 3-year survival rate (of the implant) of 97%. This is the minimum achieved by current generations of hip replacements. The elderly have the best chance of their hip replacement outliving them. Younger patients will have a high chance of revision surgery at some time in the future as the bearing surface wears down or the implant's fixation to bone loosens. Overall, about one-quarter of hip replacement surgery is for revision of an implant.

Counselling a patient about a hip replacement before surgery is essential. OA of the hip can be distressing and disabling, but is not directly life-threatening. On the other hand, surgery can be fatal. The usual indication is for failure of non-surgical management of hip arthritis. About 90% of patients achieve a pain-free hip once recovery from the operation is complete. Overall, the risks of surgery are: death, 1%; infection, 1–2%; dislocation, 1–2%; and loosening 1% per annum to 10 years. Individual surgeon, implant and patient factors will greatly modify these broad figures.

Infection after joint arthroplasty is a major concern and is often impossible to eradicate. It is possible that almost every joint is colonized by bacteria at the time of implantation, but frank infection occurs only on the rare occasions when the balance of host response to pathogen virulence favours infection. Hospital-acquired infections, such as MRSA (methicillin-resistant *Staphylococcus aureus*) and VRE (vancomycin-resistant enterococcus), have well known tenacity. Also difficult to treat is the skin-borne *Staphylococcus epidermidis*, which now contributes to more than half of infected arthroplasties. Early infections (within 2 weeks) can often be treated with joint debridement. Later infections cause loosening of the implant or cement interface with bone, and these need to be revised. This may be done in one stage (less morbidity,

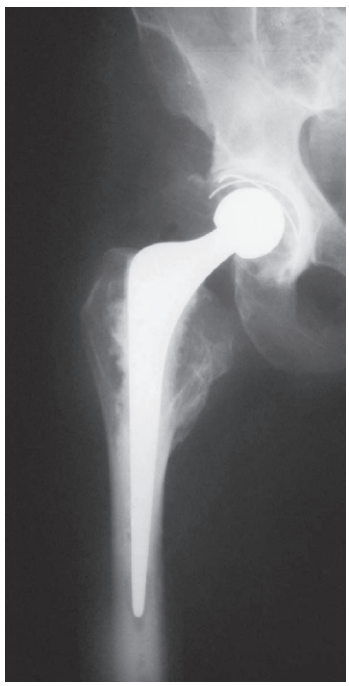


FIGURE 15.4 A fully cemented metal-on-polyethylene total hip replacement

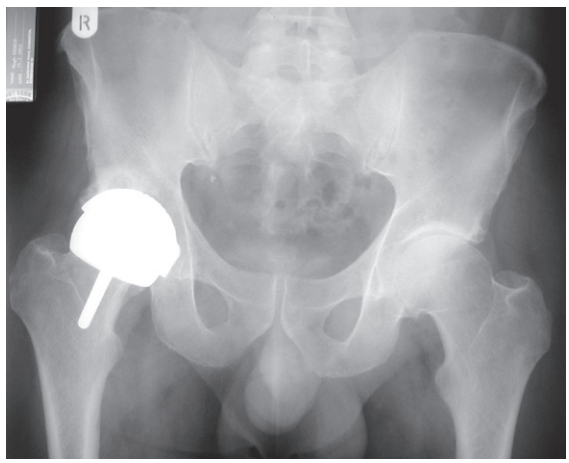


FIGURE 15.5 A resurfacing metal-on-metal total hip replacement

lower infection eradication rate), in two stages separated by 6 weeks or by implant removal, known as a Girdlestone excision arthroplasty (greater morbidity, higher infection eradication rate).

In young and physically active patients with significant symptoms from unicompartmental knee OA, high tibial osteotomy may offer an alternative intervention that can delay the need for joint replacement for about 10 years. Osteotomy and joint-preserving surgical procedures should be considered in young adults with symptomatic hip or knee OA, especially when there is dysplasia or varus/valgus deformity. Total joint replacement, however, results in pain relief and improved function within 4 months of surgery, but the range of movement may not be improved. More than 90% of these prostheses will survive for 15 years. Infection is difficult to eradicate in total joint arthroplasty, and very occasionally transfemoral amputation is undertaken for intractable infection. The risk–benefit analysis is otherwise very similar to that for total hip arthroplasty. Lateral compartment OA occurs less commonly. Reasons should be sought; these include a congenitally hypoplastic lateral femoral condyle, inflammatory arthritis and an arthritic hip causing an adducted thigh. Where hip and knee arthritis occur together, the hip is usually replaced first. Early patello-femoral arthritis can respond well to physiotherapy. In patients with unicompartmental disease, unicompartmental knee replacement is effective, although a total knee replacement may prove more durable. In patients with OA of the knee, joint fusion can be considered as a salvage procedure when joint replacement has failed.

NATURAL HISTORY AND PROGNOSIS

Progression and prognosis in patients with OA is to some extent joint-specific, with subsets of patients with knee, hip and hand OA that progress at different rates. Structural changes in knee OA usually evolve slowly over a number of years with some patients remaining stable for years at a time. Clinical and radiographic deterioration does, however, occur in one-third to two-thirds of patients followed up for 15 years despite frequent early improvement in pain and mobility.

Knee pain and radiographic evidence of OA in the contralateral knee are both predictors of disease progression. One-half to two-thirds of patients with hip OA also progress over 10 years, but patients with medial or concentric pattern OA hip, which is sometimes associated with generalized nodal OA, generally have a better prognosis. Rapid progression of hip disease was formerly thought to be associated with osteonecrosis and consumption of NSAIDs (‘analgesic hip’), but other groups of patients who have not taken analgesics have been found to have an identical clinical course and pathology. Some 50% of patients with hand OA and DIPJ involvement also show evidence of radiographic progression over 10 years, despite early improvement in symptoms. Progression of structural deterioration is generally slower in the PIP joints and the carpometacarpal (CMC) joint of the thumb. The presence of nodal OA has been found to be associated with a sixfold increase in the risk of progression of knee OA and it also increases considerably the likelihood of developing OA following meniscectomy. Other risk factors associated with *progression* of knee OA include obesity, low bone density, chondrocalcinosis, knee effusions, and low intakes of vitamins C and D, as well as mechanical determinants, such as injury, joint instability and varus–valgus mal-alignment.

CRYSTAL ARTHRITIS AND DEPOSITION-ASSOCIATED DISEASE

A variety of crystals can be associated with acute and chronic arthritis, bursitis, tendonitis, periarthritis and deposition in connective tissues (Table 15.4).

CRYSTAL FORMATION AND PATHOGENESIS (FIG. 15.6)

Crystals form in tissues when the concentration of their chemical constituents exceeds their solubility threshold, but many tissues sustain supersaturated levels of relevant solutes for long periods without crystallization because of the presence of inhibitory proteins and ions. Crystal formation is also favoured by falls in local temperature, pH and by the presence of crystal *nucleators.* Microcrystals usually stimulate inflammation only after being shed into synovial joints or bursae following loosening in the adjacent connective tissue matrix. This can follow trauma, complex changes in the matrix during intercurrent illness or surgery, or, in the

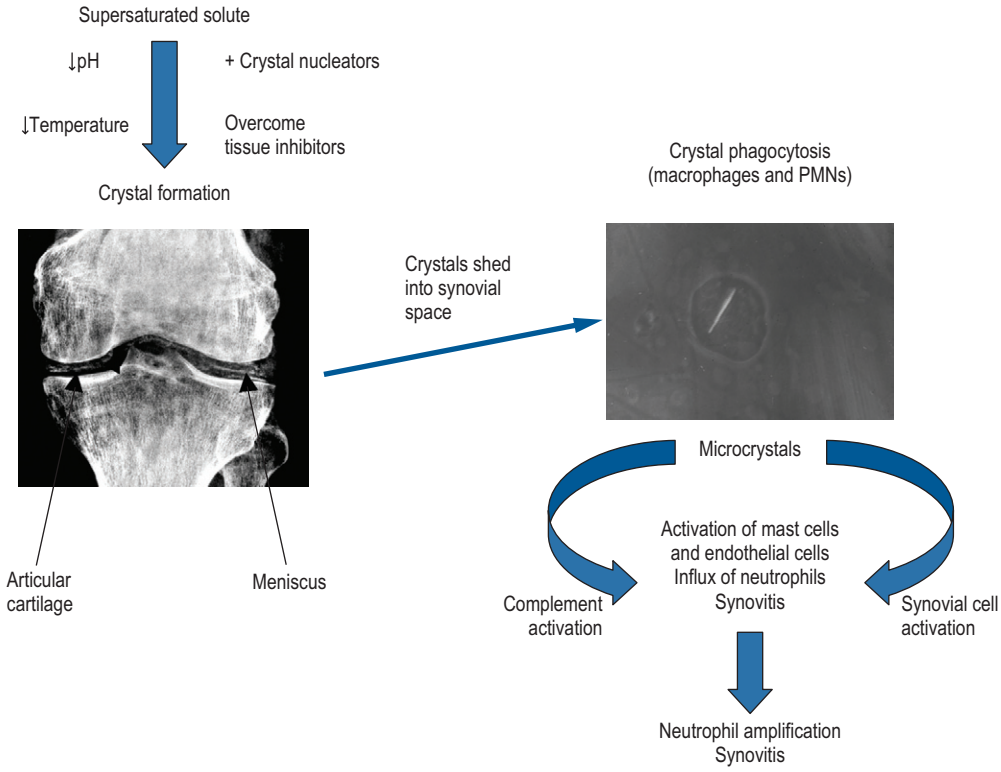


FIGURE 15.6 Mechanisms involved in crystal formation and crystal-induced inflammation. PMN, polymorphonuclear cell

Table 15.4 Common associations with crystal deposition

Crystal	Association
Calcium pyrophosphate dihydrate (CPPD)	Acute pseudo-gout Subacute/chronic arthritis Chondrocalcinosis
Basic calcium phosphates	Calcific periarthritis/tendonitis Subacute/chronic arthritis Calcinosis
Calcium oxalate	Acute arthritis in renal dialysis patients
Monosodium urate monohydrate (MSUM)	Acute gouty arthritis Subacute/chronic arthritis Tophi Renal calculous disease

Less common associations include acute arthritis/renal calculi with xanthine crystals in patients with xanthinuria, and cholesterol crystals in patients with rheumatoid arthritis and chronic joint effusions.

case of gout, after partial dissolution following the initiation of uric acid-lowering drug therapy. The microcrystals have a highly negatively charged, reactive surface that can be directly membranolytic, as well as having the capacity to activate leucocytes and bind numerous serum and cell membrane proteins. Although crystal-induced inflammation is largely a neutrophil-dependent process, driven by the capacity of protein-coated crystals to activate and recruit leucocytes, the initial interaction may be with resident macrophages through Toll-like receptors. Subsequent activation of complement and vascular endothelial cells leads to vasodilation, increased blood flow and ingress of polymorphonuclear leucocytes with release of cascades of inflammatory mediators. These include the pro-inflammatory cytokines IL-1, IL-6 and TNFα, prostaglandins and neutrophil chemotactic chemokines, such as IL-8, in addition to kinins and calgranulins that act as amplification factors.

CALCIUM PYROPHOSPHATE DIHYDRATE CRYSTAL DEPOSITION

CPPD crystals are deposited at entheses as well as in hyaline cartilage and, particularly, in fibrocartilage, where they are associated with chondrocalcinosis and degenerative changes. Shedding of crystals into the joint can provoke an attack of acute synovitis (pseudo-gout) and also a more chronic pyrophosphate arthropathy.

EPIDEMIOLOGY

Autopsy and radiographic surveys indicate that chondrocalcinosis is a common age-related phenomenon. The menisci and articular cartilage of the knees are most frequently affected, but radiographic chondrocalcinosis can also be seen in the triangular cartilage of the wrists, the intervertebral discs, the symphysis pubis and the labrum of the acetabulum of the hip, and occasionally at other sites. The prevalence of radiographic chondrocalcinosis in the knees increases from less than 5% in people under the age of 70 years to nearly 30% in those aged over 85 years. Although the presence of chondrocalcinosis is not usually associated with symptoms of joint disease, the age-adjusted prevalence of OA of the knee is modestly increased (women > men). Pyrophosphate arthropathy is two to three times more common in women than in men and usually presents in patients over the age of 70 years.

CAUSES AND ASSOCIATIONS

Although chondrocalcinosis and pseudo-gout are most frequently sporadic and idiopathic, crystal formation can follow the changes in matrix proteins and proteoglycans that occur with ageing and OA. Chondrocalcinosis, pseudo-gout and many cases of chronic pyrophosphate arthropathy can, however, be secondary to a range of inherited or acquired disorders associated with changes in pyrophosphate metabolism (Table 15.5). Overproduction of inorganic pyrophosphate (PPi), the anionic component of crystals of CPPD, by hypertrophic chondrocytes, is a feature of some of these disorders. Extracellular PPi is generated by the ecto-enzyme nucleoside triphosphate pyrophosphohydrolase (NTPPH) and the transmembrane pyrophosphate transporter *ANKH*. Mutations of the *ANKH* gene, which result in increases in extracellular PPi, have been found to be associated with some sporadic cases of pyrophosphate arthropathy,

Table 15.5 Causes of calcium pyrophosphate dihydrate crystal deposition, and associated disorders

	Association/Metabolic Cause
Sporadic	Ageing changes in matrix. ↑ Extracellular PPi due to *ANKH* mutations in some cases
Osteoarthritis	Changes in cartilage matrix
Metabolic diseases Haemochromatosis	Crystal nucleation and ↓ALP and PPi degradation by iron
Wilson's disease	Crystal nucleation and ↓ALP and PPi degradation by copper
Hypophosphatasia	↓PPi degradation due to absence of ALP
Hypomagnesaemia	Chronic diarrhoea, dietary deficiency, Bartter's disease and Gitelman syndrome lead to ↓Mg, co-factor for crystal solubility
Primary hyperparathyroidism	↑Adenylate cyclase and PPi production
Gout	Crystal nucleation/co-precipitation by urate crystals
Familial disease	CCAL 1 (chondrocalcinosis 1) is associated with mutations in chromosome 8q CCAL 2 (chondrocalcinosis 2) is associated with mutations in the *ANKH* gene on chromosome 5p Spondylo-epiphyseal dysplasia and CPPDD are associated with *COL2a* mutations

ALP, alkaline phosphatase; PPi, pyrophosphate; OA, osteoarthritis; CPPDD, calcium pyrophosphate dihydrate deposition disease.

as well as with families with CPPD deposition. Paradoxically, PPi is also a potent inhibitor of crystallization of basic calcium phosphate (BCP), so that increased levels of PPi found in patients with hypophosphatasia lead to both CPPD deposition in the form of chondrocalcinosis and defective mineralization of bone with the BCP crystal hydroxyapatitite. Conversely, polymorphisms of NTPPH, which lead to markedly reduced levels of extracellular PPi, have been associated with severe BCP crystal arthropathy.

CLINICAL PRESENTATION

CPPD is brought to clinical attention most frequently by the incidental finding of chondrocalcinosis on skeletal radiographs (Fig. 15.7).

Pseudo-gout is a common cause of acute inflammatory monoarthritis in the elderly. The knee is the site of more than half of all attacks, the duration of which can vary from a few days to 4 weeks. As its name implies, pseudo-gout can resemble acute gout with severe joint pain, swelling, tenderness and effusion associated with erythema of the overlying skin and systemic symptoms, so it is always important to consider the possibility of joint sepsis in the differential diagnosis. Subacute or 'petite' attacks are not uncommon and there is sometimes polyarticular clustering of acute episodes. Pseudo-gout occurs more frequently in men than in women.

Chronic pyrophosphate arthropathy is more common than pseudo-gout and occurs more frequently in elderly women. Symptoms and signs vary according to the intensity of the associated inflammation. A few patients have a persistent subacute inflammatory oligoarthritis lasting for months, that can be mistaken for rheumatoid arthritis, whereas more than half of all those affected have a much more indolent arthritis resembling OA, punctuated in some cases by superimposed acute or subacute attacks. The knees are most frequently affected, but chronic pyrophosphate arthritis may also involve the wrists, shoulders, elbows and MCP joints in the hands, as well as the hips and the mid-tarsal joints in the feet. An arthritis resembling OA in the second and third MCP joints commencing before the age of 50 years should alert one to the possibility of a haemochromatotic arthropathy associated with CPPD. In a minority of patients, severe destructive changes associated with CPPD and subluxation of a knee or shoulder may resemble a neuropathic arthropathy (Charcot joint), without any associated neurological deficit.

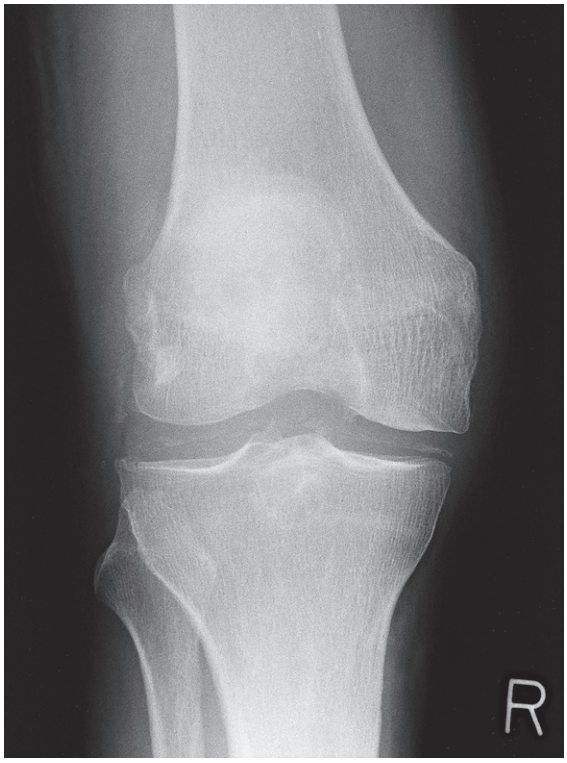


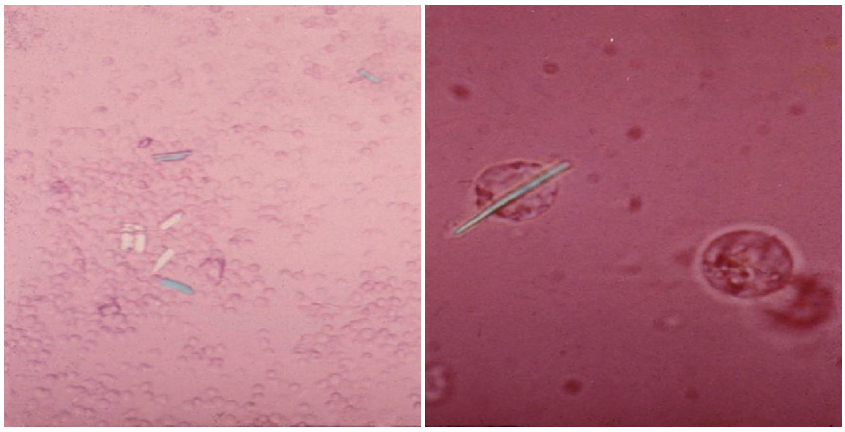
FIGURE 15.7 Chondrocalcinosis in the knee

INVESTIGATIONS

Examination of synovial fluid by compensated, polarizing, light microscopy allows CPPD crystals to be detected and distinguished from crystals of monosodium urate monohydrate (Fig. 15.8). Gram staining and culture are required to exclude bacterial infection. Radiographs may show evidence of chondrocalcinosis in fibro-cartilage or hyaline articular cartilage (see Fig. 15.7), but absence of visible chondrocalcinosis does not rule out the possibility of pseudo-gout or pyrophosphate arthritis.

TREATMENT

Joint aspiration and intra-articular injection of corticosteroids are the most effective means of treating an acute or subacute attack of pseudo-gout. NSAIDs and colchicine are less effective than in the treatment of classical gout, and great care must be taken when using them in elderly people.



A B

FIGURE 15.8 Compensated polarized light microscopy of synovial fluid. (A) Positively bi-refringent crystals of calcium pyrophosphate dihydrate (CPPD) from patient with pseudo-gout. (B) Negatively bi-refringent crystal of monosodium urate monohydrate from a patient with gout

Table 15.6 Disorders associated with basic calcium phosphate crystal deposition

Musculoskeletal Syndromes	Metabolic Disorders with Metastatic Calcification	Ectopic Dystrophic Calcification
Calcific periarthritis Milwaukee shoulder syndrome Ossification of posterior longitudinal ligament (OPLL) Osteoarthritis	Vitamin D intoxication Chronic renal dialysis Hyperparathyroidism Pseudo-hyperparathyroidism	Dermatomyositis and polymyositis Systemic sclerosis (especially limited cutaneous scleroderma) Prolapsed intervertebral discs Hip arthroplasties Myositis ossificans Paraplegia Atherosclerotic plaques Damaged heart valves Scarring of lungs, lymph nodes and adrenals Tumoral calcinosis

BASIC CALCIUM PHOSPHATE CRYSTAL DEPOSITION

Regulated deposition of the BCP crystal hydroxyapatite (HA) is essential for the formation of bones and teeth. However, pathological deposition of BCP crystals of hydroxyapatite, octacalcium phosphate, tricalcium phosphate and magnesium whitlockite in musculoskeletal tissues is associated with calcific periarthritis, the very destructive Milwaukee shoulder syndrome and many cases of OA. They are also responsible for *metastatic* calcification in a number of metabolic disorders, and for ectopic, *dystrophic* calcification in a number of autoimmune rheumatic diseases and in many situations where there has been damage to the connective tissue matrix (Table 15.6).

Calcific periarthritis results from periarticular inflammation in association with deposition of HA microcrystals. Acute episodes are characterized by local pain, heat, swelling and tenderness, sometimes accompanied by reddening of the overlying skin, and by systemic features of inflammation, such as fever and a raised C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). The shoulder region (supraspinatus tendon) is most frequently affected in middle-aged men or women, but monoarticular and polyarticular attacks can also occur in the region of the hip, knee, ankle, elbow or wrist. Attacks can be spontaneous or can follow trauma. Rarely, calcific periarthritis is familial, or secondary to metabolic disorders, such as chronic renal failure or hyperparathyroidism. In most cases, however, there is no serum biochemical abnormality.

Radiographs show evidence of tendon-associated calcinosis, which sometimes disappears spontaneously following an acute attack. Aspiration of the subacromial bursa may reveal cloudy white fluid containing masses of HA crystal aggregates that stain for calcium with Alizarin red. Definitive crystal identification involves X-ray diffraction, infra-red spectroscopy or electron microscopy, but is not required in clinical practice.

Acute attacks usually respond to symptomatic treatment with analgesics or NSAIDs. Aspiration and/or corticosteroid injection may be necessary, but surgical excision is required only very rarely if massive deposits are the cause of painful impingement.

Supraspinatus tendon deposits of HA, unassociated with symptoms, can be seen in shoulder radiographs in 3–4% of the population.

Apatite-associated destructive arthropathy (cuff tear arthropathy; Milwaukee shoulder/knee syndrome) is a relatively uncommon but distinctive type of destructive arthritis seen in the elderly. Women are affected more frequently than men. The shoulders and knees are the main joints involved, but the wrists, hips and mid-tarsal joints are occasionally affected. Sudden onset of pain and swelling in a shoulder associated with the presence of a large cool effusion and the rapid development of joint subluxation and destruction are characteristic. Ultrasonography or radiography shows evidence of rotator cuff defects with upward migration and destruction of the humeral head, with relatively little osteophyte formation or bone remodelling. Some, but not all, cases are associated with calcific periarthritis, but synovial fluid analysis reveals large volumes of a relatively non-inflammatory fluid with numerous crystals of HA and CPPD, as well as raised levels of metalloproteinase activity.

Treatment is with analgesics, NSAIDs and supportive physiotherapy, as well as joint aspiration and injection of intra-articular corticosteroids. Occasionally a shoulder replacement arthroplasty is required.

GOUT

Gout results from tissue deposition of microcrystals of monosodium urate monohydrate (MSUM) from hyperuricaemic body fluids. Clinical manifestations include acute arthritis, bursitis, tenosynovitis and cellulitis, tophaceous deposits, chronic arthritis, renal disease and urolithiasis.

Prolonged hyperuricaemia is necessary but not sufficient for the development of gout. Hyperuricaemia is usually defined as a serum uric acid (SUA) level greater than two standard deviations above the population mean (>0.42 mmol/l in men and >0.36 mmol/l in women), although the solubility threshold for MSUM in tissue fluids is approximately 0.4 mmol/l in both sexes and SUA levels higher than this constitute *physiological hyperuricaemia*. Gout and hyperuricaemia can be *primary* or *secondary* to drugs or disorders that interfere with uric acid excretion or augment the production of uric acid (Table 15.7).

The epidemiology of gout and that of hyperuricaemia are closely related. SUA concentrations are distributed in the community as a continuous variable. Levels are influenced by age, sex, body mass, ethnicity and genetic constitution as well as by dietary intake of purines and alcohol. SUA levels are higher in men than in women, rising after puberty in males and only after the menopause in females. The incidence of gout is about 1.4 per 1000 per year and the overall prevalence in general practice is about 1.4%, but increases to about 7% in men and 3% in women over the age of 75 years. Asymptomatic hyperuricaemia is 10 times more common. *Primary* gout occurs predominantly in men, and gouty arthritis is exceptionally rare in women before the menopause. Gout in older women is usually s*econdary* and often associated with renal insufficiency, hypertension and/or diuretic drug therapy. *Primary* gout is the most common cause of inflammatory arthritis in men over the age of 40 years and is an increasingly frequent cause of inflammatory arthritis in postmenopausal women. It is age related, with a peak onset in men between 40 and 50 years of age. The incidence and prevalence of gout increase with the level of SUA. The risk of developing gout in men rises from 0.5% per annum when the SUA level is 0.42 mmol/l to 5.5% per annum in those with a SUA concentration of 0.54 mmol/l. Recent evidence suggests that the incidence and prevalence of gout and hyperuricaemia are increasing as the age structure of the population changes, and also probably as a consequence of rising levels of SUA associated with obesity and affluent lifestyles. Some 75% of patients with gout have features of the metabolic syndrome (central obesity, hypertension, hyperglycaemia, hypertriglyceridaemia and low levels of high-density lipoprotein (HDL)) and

Table 15.7 Some factors contributing to the development of hyperuricaemia and gout

Primary	Secondary
Diminished Renal Excretion of Uric Acid	
Isolated renal tubular defect in fractional clearance of uric acid (most patients)	Renal insufficiency
Familial juvenile hyperuricaemic nephropathy	Hypertension
	Drug administration: • Any diuretic (but particularly thiazides) • Low-dose salicylates • Ciclosporin • Pyrazinamide
	Lactic acidosis e.g. due to alcohol, fasting, or vomiting or rigorous exercise
	Volume depletion
	Lead toxicity
	Glucose-6-phosphatase deficiency
Increased Production of Urate	
Increased purine synthesis *de novo*: • Idiopathic • Hypoxanthine–guanine phosphoribosyl transferase deficiency • Phosphoribosyl pyrophosphate synthetase superactivity	Increased turnover of purine nucleotides: • Myeloproliferative disorders, e.g. polycythaemia rubra vera, chronic granulocytic leukaemia • Lymphoproliferative disorders, e.g. chronic lymphocytic leukaemia • Severe exfoliative psoriasis
	Accelerated catabolism of purine nucleotides: • Cytotoxic drug therapy ('tumour lysis syndrome') • Alcohol ingestion • Fructose ingestion/intolerance • Glucose-6-phosphatase deficiency (GSD type I) • Myogenic (GSD types III, V and VII)

recent epidemiological studies have confirmed that consumption of alcohol (especially beer) or of fructose-containing carbonated drinks and diets high in red meat and shellfish are risk factors for the development of gout, whereas diets rich in dairy products, which are uricosuric, are protective.

AETIOLOGY

Purine nucleotide synthesis and degradation are regulated by a balanced interaction of biochemical pathways (Fig. 15.9). Uric acid is the end product of purine metabolism in humans, who lack the enzyme uricase that degrades uric acid to allantoin in most mammals. The miscible pool of uric acid in normal individuals is about 1200 mg. More than half of this is derived from endogenously synthesized purine nucleotides and the rest from ingested dietary purines. Sixty per cent of the uric acid pool is replenished daily from the catabolism of purine nucleotides and bases. Two-thirds of the uric acid formed each day is excreted by the kidney and one-third is eliminated via the gastrointestinal tract (Fig. 15.10). Renal clearance of uric acid follows three main processes: filtration at the glomerulus; proximal tubular reabsorption facilitated by the membrane urate transporter protein URAT1; and active tubular secretion in various parts of the renal tubule mediated by the organic anion transporter OAT, the sodium-dependent phosphate

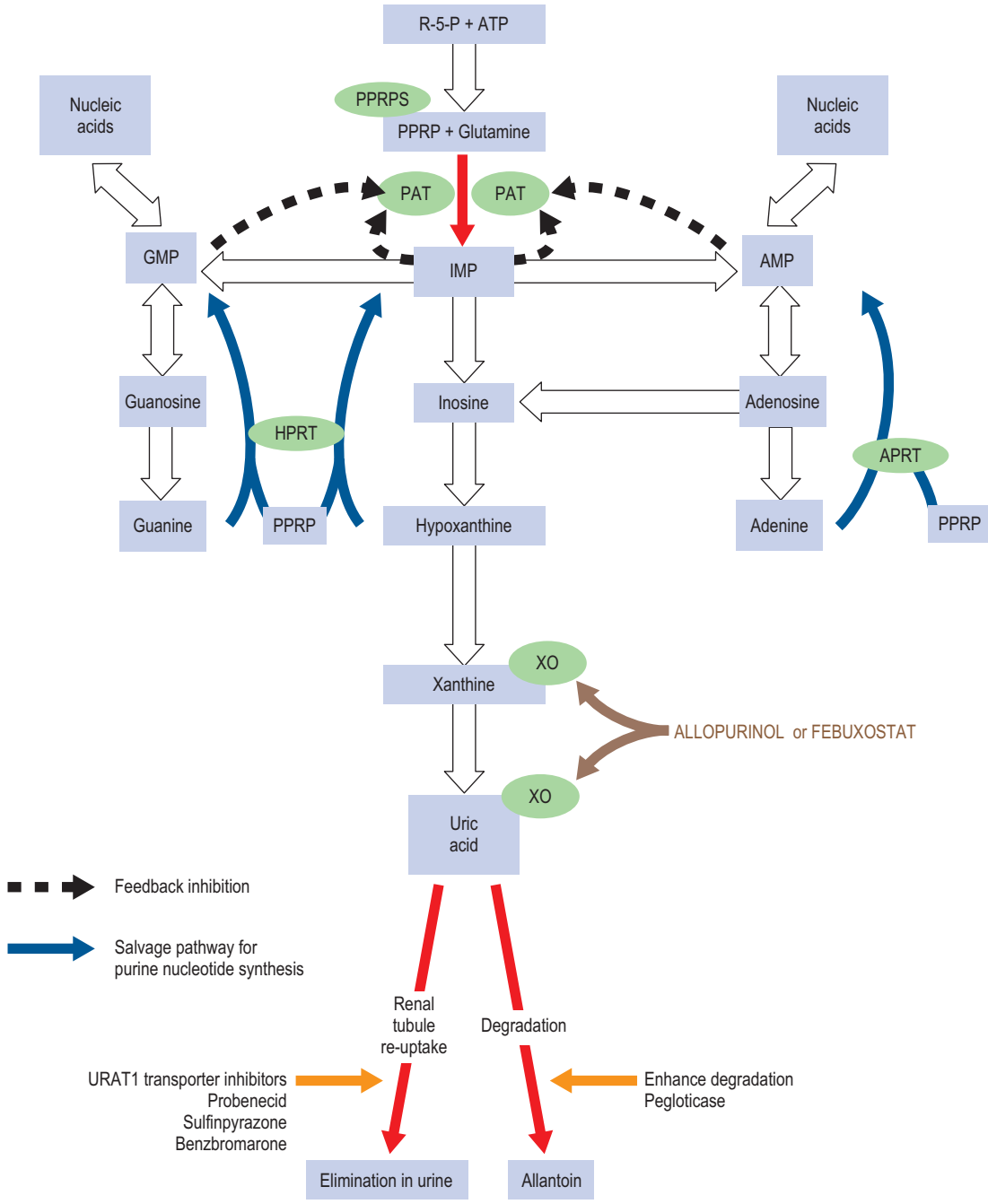


FIGURE 15.9 Pathways of purine synthesis and degradation. AMP, adenosine monophosphate; APRT, adenine phosphoribosyl transferase; ATP, adenosine triphosphate; GMP, guanosine monophosphate; HPRT, hypoxanthine–guanine phosphoribosyl transferase; IMP, inosine monophosphate; PAT, phosphoribosyl pyrophosphate amidotransferase; PPRP, phosphoribosyl pyrophosphate; PPRPS, phosphoribosyl pyrophosphate synthetase; R-5-P, ribose-5-phosphate; URAT1, urate transporter protein 1; XO, xanthine oxidase

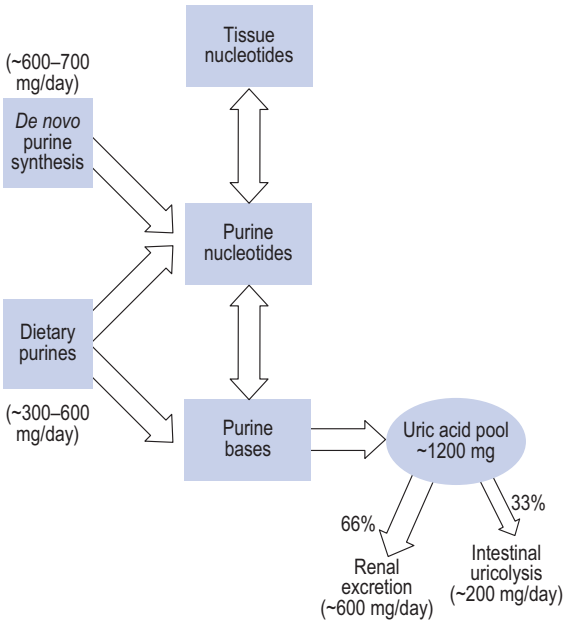


FIGURE 15.10 The uric acid pool. Origin and fate of uric acid in normal humans

co-transporter NPT1 and the urate-channelling protein UAT.

Genetic and environmental factors lead to gout and hyperuricaemia by increasing the production of uric acid and/or reducing its excretion (see Table 15.7). In about 90% of patients with *primary* gout, hyperuricaemia is associated with a genetically determined renal tubular defect in which the capacity to increase uric acid excretion in response to a purine load is impaired. A similar, but more profound, defect in fractional clearance of uric acid occurs in Maoris and Polynesians, and in a rare form of familial juvenile hyperuricaemic nephropathy associated with mutations in uromodulin (the Tamm–Horsfall urinary protein). In 10% of patients with gout there is increased production of uric acid, usually as a result of increased turnover of cellular nucleoproteins. In less than 1% of mutations in the purine salvage enzyme hypoxanthine–guanine phosphoribosyl transferase (HPRT), the *de novo* purine pathway enzyme phosphoribosyl pyrophosphate synthetase (PPRPS) or the glycogenolytic enzyme glucose-6-phosphatase (G-6-P) leads to accelerated *de novo* purine nucleotide synthesis and overproduction of uric acid (see Fig. 15.9 & Table 15.7).

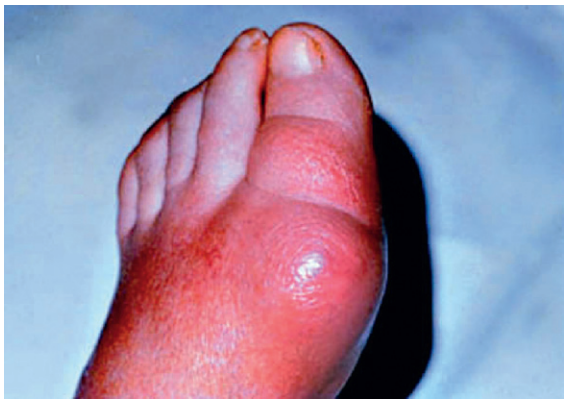


FIGURE 15.11 Acute gouty arthritis ('podagra')

CLINICAL FEATURES

Acute gout presents most frequently as an acute monoarthritis in one of the distal joints of the foot or hand. The metatarsal joint of the great toe is the first joint affected in more than 50% of patients ('podagra') (Fig. 15.11), but attacks may also occur in the ankle, subtalar or mid tarsal joints, the knee, wrist, elbow or small joints of the hands. The hips, shoulders and joints of the axial skeleton are not affected. The onset may be insidious, but more typically is explosively sudden, frequently waking the patient from sleep. The affected joint becomes hot, red, swollen and extremely tender to any touch. Very acute attacks may be accompanied by fever and systemic symptoms of inflammation, and are sometimes preceded by prodromal symptoms of anorexia, nausea or change in mood. Untreated first attacks will typically resolve spontaneously and completely in 1–2 weeks, sometimes with pruritus and desquamation of the overlying skin. Some patients suffer a single attack or experience another only after many years, but most patients will have a second attack within 12–18 months. If left untreated, patients tend to suffer recurrent acute or subacute attacks with increasing frequency. These may be more prolonged with progressive shortening of the symptom-free 'intercritical' period between attacks. In such individuals, polyarticular acute gouty arthritis, bursitis and cellulitis are not uncommon and can lead to diagnostic confusion. Acute attacks of gout may be precipitated by a number of factors (Box 15.1).

Box 15.1
Events responsible for provoking attacks of acute gout

- Alcohol
- Dietary excess
- Drugs:
  - diuretics (especially thiazides)
  - initiation of uric acid-lowering drug therapy with allopurinol or uricosurics
  - cytotoxics
- Fasting or severe dieting
- Surgery
- Systemic illness
- Trauma
- Unusual physical exercise

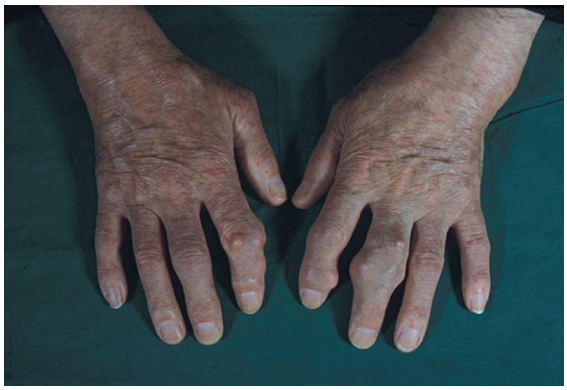


FIGURE 15.12 Chronic tophaceous gout

CHRONIC TOPHACEOUS GOUT

First attacks of gouty arthritis are seldom associated with residual deformity or disability, but recurrent attacks are followed by progressive cartilage and bone erosion, deposition of palpable masses of urate crystals ('tophi') and an asymmetrical inflammatory polyarthritis in the feet, hands or wrists, with secondary OA and disability associated with deformities and restriction of joint movements (Fig. 15.12). Tophi develop in the helix of the ear as well as in bursae, tendon sheaths and periarticular tissues. The severity of the joint damage and the speed with which tophi develop are related to the SUA level. Although visible, papable tophi are usually observed only after about 10 years of recurrent gout in untreated, or inadequately treated, patients, they can develop much more rapidly in the hands or feet in patients with *secondary* gout, such as transplant patients receiving ciclosporin or post-menopausal women with heart failure and renal insufficiency receiving diuretic drugs. Sub-clinical deposition of urate crystals precedes the onset of symptomatic gout.

A history of renal colic associated with uric acid calculi is found in about 10% of patients with gout attending hospital clinics in the UK. Uric acid urolithiasis is also associated with:

- Hot climates, dehydration and low urine flow
- Low urine pH (e.g. chronic diarrhoeal diseases or ileostomy)
- Hyperuricosuria
- Purine overproduction
- High intake of dietary purines
- Treatment with uricosuric drugs
- Defects in tubular resorption of uric acid.

Chronic renal disease can complicate chronic tophaceous gout, as a result of MSUM crystal deposition in the renal medulla variably combined with the effects of renal tubular obstruction with crystals of uric acid, hypertension, glomerulo-sclerosis and secondary pyelonephritis in patients with gout and prolonged, uncontrolled hyperuricaemia. In treated patients, minimal renal insufficiency is largely age related, and proteinuria is mild and non-progressive.

Acute crystal nephropathy can result from sudden obstruction of the collecting ducts and ureters with uric acid crystals following treatment of leukaemia or lymphoma with cytotoxic drugs ('tumour lysis syndrome'). The problem can usually be avoided by prophylaxis with allopurinol, high fluid intake and urine alkalinization before chemotherapy, but care needs to be undertaken to discontinue alkalinization of the urine in hyper-phosphataemic patients to avoid precipitation of calcium phosphate crystals in the renal tubules.

INVESTIGATIONS

Certainty of the diagnosis requires the identification of MSUM crystals from tophi, synovial or bursal fluid by compensated, polarizing light microscopy (see Fig. 15.8). Synovial fluid from patients with acute gouty arthritis is frequently turbid with a high polymorphonuclear leucocyte count, and Gram staining and culture are required to exclude bacterial infection. Blood tests usually

show evidence of a systemic inflammatory response with a raised CRP and ESR, and sometimes a moderate neutrophil leucocytosis and reactive thrombocytosis. The SUA level should be measured, but has very limited diagnostic value because asymptomatic hyperuricaemia is very common and the SUA concentration is raised at the time of an acute attack of gout in only about 60% of patients.

Radiographs are seldom helpful at the time of the first attack, but can be used to assess joint damage in patients who have had recurrent episodes. Patients with chronic tophaceous gout may have periarticular soft-tissue swelling flecked with calcification on plain radiographs, as well as characteristic 'punched out' erosions with sclerotic margins, overhanging edges and relatively little periarticular osteoporosis (Fig. 15.13), but in many cases the radiographic appearances are similar to those in patients with other types of inflammatory joint disease and OA. The finding of a characteristic 'double contour' on ultrasonography is being used increasingly in clinical practice to detect urate crystal deposits on the surface of articular cartilage and tendons before radiographic changes occur.

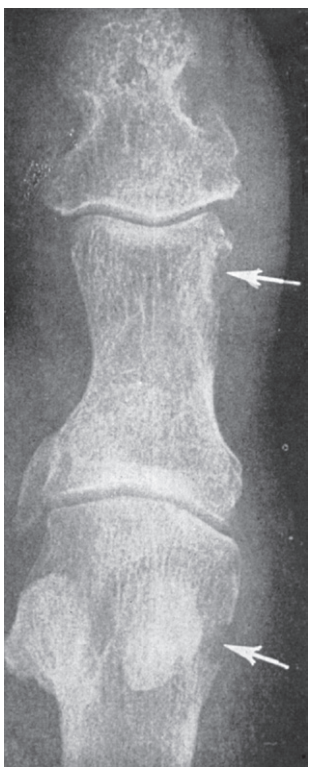


FIGURE 15.13 Chronic tophaceous gout. Radiograph showing characteristic punched-out erosions with overhanging margins (arrowed)

All patients with gout should have measurements of blood pressure and renal function, and be further assessed for cardiovascular risk, with screening tests for diabetes mellitus, hyperlipidaemia and the metabolic syndrome.

When a diagnosis of gout has been established, possible causes of primary and secondary hyperuricaemia should be considered (see Table 15.7).

If there is reason to suspect overproduction, rather than underexcretion, of uric acid, this can be established, in the absence of renal impairment, by finding a 24-hour urine uric acid excretion of more than 1 g (6 mmol) while on a low-purine diet. The possibility of specific enzyme defects associated with an increase in *de novo* purine synthesis should be suspected:

- in the absence of disorders associated with increased turnover or breakdown of purine nucleotides
- if gout develops before the age of 20 years
- when there is a family history of gout commencing at an early age
- when uric acid lithiasis is the presenting feature in a young person.

TREATMENT

Patient education and understanding the rationale for therapy are vital for the successful management of gout.

ACUTE GOUT

Rest and prompt treatment with full doses of a rapidly acting oral NSAID, such as naproxen or indometacin, are the treatment of choice for acute attacks, provided that there are no contraindications. NSAIDs should be avoided in patients with heart failure, renal insufficiency or a recent history of gastrointestinal ulcer, bleed or perforation, and should be used with great circumspection in frail elderly patients with multiple pathology and in patients with cardiovascular disease. In patients with increased risk of development of peptic ulcer, bleeding or perforation, the use of a NSAID with co-prescription of a gastro-protective agent, or the use of a highly selective COX2 inhibitor, such as etoricoxib 120 mg once daily, can be considered for treating acute gout. However, selective COX2 inhibitors should not be used in patients with

established ischaemic heart disease, cerebrovascular disease or peripheral vascular disease.

Colchicine, which inhibits neutrophil phagocytosis, can be used as an effective alternative to NSAIDs for the treatment of acute gout. Despite being slower to act, it is best given in a relatively low oral dose (e.g. 0.5 mg 8-hourly), because it has a low therapeutic index, and nausea, diarrhoea or abdominal cramps commonly supervene before resolution of the acute arthritis. Intravenous colchicine has been associated with a number of sudden deaths and should not be used.

If oral therapy is precluded, a parenteral NSAID or NSAID suppository can be used if NSAIDs are not otherwise contraindicated. Alternatively, joint aspiration, intra-articular injection of a corticosteroid or a short course of systemic corticosteroids can be safe and effective. Use of the IL-1β receptor antagonist anakinra, the decoy fusion protein rilonacept or the IL-1β monoclonal antibody canakinumab are currently being considered as alternatives for patients with very severe, prolonged and frequently recurrent acute gout.

Treatment with uric acid-lowering drugs should not be started until the acute attack has settled completely, because they can prolong the acute attack or trigger further episodes. Treatment with very low doses of aspirin for cardiovascular prophylaxis should be continued, and has very little effect on SUA levels, but patients should be advised to avoid aspirin and salicylate-containing medicines for analgesia because these can interfere with uric acid excretion and precipitate an attack of gout.

RECURRENT, INTERCRITICAL AND CHRONIC GOUT

Treatment is aimed at reducing the SUA level to a target of 0.30–0.36 mmol/l (i.e. well below the solubility threshold of urate) in order to prevent crystal formation and optimize dissolution of existing MSUM crystals in tissues. Initially, attention should be given to the avoidance of modifiable risk factors and to lifestyle modifications when these are appropriate, e.g.:

- Avoid or discontinue diuretic drugs when these are not absolutely required for the control of cardiac failure
- Gradual weight loss in obese patients
- Restriction of consumption of alcohol (especially beer) or fructose containing carbonated drinks
- Avoid high intake of foods with high purine content (especially shellfish, red meat and offal).

Prolonged administration of uric acid-lowering drugs should be started in the following circumstances:

- The patient has suffered recurrent acute attacks.
- There is evidence of tophi or chronic gouty arthritis.
- There is associated renal disease or urate lithiasis.
- The SUA level is very raised (>0.54 mmol/l).
- The patient needs to continue to take diuretic drugs.
- Normal levels of SUA cannot be achieved by risk factor/lifestyle modification.

There are three principal methods to lower uric acid levels and for each there is at least one effective compound: inhibit production (allopurinol or febuxostat), increase breakdown (pegloticase) or increase excretion (probenecid, benzbromarone, sulfinpyrazone).

Allopurinol is the drug of choice for the long-term management of gout because of its efficacy, safety and convenience. It lowers the SUA level by inhibiting the enzyme xanthine oxidase, which converts the purine bases xanthine and hypoxanthine to uric acid (see Fig. 15.9). Renal function should be checked before commencing therapy. In patients with normal renal function, oral treatment should be commenced at 100 mg daily with a NSAID, or colchicine 0.5 mg 12-hourly to prevent ‘breakthrough’ attacks of acute gout that otherwise often follow the commencement of treatment with uric acid-lowering drugs. The SUA level should be measured monthly and the dose of allopurinol increased in 100-mg increments to a maximum of 900 mg/day to reduce and maintain the SUA to a target level no higher than 0.36 mmol/l (6 mg/dl). If renal function is impaired, lower doses of allopurinol should be used (creatinine clearance 60 ml/min – 200 mg daily; creatinine clearance 20 ml/min – 100 mg daily). Side-effects of allopurinol include mild rashes in about 2% of patients and much rarer, severe, and even life-threatening hypersensitivity reactions, as well as potentially dangerous drug interactions with oral anticoagulants and azathioprine. Allopurinol desensitization can be undertaken in patients who have developed

mild hypersensitivity rashes, but should not be attempted in those who have suffered more severe reactions, epidermal necrolysis or drug-induced vasculitis.

The non-purine xanthine oxidase inhibitor febuxostat can be used in patients unable to tolerate allopurinol. The initial dose should be 80 mg/day, increasing if necessary to 120 mg/day to achieve target reduction of the SUA level to 0.36 mmol/l. Alternatively the uricosuric drug sulfinpyrazone (100 mg 8-hourly) can be used if renal function is normal, or the more potent uricosuric benzbromarone (100 mg/day) in patients with mild to moderate renal impairment. Uricosuric drugs are contraindicated in patients with a history of renal calculi and in urate overproducers with heavy uricosuria. Prophylactic doses of colchicine or a NSAID (see above) should be co-administered when starting all urate-lowering drugs and continued for up to 6 months.

Gout is frequently associated with hypertension and hyperlipidaemia, which require treatment to reduce cardiovascular risk. Losartan, an angiotensin-1 receptor antagonist that is effective in hypertension, and the hypolipidaemic agent fenofibrate both have uricosuric properties. Although they are not recommended as substitutes for allopurinol or standard uricosuric drugs for lowering the SUA level, they can be considered as an option for the treatment of hypertension or hyperlipidaemia in patients with gout. In patients with severe, symptomatic, tophaceous gout who fail to respond to uricostatic or uricosuric drugs, or in whom they are contraindicated, treatment with the pegylated uricase, pegloticase, can be considered.

ASYMPTOMATIC HYPERURICAEMIA

Most people with asymptomatic hyperuricaemia never develop gout, and, in those that do, renal complications rarely precede the first attack of gouty arthritis. Consequently, it is unnecessary to treat the majority of people with asymptomatic hyperuricaemia before they have experienced a first attack of gout. Uric acid-lowering treatment should, however, be considered from the outset in young people with persistently very high SUA levels (>0.6 mmol/l), especially when there is a strong family history of gout, renal disease or urolithiasis; or in persons known to have inborn errors of purine metabolism associated with increases in *de novo* purine synthesis, because renal damage may precede joint pathology in these patients.

Aside from gout there is compelling epidemiological evidence to suggest that hyperuricaemia is associated with a poor outcome in patients with hypertension, heart failure, cerebrovascular disease and glomerulonephritis. However, evidence that hyperuricaemia is the cause, rather than the consequence, of the underlying pathology is inconclusive, as is evidence to suggest that raised levels of SUA may be an independent risk factor for ischaemic heart disease. Although there is insufficient evidence at the present time to suggest that treatment of asymptomatic hyperuricaemia would reduce cardiovascular risk, the finding of persistent hyperuricaemia should not be ignored. Rather it should stimulate a search for secondary causes of hyperuricaemia (see Table 15.7), careful examination and investigation of the patient for features of the metabolic syndrome, and a detailed assessment for other, established, cardiovascular risk factors.

FURTHER READING

Dieppe P, Lim K, Lohmander S. Who should have knee joint replacement surgery for osteoarthritis? Int J Rheum Dis 2011; 14:175–180.

Hunter DJ. Pharmacologic therapy for osteoarthritis – the era of disease modification. Nat Rev Rheumatol 2011; 7:13–22.

Jordan KM, Cameron JS, Snaith M et al. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. Rheumatology (Oxford) 2007; 46:1372–1374.

Pandit H, Aslam N, Pirpiris M et al. Total knee arthroplasty: the future. J Surg Orthop Adv 2006; 15:79–85.

Rosenthal AK. Calcium crystal deposition and osteoarthritis. Rheum Dis Clin North Am 2006; 32:401–412, vii.

Teng GG, Nair R, Saag KG. Pathophysiology, clinical presentation and treatment of gout. Drugs 2006; 66:1547–1563.

Terkeltaub R (ed.) Gout and Other Crystal Arthropathies. Elsevier, Philadelphia; 2012.

Zhang W, Doherty M, Bardin T et al. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2006; 65:1312–1324.

Zhang W, Doherty M, Pascual E et al. EULAR recommendations for calcium pyrophosphate

deposition. Part II: management. Ann Rheum Dis 2011; 70:571–575.

Zhang W, Moskowitz RW, Nuki G et al. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. Osteoarthritis Cartilage 2007; 15:981–1000.

Zhang W, Moskowitz RW, Nuki G et al. OARSI recommendations for the management of hip and knee osteoarthritis, part II: OARSI evidence-based consensus guidelines. Osteoarthritis Cartilage 2008; 16:137–162.

16

INFLAMMATORY ARTHRITIS

J. S. Hill Gaston and Mark Lillicrap

Cases relevant to this chapter

21, 68, 70, 72, 75, 77–82, 85–86, 100

Essential facts

1. Rheumatoid arthritis (RA) is a common destructive inflammatory polyarthritis affecting 1% of the population.
2. Patients with persistent early morning stiffness and pain or swelling in at least three joint areas should be investigated for an inflammatory arthropathy.
3. In all cases of RA, disease-modifying anti-rheumatic therapy should be started as soon as possible.
4. Multidisciplinary management of RA helps patients to maintain long-term function.
5. Surgery may be required in RA to improve function and to relieve pain.
6. A diagnosis of ankylosing spondylitis is often delayed by 8–10 years, because back pain is so common.
7. Reactive arthritis is a form of spondyloarthritis triggered by particular infections of the gastrointestinal or genitourinary tract.
8. Post-infectious arthritis (distinct from reactive arthritis) is associated with viral or bacterial infections.
9. In many patients with inflammatory arthritis, pregnancy exerts an immunosuppressive effect, with the exception of systemic lupus erythematosus (SLE), which typically flares during pregnancy.

RHEUMATOID ARTHRITIS

DEFINITION

Rheumatoid arthritis (RA) is a common systemic inflammatory disease (affecting approximately 1% of the population and women more commonly than men) characterized by the presence of a destructive inflammatory polyarthritis. The inflammatory arthritis has a predisposition for the hands, particularly the proximal interphalangeal joints, the metacarpophalangeal joints and the wrists, but can affect any synovial joint. Although synovitis is the characteristic feature, RA is a multi-system disease with potential involvement of the lungs, heart, eyes, vascular tree, haematopoietic system and nervous system (known as extra-articular manifestations). Some 80% of adults affected by RA have a positive rheumatoid factor (RF – immunoglobulin (Ig) G or IgM antibodies recognizing IgG) at some point during the disease (although up to 60% of patients may be rheumatoid factor-negative at presentation and up to 10% of the normal population may have a positive rheumatoid factor). More recently, antibodies to cyclic citrullinated peptides (ACPA) have been shown to have greater specificity and similar sensitivity to RF. Importantly ACPA titres often rise several months or years prior to the onset of symptoms, making

them more helpful in diagnosing and classifying early disease.

Classification criteria for RA were defined by the American Rheumatology Association (ARA) in 1987 and have been used extensively in research studies, showing high sensitivity and specificity for the diagnosis of RA. These criteria (Box 16.1), particularly the four joint-associated clinical components (i.e. prolonged early morning stiffness with polyarticular symmetrical hand joint involvement), still give a useful guide to the most common clinical features of RA. However, these criteria have now been superseded by the 2010 EULAR (European League Against Rheumatism)/ACR (American College of Rheumatology) Classification Criteria. The 2010 criteria (Box 16.2) have been shown to have greater sensitivity and specificity in early RA.

RA, as defined by either of these classifications, is probably a heterogeneous syndrome rather than a single disorder, and the variability of the disease (including the pattern of presentation, presence or absence of particular antibodies, prognosis, response to treatment and extra-articular manifestations) probably reflects this.

AETIOLOGY AND PATHOGENESIS

The cause of RA is unknown. There is evidence of a genetic contribution; individuals with certain HLA types are at increased risk of disease, and having an identical twin with the disease markedly increases the risk. As is discussed in Chapter 3 (Epidemiology and genetics of rheumatic diseases), several allelic variations of the HLA-DRB1 gene (such as HLA-DRB1 0401 and 0404) have been shown to be associated with disease development in different populations; these alleles share a common amino acid sequence in the DR-β chain (residues 70–74 – the 'shared epitope'), although how this is involved in the disease aetiology remains an active research question. Although it is a risk factor, carrying an HLA genotype associated with RA or having an identical twin affected does not inevitably mean that disease will develop. Additional environmental processes must also be important. Smoking is certainly one of the contributory environmental processes associated with a significantly increased risk, particularly in

Box 16.1
1987 American College of Rheumatology Criteria for classification of rheumatoid arthritis

- Early morning stiffness
- Arthritis affecting three or more joint areas
- Hand joint arthritis
- Symmetrical arthritis
- Rheumatoid nodules
- Rheumatoid factor
- Bone erosions

The presence of at least four of the above criteria is required to classify a patient as having rheumatoid arthritis.

Box 16.2
2010 EULAR/ACR classification criteria for rheumatoid arthritis

Add the scores of categories A–D

A score ≥6 indicates DEFINITE RHEUMATOID ARTHRITIS

		SCORE
A	Joint involvement* (swollen/tender)	
	1 large joint	0
	2–10 large joints	1
	1–3 small joints (with or without large joints)	2
	4–10 small joints (with or without large joints)	3
	>10 joints (at least one small joint)	5
B	Serology	
	Negative rheumatoid factor and negative CCP	0
	Low positive rheumatoid factor or CCP	2
	High positive rheumatoid factor or CCP	3
C	Acute-phase reactants	
	Normal CRP and normal ESR	0
	Raised CRP or ESR	1
D	Duration of symptoms	
	<6 weeks	0
	≥6 weeks	1

Large joints: shoulders, elbows, hips, knees and ankles

Small joints: excludes DIPJs, 1st MCPJs and 1st MTPJs

patients carrying the shared epitope and who are seropositive for either RF or ACPA. Perhaps the most likely hypothesis, given the association with HLA-DR alleles, is that an aberrant T-lymphocyte response to an antigen results in activation of the immune system (including B-lymphocyte production of rheumatoid factor and ACPA) and an autoimmune driven inflammatory response focused on the synovium. The specific antigen involved in RA has not been clearly identified, although much interest has centred recently on the role of citrullinated proteins, following the identification of ACPA as a disease marker in a subgroup of patients with RA. Citrullination is the post-translation modification of the amino acid arginine (positively charged at physiological pH) to citrulline (uncharged) in a protein. Citrullination changes both the peptide sequence and the charge, and could therefore allow a novel peptide sequence to occur which could escape conventional tolerance mechanisms. Bacterial proteins can also be citrullinated – *Porphyromonas gingivalis* (a bacterium responsible for periodontitis, frequently found in smokers) unusually has an enzyme that can convert arginine to citrulline. Therefore, bacterial citrullination of self-proteins at sites of inflammation could also break tolerance.

Whatever triggers the initial immune activation, there is clear evidence of an active downstream innate and acquired immune response in patients with RA. It is this chronic inflammatory response within the synovium that accounts for the musculoskeletal clinical features. It also causes the destructive changes in the cartilage and bone that are characteristic of the disease. Treatment with disease-modifying agents aims to control this process. In the majority of patients with RA, the inflammatory process is associated with a pro-inflammatory cytokine milieu dominated by cytokines such as tumour necrosis factor (TNF) and interleukin (IL)-6, produced by macrophage-like synoviocytes. This cytokine production may be driven by either autoreactive T cells, immune complexes containing RF and other autoantibodies, or activation of innate immunity. One of the most dramatic recent developments in RA has been the use of antibodies and fusion proteins that specifically block the action of these cytokines. These therapies show marked efficacy, not only in reducing symptoms but also in slowing disease progression.

CLINICAL FEATURES

HISTORY

As highlighted in Chapter 1 (Clinical history and examination), the characteristic clinical history feature of any inflammatory arthritis is early morning stiffness. In inflammatory arthritis this stiffness is present for at least 30 minutes, and usually for several hours on waking. It is often better in the afternoon but recurs with immobility and towards the evening (diurnal variation). Any patient who spontaneously offers a history of early morning stiffness needs thorough investigation to exclude an inflammatory arthropathy.

In RA, the joint stiffness is characteristically accompanied by pain and swelling, most commonly initially of the wrists, the small joints of the hands and the feet in a symmetrical distribution. However, the arthritis can affect any synovial joint and, although patients frequently present with hand symptoms, presentation with other joint involvement does not exclude the diagnosis. An additional useful indicator that symptoms reflect an underlying inflammatory arthritis is the responsiveness of symptoms to non-steroidal anti-inflammatory drugs (NSAIDs), and this should be explored in the history. (It is of note that over-the-counter doses of ibuprofen are not anti-inflammatory.)

RA can cause significant disability through functional impairment, restricted participation and limitation of activities. It is important to enquire about the impact of the disease on the patient's activities of daily living (ADLs) and occupational/recreational participation, so that these areas can be addressed appropriately. It is also useful to explore other patient-specific factors that could impact on a patient's disability (Fig. 16.1). Extra-articular manifestations usually occur later in the disease course. However, they can occur early and a thorough review of all systems is also required when taking a history.

EXAMINATION

If allowed appropriate opportunity, the patient will usually have given the clinician enough information to make the diagnosis of inflammatory arthritis from the history. Examination then allows the clinician to confirm the diagnosis. Chapter 1 describes a system for comprehensive history-taking and screening examination of the musculoskeletal

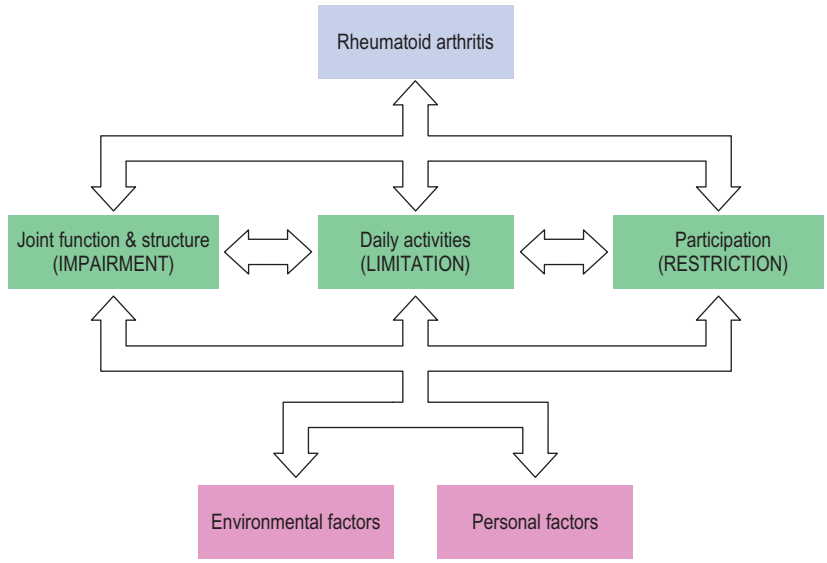


FIGURE 16.1 A model of disability

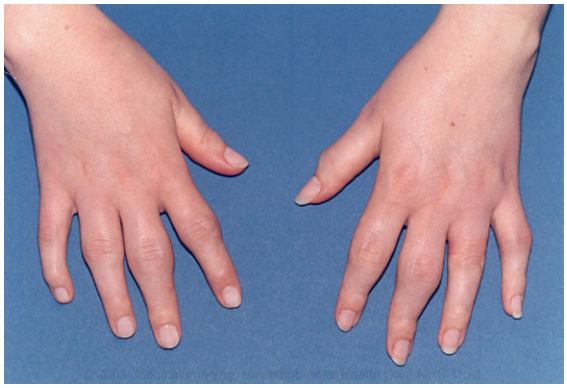


FIGURE 16.2 Symmetrical polyarthritis in a patient with rheumatoid arthritis. The wrists, metacarpophalangeal and proximal interphalangeal joints are symmetrically involved

system and allows the clinician to identify involved joints that can then be assessed further with appropriate regional examination. The typical examination features in a patient presenting with RA are of swelling, warmth and joint-line tenderness of affected joints. Erythema is unusual. The pattern of joint involvement (Fig. 16.2) most frequently includes the wrists (carpi and distal radio-ulnar joints), the proximal interphalangeal joints (particularly index and middle fingers) and the metacarpophalangeal joints (again index and middle fingers). The feet should be examined because early foot involvement is associated with a worse prognosis and could indicate a need for more aggressive early treatment. Metacarpophalangeal and metatarsophalangeal squeeze tests, in which the heads of the metacarpals and metatarsals are squeezed gently (until the examiner's fingernail just blanches) between thumb and middle finger, are sensitive indicators of underlying synovitis. The characteristic changes (including boutonnière and swan neck deformities of the fingers, ulnar deviation of the metacarpals or radial deviation of the wrist) are usually only seen in established disease.

A systemic examination looking for rheumatoid nodules (most often seen on the elbows) and extra-articular features should also be undertaken. RF-positive patients and those who are also homozygous for the HLA-DR shared epitope are at increased risk of extra-articular manifestations of the disease; these are also associated with worse joint disease and an increased mortality. These are discussed in Chapter 18 (Systemic complications of rheumatic diseases).

EARLY RHEUMATOID ARTHRITIS

The 2010 EULAR/ACR classification criteria for RA allow a greater proportion of patients presenting with early inflammatory arthritis to be appropriately classified as having RA than was the case with the 1987 ARA criteria. Aggressive early treatment can be effective in preventing irreversible loss of joint function and subsequent disability. At first presentation, many patients who go on to develop chronic RA will have normal radiographs and a negative RF. Some patients may not have an increased systemic inflammatory response (C-reactive protein (CRP) and erythrocyte

sedimentation rate (ESR)). Determination of ACPA is more sensitive and specific in early disease and is a very useful investigation to guide classification. However, a diagnosis of RA should be a clinical one; approximately 30% of patients with RA do not have detectable levels of ACPA.

There is robust clinical evidence that early aggressive treatment of patients with early RA (with combination disease-modifying anti-rheumatic drug (DMARD) treatment including methotrexate) improves the long-term outcome. A fast-track referral is recommended for patients with possible inflammatory arthritis, to allow early specialist involvement. Unfortunately, owing to limited resources, this is not always possible. The pattern of disease, involvement of the feet, a rising CRP level, positive RF and the presence of ACPA have all been shown to have predictive value in determining prognosis. There is also evidence that the presence of the shared epitope (especially homozygosity) predicts the development of more severe disease (see Chapter 3). Currently these are research findings and routine investigation does not include HLA typing in suspected RA.

INVESTIGATION

Although the diagnosis of RA can be made largely through appropriate history-taking and examination, investigations are frequently confirmatory and contribute to subsequent management decisions. Blood tests should include a full blood count, renal and hepatic biochemistry, inflammatory markers (ESR and CRP), RF, ACPA and, in some cases, anti-nuclear antibodies (ANA). A full blood count may show a normochromic normocytic anaemia and less frequently a raised platelet count, in keeping with a systemic inflammatory response. Patients may have low serum albumin and increased alkaline phosphatase levels (again usually due to the systemic inflammatory response). RF is not diagnostic of RA, being found in otherwise healthy individuals, and not infrequently being negative in RA (particularly in early disease). However, a positive RF result correlates with more severe disease and is seen much more frequently in patients with extra-articular manifestations. ACPA is more specific for RA in early disease. Inflammatory arthritis is a feature of SLE and, although the pattern of joint involvement is often different, ANA should be checked in cases where there is diagnostic uncertainty. If the ANA result is positive, there is some evidence that sulfasalazine is a less favourable choice of treatment.

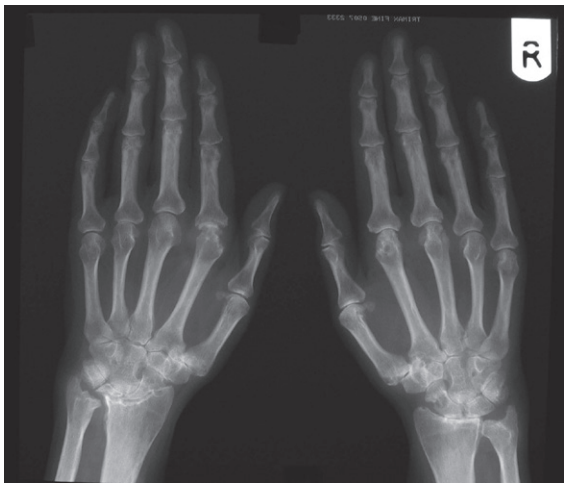


FIGURE 16.3 Radiographs of hands to show erosive arthritis affecting metacarpophalangeal joints and wrists

In early disease a viral arthritis screen should also be undertaken, looking particularly for evidence of recent exposure to parvovirus B19, which can cause a transient symmetrical polyarticular synovitis clinically indistinguishable from RA.

Imaging studies should include hand and foot radiographs (looking for peri-articular osteopenia or erosive changes; Fig. 16.3), a chest X-ray (paraneoplastic arthritis can be similar to RA, sarcoid can cause an inflammatory arthritis, particularly of the ankles, and latent tuberculosis and undiagnosed interstitial lung disease are relative contraindications to certain treatments). Other imaging modalities (ultrasonography and magnetic resonance imaging (MRI)) can also be helpful in supplementing clinical examination of the joints in early inflammatory arthritis. This can be particularly helpful where the findings are equivocal. Ultrasound imaging is increasingly used routinely by many rheumatologists in their clinical practice for this reason. MRI is more sensitive than ultrasonography for detecting both mild synovitis and early erosive changes, but is more costly and time-consuming. See Chapter 4 (Investigations) for further discussion of imaging modalities.

TREATMENT

Once a diagnosis has been confirmed, treatment should be initiated. The traditional approach to RA management was to treat symptomatically with NSAIDs, then, if required, to add weaker,

slow-acting DMARDs, gradually escalating the dose to try to achieve control before moving on to more potent therapies. The paradigm has been challenged by many high-quality studies that have shown benefit from early aggressive treatment of RA. It is clear that both erosive damage and functional impairment occur early and can be controlled more effectively early in the disease. This emphasizes the need for a fast-track referral system and accurate early diagnosis for patients with possible RA.

NSAID responsiveness is frequently seen in RA, but this is only symptomatic therapy. This can be helpful diagnostically. However, monotherapy with NSAIDs has no impact on the progression of rheumatoid damage. Therefore, even if symptoms are controllable with NSAIDs, additional therapy with DMARDs is still required. The mechanism of action of NSAIDs is discussed in Chapter 5 (Medical management of arthritis). There is no difference in efficacy between conventional and cyclo-oxygenase (COX)-2-specific NSAIDs, although the side-effect profile of COX-2-specific drugs is preferable, particularly with regard to the gastrointestinal tract (in younger patients with low risk of cardiovascular disease). Given the requirements in RA for long-term therapy at high doses, COX-2-selective treatments are frequently favoured in patients with gastrointestinal risk factors. All NSAIDs (with the possible exception of naproxen) are associated with an increased cardiovascular risk and should be used with caution in patients with other cardiovascular risk factors.

Corticosteroids can, like NSAIDs, significantly improve inflammatory symptoms. Intramuscular pulses of steroids can be helpful in controlling symptoms but have not been shown to modify disease progression. By contrast, and unlike NSAIDs, low-dose prednisolone (7.5 mg per day) has been shown to reduce both the rate of progression of erosive disease and the chances of developing erosive damage in the early years of RA. Prednisolone is therefore both symptom-relieving and disease-modifying. However, although in studies there were no significant adverse events on treatment, osteoporotic prophylaxis is required and some clinicians have understandable reservations about the risks of long-term steroid use. The situation is compounded because the duration of steroid treatment required, and whether the benefits are lost on discontinuation, remains unknown.

DMARD therapy should be initiated promptly. Conventional DMARDs are a diverse group of drugs, probably having an effect at a number of levels of the inflammatory cascade (for further details see Chapter 5, Medical management of arthritis). Weekly methotrexate (up to 25 mg/week) is a common first-line treatment, although daily sulfasalazine (up to 3 g/day) is another option. Both of these treatments are known to be efficacious, although the evidence for methotrexate is stronger and longitudinal studies show it is better tolerated. Folic acid (5 mg weekly or more frequently) has been shown to reduce the side-effects of methotrexate (mouth ulcers, gastrointestinal upset, and possibly hepatic and haematological disturbance). The authors' practice is to prescribe *M*ethotrexate on a *M*onday and *F*olic acid on a *F*riday to aid compliance.

Other DMARDs include leflunomide, hydroxychloroquine, intramuscular gold, ciclosporin and azathioprine. All DMARD treatments take between 6 and 12 weeks to take effect, and all patients need to be educated about the need to take the therapy regularly and the risk associated with the different treatments. With the exception of hydroxychloroquine, all of these treatments require regular blood test monitoring. There is also robust evidence that combination therapy with two or more DMARDs (including methotrexate as one of these) is more efficacious than monotherapy. The authors recommend combination treatment with methotrexate and hydroxychloroquine in the first instance, together with a short course of systemic steroids (typically monthly intramuscular injections of methylprednisolone on three occasions or low-dose oral prednisolone for the first few months) to patients with newly diagnosed RA.

Biological treatments specifically target points in the pathogenic process and are used in patients who fail to respond to the conventional DMARDs. TNF had been shown to be a critically important cytokine in RA disease pathogenesis, and was an attractive first target for anti-cytokine therapy. Five anti-TNF therapies are currently licensed – infliximab, adalimumab, golimumab, certolizumab (all are chimeric antibody-based treatments targeting TNF) and etanercept (recombinant soluble TNF receptor) – and all have shown efficacy in randomized controlled trials. They reduce signs and symptoms of disease, preserve function, reduce radiological progression and improve patients' quality of life. The major risk of anti-TNF treatment seems to be reactivation of latent infection (particularly tuberculosis), because TNF is an important cytokine in maintenance of the granulomata that

confine mycobacteria. Pre-treatment screening and vigilance during treatment is therefore critical. Not all patients respond to anti-TNF therapy, perhaps reflecting the heterogeneous nature of what is classified as RA. Studies suggest that approximately two-thirds of patients will derive some benefit from anti-TNF treatment. In patients who have failed to respond to anti-TNF therapy, other biological treatments such as rituximab (an anti-B-cell antibody), tocilizumab (an anti-IL-6 receptor antibody) and abatacept (cytotoxic T-lymphocyte antigen (CTLA)-4 immunoglobulin, which reduces co-stimulation of T cells and may affect antigen presenting cells) are used. Most biological treatments have greater efficacy when used in combination with conventional DMARDs (particularly methotrexate), but there is no evidence currently that combining biological treatments together provides any benefit. Biological treatments are not curative and they must be administered indefinitely. However, the possibility that their use early in disease might result in long periods of remission (particularly using anti-TNF treatment) is under investigation.

Conventional analgesic pain management is also important, particularly in patients with secondary damage from previously active inflammation, as an adjunct to the anti-inflammatory approaches discussed above. Further discussion on the medical management of RA can be found in Chapter 5.

NON-PHARMACOLOGICAL THERAPY

Treatment of RA is not solely pharmacological, and patient education, physiotherapy and occupational therapy are also core aspects of management. All patients should have access to education, physiotherapy and occupational therapy services at an early stage and throughout their disease; multidisciplinary management improves the chances of patients maintaining long-term function. Surgery may be required both to relieve pain and to improve function. Chapter 7 provides more detailed information on the non-pharmacological management of RA, and Chapter 8 on surgical management.

MONITORING RESPONSE TO TREATMENT

It is important to monitor the activity of RA to guide treatment decisions and assess whether the disease is controlled. The most commonly used tool for monitoring disease activity is the Disease Activity Score in 28 joints (the DAS28 score). The DAS28 score requires assessment of tenderness and swelling of the 28 joints highlighted in Figure 16.4. In addition to the tender joint count (TJC) and swollen joint count (SJC), the ESR (or CRP) and the patient's global assessment on a 0–100 visual analogue scale of their disease activity (0 = no activity, 100 = worst activity) are used:

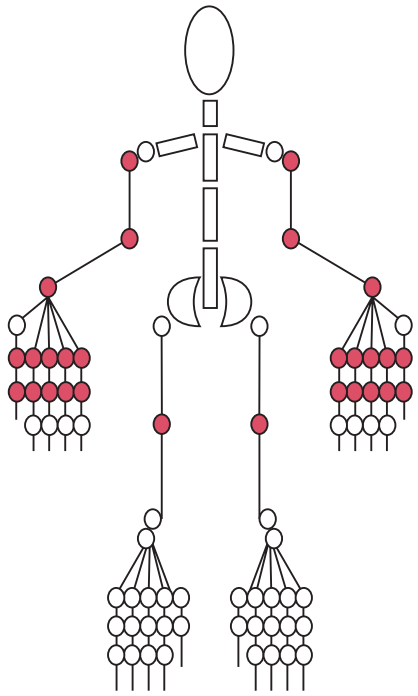


FIGURE 16.4 Joints assessed in the DAS28 score

$$\text{DAS28} = 0.56 \times \sqrt{\text{TJC}} + 0.28 \times \sqrt{\text{SJC}} + 0.7 \times \ln\text{ESR} + 0.014 \times \text{Global health score (VAS)}$$

This equation is clearly very complex and cannot easily be calculated in a busy clinic (or even a quiet clinic!). There are several calculators available online, and many rheumatology departments have their own versions, developed in-house on a computer or provided as a free service by drug companies who make biological agents. The DAS28 produces a score between approximately 1.5 and 9.5. The severity of disease activity can be stratified according to the score:

<2.6 disease remission/control
2.6–3.1 mildly active disease
3.2–5.1 moderately active disease
>5.1 severely active disease.

A response to treatment is defined by an improvement (reduction) in the DAS28 by at least 1.2 points.

RA can cause destructive/erosive joint damage (see Fig. 16.3), which itself is a significant cause of later disability. It is therefore helpful to monitor for radiographic changes on a regular basis (usually yearly at the start of the disease), irrespective of how well the DAS28 score is controlled. The impact of RA on a patient's day-to-day function and quality of life can also be monitored regularly using a variety of validated instruments (e.g. the Health Assessment Questionnaire and the SF36 health survey).

PROGNOSIS

Although current treatments have undoubtedly improved the control of RA symptoms and reduced the rate of progression of erosive damage to the joints, the disease is still associated with significant morbidity, with decreased quality-of-life scores, and a significant risk of unemployment and disability. Standardized employment ratios are reduced to about 0.8 (1.0 for the general population) for patients with RA, even with current treatments. Standardized mortality rates are increased to approximately 1.5. Part of this increased mortality is attributable to an increased risk of cardiovascular disease. The cardiovascular risk is independent of conventional risk factors such as smoking and cholesterol, suggesting that RA itself is a risk factor. The standardized mortality rates are greatest in patients with increased disease activity at baseline and in those with extra-articular disease (discussed further in Chapter 18). Further studies will address whether current treatment of RA modifies the mortality rates.

SPONDYLOARTHRITIS

The spondyloarthritides have a prevalence slightly lower than that of RA. Spondyloarthritis can be subdivided into five conditions (Box 16.3).

Box 16.3
Diseases classified as forms of spondyloarthritis

- Ankylosing spondylitis
- Psoriatic arthritis
- Reactive arthritis
- Arthritis associated with Crohn's disease or ulcerative colitis
- Undifferentiated spondyloarthritis: arthritis that fulfils criteria for spondyloarthritis, but does not fall into any of the other four categories

ANKYLOSING SPONDYLITIS

DEFINITION

Ankylosing spondylitis (AS), which has a prevalence of between 0.5% and 1%, is the principal inflammatory disease of the axial skeleton.

AETIOLOGY/PATHOGENESIS

The aetiology remains unknown; the association with HLA-B27 is striking because more than 90% of patients are positive. Although discovered more than 30 years ago, the explanation for the association remains elusive. The initial assumption was that B27 must act by performing its usual physiological role of presenting antigenic peptides to CD8+ T lymphocytes. However, arthritogenic peptides, from infectious agents or autoantigens, have not been defined. More recent theories have implicated unusual features of HLA-B27, such as expression of the B27 heavy chain on the cell surface without its usual partner, β_2-microglobulin, or as heavy-chain homodimers (which consist of two identical copies of the heavy chain). The homodimers can interact with receptors on lymphocytes and monocyte/macrophages to alter their behaviour. Within the cell, unusually inefficient folding of the B27 heavy chain in the endoplasmic reticulum elicits the 'unfolded protein response', which also alters cytokine production by cells.

In addition to HLA-B27, genome-wide association studies have implicated several other genes, notably *ERAP1*, which trims antigenic peptides to fit into class I MHC antigens such as HLA-B27, and *IL-23R*, which encodes the receptor for IL-23, a cytokine responsible for controlling IL-17 production.

CLINICAL FEATURES

HISTORY

The typical presentation is of insidious low back pain in a male in his twenties; a family history is often reported. There are associated inflammatory features, particularly early morning stiffness and stiffness after immobility. Symptoms improve during the day and with exercise, unlike mechanical back pain. Sacroiliac joint (SIJ) involvement

produces buttock pain, and alternating buttock pain with walking is well recognized. As the disease progresses, symptoms from involvement of cervical and thoracic spine may become more prominent. Peripheral joints, particularly the hips and shoulders, are frequently involved. Enthesitis (inflammation at points of insertion of ligaments and tendons) is characteristic of spondyloarthritis and produces heel, plantar and chest pain.

Extra-articular features may give rise to symptoms. Uveitis is common (25–40%) and may predate spinal symptoms, and patients with acute anterior uveitis have an increased incidence of HLA-B27 in the absence of joint or spine symptoms. The eye is red and painful. The patient has photophobia and requires prompt examination by an ophthalmologist. Local steroid drops are usually adequate to treat the condition, but inflammation of the iris can result in its adhesion to the cornea or lens ('synechiae'), leading later to glaucoma and cataract. Less common extra-articular features include aortic incompetence and cardiac conduction abnormalities, apical lung fibrosis and cauda equina syndrome.

EXAMINATION

The range of movement in the lumbar spine is measured, looking for restriction in all planes. Schober's test (see Chapter 1) is a useful and reproducible measure of lumbar flexion, and can aid assessment of disease progression as well as diagnosis. Cervical spine movement should also be assessed, as well as the distance between the occiput or tragus and a wall (with the patient standing as close as possible to a wall). Normally the occiput will readily touch the wall, whereas the tragus–wall distance varies from individual to individual. This measurement is useful for assessing an increasing kyphosis. Chest expansion is measured to assess involvement of the thoracic spine and costo-vertebral joints (<2.5 cm is abnormal). SIJ tenderness is assessed by stressing the joint, e.g. by compression of the pelvis or forcibly flexing the hip towards the contralateral iliac crest. These tests have relatively low sensitivity and specificity for sacro-iliitis. Extra-articular features should be sought during systematic examination.

TESTS

Diagnosis is too often delayed by 8–10 years, mainly because of the high prevalence of back pain in the community, and may be missed in women who often have milder disease. The delay is potentially serious, because patients may have an irreversible loss of spinal mobility by the time the diagnosis is made.

Few tests are helpful; ESR and CRP levels are not always raised, and radiographs will be normal in early disease. HLA-B27 status is not helpful diagnostically: it is present in 8% of the population, many of whom will have back pain and, therefore, the B27 status is potentially misleading. However, if the patient is B27-*negative* the risk of AS is considerably less, and this may be helpful. MRI (Fig. 16.5) with gadolinium enhancement is the most sensitive technique to detect SIJ and lumbar spine inflammation, and is the initial imaging of choice. Computed tomography of the SIJ shows erosive changes better than plain films. Finally, isotope scintigraphy may show increased uptake in the SIJ before changes become apparent on X-ray.

TREATMENT

Regular exercises are important for maintaining range of movement and all patients require instruction by physiotherapists. Patients should have

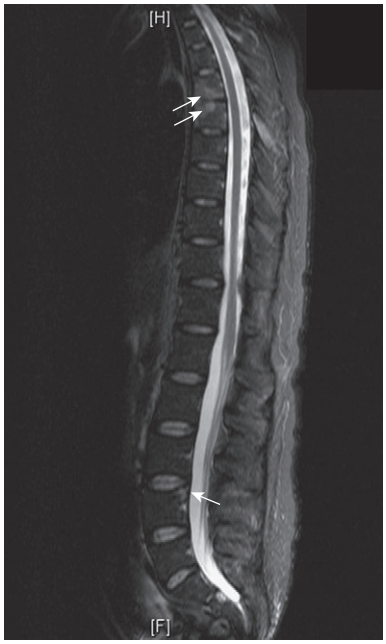


FIGURE 16.5 MRI appearances of spine in ankylosing spondylitis to show Romanus lesions – these 'shiny corners' indicate localized bone oedema at the site of the entheses

regular follow-up to document any loss of movement and to provide incentives to continue daily exercise, which improves long-term outcome. Most patients require high doses of the more powerful NSAIDs; some patients respond only to phenylbutazone, a NSAID not otherwise used owing to its unacceptable toxicity in some patients. Etoricoxib seems to be the most effective of the COX-2-selective NSAIDs; the increased cardiovascular risks associated with etoricoxib compared with naproxen are greatly outweighed in the relatively young AS population (with low cardiovascular risk) by the much greater chance of gastrointestinal bleeding associated with naproxen. Sulfasalazine is useful for the peripheral arthritis associated with AS, but has no effect on spinal disease. Anti-TNFα therapies have proven remarkably effective in controlling fatigue and malaise along with spine symptoms, and have transformed many patients' lives. Whether treatment with anti-TNFα can be continued for many decades must remain questionable. Bisphosphonates have been reported to give benefit to some patients, but did not produce significant effects in a recent controlled trial.

PROGNOSIS

The course and prognosis of AS is variable; the disease often appears to be most active for the first decade of the disease followed by decades of lower-grade activity. The chronic changes of patients with AS involve reduced standardized employment rates (0.9) and reduced quality-of-life scores compared with the general population. Poor prognostic factors for AS include early hip involvement, persistently increased ESR, hypergammaglobulinaemia and early limitation of spinal movements. Like those with RA and psoriatic arthritis, patients with AS have an increased cardiovascular mortality and morbidity, and an increased standardized mortality rate of approximately 1.5. This is not entirely attributable to orthodox cardiovascular risk factors.

PSORIATIC ARTHRITIS

DEFINITION

Psoriasis is a common condition affecting 1–3% of the population, so that many people with psoriasis also suffer various rheumatic disorders. However, the incidence of inflammatory arthritis is significantly higher in patients with psoriasis than in non-psoriatic control populations. Consistent differences in synovial histology between psoriatic arthritis (PsA) and RA have been reported, with more prominent angiogenesis, a less expanded lining area, and increased neutrophil infiltration in PsA. Likewise, even in patients with symmetrical polyarthropathy, RF is not present at high titres and ACPA is generally absent in PsA.

AETIOLOGY/PATHOGENESIS

The pathogenesis of PsA is unknown. One hypothesis is that it represents an intra-articular 'Koebner' phenomenon, i.e. the equivalent of the lesions that develop in skin at sites of trauma. Joints commonly undergo trauma and could be susceptible. Psoriasis also affects the normal relationship with skin bacteria, and abnormal responses to bacterial antigens may play a role in PsA, as in other forms of spondyloarthritis. Genes in the HLA region (alleles of HLA-C and MICA) have been associated with disease. Some genes associated with AS are also associated with PsA, notably *ERAP1* in those carrying the PsA-associated HLA-C allele.

CLINICAL FEATURES

Several features are particularly characteristic of PsA (Box 16.4). Dactylitis represents a combination of tendonitis and synovitis; enthesitis (inflammation of tendon and ligament insertions) is common. Classifications of different forms of PsA have been attempted, but patients commonly have different combinations of features, e.g. distal interphalangeal involvement (Fig. 16.6), sacro-iliitis and oligoarthritis, and these may evolve, for example from oligoarthritis to polyarthritis. Some patients have arthritis that is clinically indistinguishable from RA, but it is usually RF-seronegative and in most cases should be considered a separate disorder.

Box 16.4
Clinical features of psoriatic arthritis

- Dactylitis and enthesitis
- Oligoarthritis, particularly in weight-bearing joints
- Distal interphalangeal joint involvement, usually in association with psoriatic nail disease
- Sacro-iliitis
- Osteolysis, leading to 'telescoping' of digits following loss of bone from phalanges

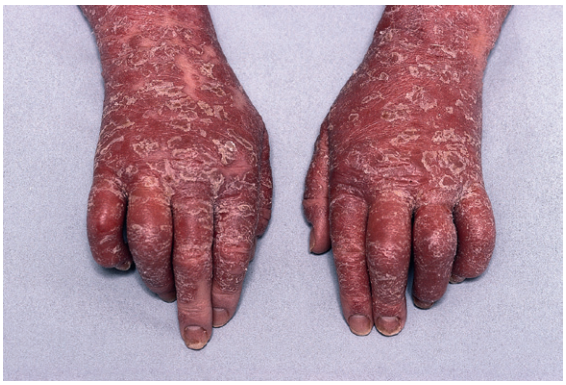


FIGURE 16.6 Distal and proximal interphalangeal joint inflammation in a patient with psoriatic arthritis

Spinal involvement may be clinically indistinguishable from AS. Enthesitis, e.g. plantar fasciitis, is common.

The skin lesions of psoriasis are often obvious, but may be mild and very limited, and possibly not known to the patient – check scalp, umbilicus and natal cleft. Nail changes are common, including dystrophy, pitting, ridging and onycholysis; nail changes may be the only evidence of psoriasis. In some patients, arthritis precedes the development of skin disease ('psoriatic arthritis sine psoriasis'), but the diagnosis is then based on features that are typical of spondyloarthritis (e.g. dactylitis and enthesopathy) and/or a strong family history of psoriasis. In children, joint disease often precedes skin disease, and a family history of psoriasis is included as a minor criterion for diagnosis.

TESTS

Apart from an acute-phase response and the absence of RF or other autoantibodies, there is little help from the laboratory. HLA-B27 is present in 50% of those with spinal involvement. In later stages, radiographs may show the characteristic osteolysis involving the digits, leading to a characteristic 'pencil-in-cup' appearance. Signs of enthesopathy, such as plantar spurs, may be present, together with sacro-iliitis, which may be asymmetrical. Early sacro-iliitis and spinal involvement is best detected by MRI, whereas ultrasound imaging can show enthesitis.

TREATMENT

The treatment follows the same guidelines as for RA, or for AS if spondylitis is the dominant feature. Leflunomide is often the DMARD of choice, but methotrexate will also help the skin disease; conversely, hydroxychloroquine is generally avoided because of exacerbations in skin disease. The evidence base for DMARDs in PsA is much less extensive than in RA; a recent trial suggested that methotrexate is not effective, but this has not generally been accepted. Anti-TNFα therapies have been impressive in improving both skin and joint disease.

PROGNOSIS

Like patients with RA, those with PsA show reduced quality-of-life scores and reduced standardized employment rates (0.9 for PsA compared with 0.8 for RA). Although not studied as extensively as in RA, the limited available data suggest a similar increase in the standardized mortality rate for patients with PsA, at 1.6. As in patients with RA, the main contributor to mortality is cardiovascular disease and, again, severe disease at presentation is a major risk factor along with the presence of erosive disease.

REACTIVE ARTHRITIS

DEFINITION

Reactive arthritis is a form of spondyloarthritis that is usually triggered by specific infections of the gastrointestinal or genitourinary tract. The incidence is approximately 40–50 per million for reactive arthritis triggered by either enteric infection or *Chlamydia trachomatis*. Although it is a form of post-infectious arthritis, it is useful to distinguish reactive arthritis from other post-infectious conditions such as post-viral arthritis and post-streptococcal arthritis (see below), because they have different clinical features and are not part of the spondyloarthritis group.

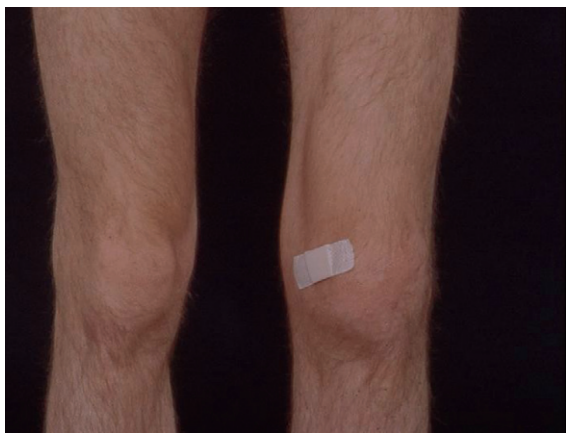
AETIOLOGY AND PATHOGENESIS

The disease is caused by specific bacteria in a susceptible host. The principal organisms involved are *Salmonella* spp., *Campylobacter jejuni* and *C. coli*, *Yersinia enterocolitica* and *Y. pseudotuberculosis*, *Shigella* spp. and *C. trachomatis*. Other organisms, such as *Clostridium difficile* and *Chlamydia pneumoniae*, are sometimes implicated. Only a small proportion of those infected develop arthritis, and the percentage varies. It is higher in HLA-B27-positive subjects, but B27 also predisposes to more severe and long-lasting arthritis.

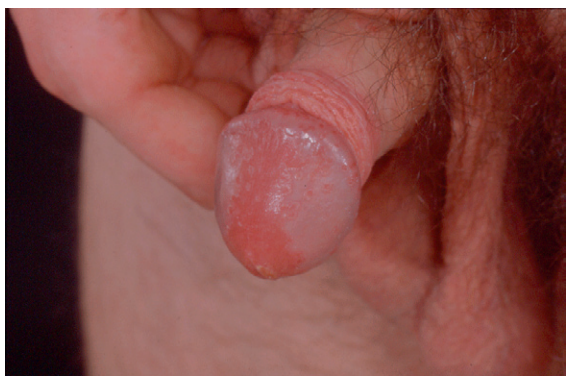
The aetiology is not fully understood; organisms cannot be cultured from affected joints, but antigenic material and, particularly in the case of *C. trachomatis,* the organism itself reaches the synovium, but in a non-dividing state. Vigorous immune responses to the infection are detectable in the joint. It has been suggested that autoimmune responses develop in chronic disease ('molecular mimicry' – an immune response to the bacterium cross-reacting with something in the joint), but this is unproven.

CLINICAL FEATURES

The arthritis is acute and is usually oligoarticular, with a predilection for weight-bearing joints. Inflammatory backache and/or sacro-iliac joint tenderness are seen. Fever and malaise are common. Joints are usually obviously swollen (Fig. 16.7A) and hot so that septic arthritis and crystal arthritis become the principal differential diagnoses. Diagnosis relies heavily on a history of previous infection. Note that symptoms from reactive arthritis-inducing enteric infection can be surprisingly mild, particularly in *Yersinia* infection. Likewise, *Chlamydia* infection is commonly asymptomatic, so that a history of a new sexual partner should be sought. In addition, extra-articular features may be very helpful in reaching a diagnosis (Table 16.1 & Fig. 16.7B).



A



B

FIGURE 16.7 (A) Oligoarthritis – a knee effusion in the patient shown in (B). (B) Urethritis and circinate balanitis – an extra-articular manifestation of reactive arthritis

TESTS

ESR and CRP levels are raised, often grossly, and there may be neutrophilia. Autoantibodies are not present. Synovial fluid contains numerous white cells, but is sterile. Other tests can identify the preceding infection responsible for triggering reactive arthritis: stool and urethral culture and polymerase chain reaction (PCR)/locus control region (LCR) tests for *Chlamydia* in urine are required. *Shigella* should be sought, particularly in those who acquired enteritis abroad. IgM antibodies or rising titres of IgG and IgA antibodies for enteric pathogens such as *Yersinia* and *Campylobacter* are useful. Radiographs are not helpful in acute diagnosis. Typing for HLA-B27 may be useful in estimating prognosis.

TREATMENT

Full-dose NSAIDs and additional analgesics are required acutely. Affected joints should be aspirated to exclude other diagnoses; when infection is excluded, intra-articular steroids should be given and repeated as needed. Disease-modifying drugs

Table 16.1 Extra-articular features of reactive arthritis

Site	Manifestation
Skin	Keratoderma blennorrhagica (a psoriatic rash) on the soles or hands Circinate balanitis on the prepuce
Mucous membranes	Painless palatal ulcers
Eyes	Conjunctivitis, often transitory, or rarely uveitis
Entheses	Tenderness of the plantar fascia and/or Achilles tendon insertions to the calcaneum

are not usually required, but when disease persists sulfasalazine or methotrexate are reasonable choices, although there are no controlled trial data. Long-term antibiotics have been used assuming that the arthritis is maintained by persistent infection, but controlled trials have not supported their use. The exception is a recent trial that reported efficacy using a combination of rifampicin with doxycycline or azithromycin in chronic *Chlamydia*-induced disease. Although this report on long-term antibiotics requires confirmation, all patients with *Chlamydia* infection require conventional short-term antibiotic treatment.

The prognosis is generally favourable; many patients have mild arthritis, inflammatory back pain or enthesopathy, which does not come to medical attention. Those seen in hospital have an 80% chance of being symptom-free with no residual joint damage at 1 year, and a further 10% resolve in the next year. However, 10% – mainly those who are HLA-B27-positive – have persistent oligoarthritis or evolve into AS or undifferentiated spondyloarthritis.

ARTHRITIS ASSOCIATED WITH INFLAMMATORY BOWEL DISEASE

DEFINITION

Many patients with inflammatory bowel disease (IBD) also have an inflammatory arthritis, usually with features that are associated with other forms of spondyloarthritis. Approximately 10% have peripheral arthritis, and a further 5% have AS-like disease.

AETIOLOGY/PATHOGENESIS

This is unknown, but may be similar to that of reactive arthritis with gut flora playing the role attributed to the specific pathogens in reactive arthritis. Spondylitis and IBD seem to be closely linked: a proportion of patients with AS have asymptomatic IBD, whereas some B27-transgenic rats (which develop AS-like disease) display Crohn's-like bowel disease.

CLINICAL FEATURES

Peripheral arthritis has been subdivided into types I and II. Type I is oligoarticular, asymmetrical, and associated with active bowel disease. This is conceptually similar to reactive arthritis triggered by enteric infection. Type II arthritis is symmetrical and polyarticular (more than five joints), and is not related to the activity of the bowel disease. There are distinct differences in the frequencies of HLA antigens in these two forms, supporting the clinical distinction. Enthesopathy is common in both subtypes. Extra-articular features include uveitis and skin lesions, such as erythema nodosum and pyoderma gangrenosum.

TESTS

The presence of IBD in a patient with spondyloarthritis is confirmed by radiological and endoscopic examination; technetium scans and indium-labelled leucocyte scans are also sometimes useful to demonstrate occult IBD. Mucosal biopsies normally distinguish between ulcerative colitis and Crohn's disease.

TREATMENT

Treatment is broadly similar to that for other forms of spondyloarthritis, except that sulfasalazine is the DMARD of choice because of its additional effect on IBD. Note that drugs that do not have a sulphonamide component are effective against IBD, but not against arthritis, so patients receiving these agents for IBD may need to switch to sulfasalazine. NSAIDs can exacerbate IBD, so the treatment requirements of the arthritis and IBD may conflict. Methotrexate can exacerbate IBD, although in many patients it is an effective treatment for both conditions. Lastly, anti-TNFα drugs are useful for the arthritis and for Crohn's disease, but ineffective in ulcerative colitis. Patients with ulcerative colitis who require total colectomy will have improvement in type I peripheral arthritis, but this may flare if they develop 'pouchitis' – inflammation in the ileal reservoir that is usually fashioned after colectomy.

POST-INFECTIOUS ARTHRITIS

DEFINITION

The principal post-infectious arthritides (distinct from reactive arthritis) are associated with viral or bacterial infections. These arthritides are not associated with the other features common to spondyloarthritis (enthesitis, sacro-iliitis, etc.), or with HLA-B27.

VIRAL INFECTIONS

Arthritis commonly follows parvovirus or rubella infection in adults, but can occur after many viral

infections including human immunodeficiency virus (HIV), Epstein–Barr virus (EBV) and cytomegalovirus (CMV). Infection with parvovirus can mimic early RA but is RF-negative. Some countries have endemic arthritis-inducing α-viruses, e.g. Ross River virus in Australia, O'nyong-nyong in East Africa, and Chikungunya virus in East Africa and, more recently, the Far East.

BACTERIAL INFECTIONS

Diseases in which the organism can be detected in the joint include Lyme disease and Whipple's disease, but, as in reactive arthritis, the joints do not appear conventionally septic. This is either because the number of organisms present is very small, as in Lyme disease, or the bacterium cannot be cultured, e.g. *Tropheryma whippelii*, which causes Whipple's disease.

Infections with *Streptococcus* and *Neisseria* (gonococcus and meningococcus) are triggers of inflammatory arthritis, but the features of spondyloarthritis including its extra-articular manifestations are absent. Both organisms can also cause septic arthritis as well as post-infectious arthritis. In Western countries rheumatic fever is very rare, but should still be considered in patients with arthritis and a streptococcal infection. Cardiac involvement or erythema marginatum should be looked for, but a 'pure' post-streptococcal arthritis is a much commoner sequel to infection, especially in adults.

CLINICAL FEATURES

HISTORY

It is useful to enquire about: recent throat infections; new sexual partners; fever; lymphadenopathy or weight loss; tick bites or travel to areas where Lyme disease or viral arthritides are endemic; and contact with small children – and, if so, whether there has been a recent outbreak of 'slapped cheek' disease in the local school, indicating a parvovirus epidemic.

EXAMINATION

In addition to the arthritis, there may be features associated with the primary infection. Rashes may be evident, particularly in gonococcal disease where small pustules on peripheries are characteristic but easily missed. The rash of Lyme disease, erythema chronicum migrans, is not usually present by the time arthritis begins.

TESTS

Streptococcus and *Neisseria* can be cultured from appropriate sites, and IgM antibodies for viral infections should be sought. Note that the majority of adults will have IgG antibodies to parvovirus, rubella, EBV and CMV, so only IgM antibodies are helpful. The anti-streptococcal antibodies (anti-streptolysin O and anti-DNase), which may persist for long periods, should be measured, as well as antibodies to *Borrelia burgdorferi,* which causes Lyme disease. Currently, Whipple's disease is best diagnosed by using PCR for the uncultivable *T. whippelii* on intestinal biopsies or synovial fluid or tissue.

TREATMENT

Treatment is directed at the underlying infection; in most cases the arthritis requires only symptomatic measures, as it will be self-limiting once the infection has been treated. An exception is post-streptococcal arthritis, which may pursue a chronic course, and a proportion of patients with Lyme disease also have arthritis that is resistant to antibiotics.

PREGNANCY AND THE RHEUMATIC DISEASES

Approximately 50% of all pregnant women experience back pain during pregnancy. Significant back pain occurs in about 25%, and severe disability in about 8% of patients. After pregnancy, problems are serious in about 7%. Autoimmune rheumatic diseases frequently affect women during childbearing years. Fertility may be reduced in some cases, but for the majority of patients monitoring and treatment in pregnancy is complicated and best managed by close collaboration between gynaecologists, rheumatologists and paediatricians.

INFLUENCE OF PREGNANCY ON AUTOIMMUNE DISEASES

In many patients with inflammatory arthritis pregnancy exerts an immunosuppressive effect and patients may go into remission. Typically, this is short-lived, and flares occur in the post-partum period. SLE and anti-phospholipid antibody syndrome may develop during pregnancy and should be considered in the differential diagnosis for any pregnant woman with a new onset of arthritis. In established SLE maternal flares may occur in

one-third of patients, especially in the second trimester and post-partum. The risk is highest for women with active lupus at the time of conception and those who have anti-phospholipid antibody and hypertension. By contrast, if SLE is in remission at conception, the risk of flare is about 15%.

Fetal cells persist in the circulation of women who have been pregnant (micro-chimerism); there have been suggestions that this could be a possible cause of auto-immune disorders in women.

EFFECTS ON THE FETUS

Fetal loss is a recognized risk in SLE and anti-phospholipid antibody syndrome. Untreated primiparous women who have SLE or SLE-like disease and anti-phospholipid antibody have an approximately 30% probability of losing a pregnancy, often in the second trimester. Mothers who have circulating anti-Ro and anti-La antibodies may be completely asymptomatic, but there is a 1% risk of fetal heart block, as these antibodies are able to cross the placenta and bind to fetal heart tissue. Anti-phospholipid antibody syndrome is a major cause of fetal loss, pre-eclampsia and premature birth.

DRUGS IN PREGNANCY

NSAIDs are not teratogenic, but if given in late pregnancy can induce renal and cardiac side-effects in the fetus. NSAIDs should, therefore, be stopped by gestational week 32. Corticosteroids are frequently necessary to control rheumatic disease flares and for prevention of serious organ manifestations. However, due to an increased risk of cleft palate, high doses (1–2 mg/kg) should be avoided in the first trimester. Among disease-modifying drugs, sulfasalazine, azathioprine and antimalarials have the safest record – although sulfasalazine impairs male fertility. Ciclosporin can be given throughout pregnancy if necessary. Insufficient data exist for treatment of pregnant patients with TNF inhibitors, but no increase in adverse outcomes has been observed thus far. The severity of the disease under treatment determines whether continuation of one of these drugs is justified. Prophylactic withdrawal of drugs before pregnancy is mandatory for leflunomide, methotrexate and cyclophosphamide. It is essential to ensure effective contraception during treatment and to discontinue drugs before conception is planned. There may be fertility problems for patients who have received significant accumulated doses of cyclophosphamide. Most drugs are secreted into breast milk and, therefore, any treatment offered to a mother post-partum can carry risks to the child and may influence the decision regarding breast- or bottle-feeding. Ideally, mothers should be encouraged to breast-feed, but if they are suffering a flare of disease it would be better to stop breast-feeding so that they can receive appropriate therapy without potential harm to the baby.

FURTHER READING

Arthritis Research UK. Rheumatoid arthritis. Online. Available: http://www.arthritisresearchuk.org/arthritis-information/conditions/rheumatoid-arthritis.aspx [accessed 21 May 2012].

Gaston JSH. Mechanisms of disease: the immunopathogenesis of spondyloarthropathies. Nat Clin Pract Rheumatol 2006; 2:383–392.

Sieper J, Rudwaleit M, Baraliakos X et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis 2009; 68(Suppl 2):ii1–ii44.

Smolen JS, Landewé R, Breedveld FC et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010; 69(6):964–975.

The Australo-Anglo-American Spondyloarthritis Consortium (TASC); Reveille JD, Sims AM, Danoy P et al. Genome-wide association study of ankylosing spondylitis identifies non-MHC susceptibility loci. Nat Genet 2010; 42:123–127.

17

SYSTEMIC DISEASES

Ian N. Bruce, Nick Wilkinson, Julia L. Newton and Raashid Luqmani

Cases relevant to this chapter

72, 84–85, 87–90, 93–94, 96, 99

Essential facts

1. The symptoms and signs of systemic lupus erythematosus (SLE) are diverse; non-specific constitutional upset characterized by malaise, low-grade fever, fatigue and unexplained weight loss is common.
2. The antiphospholipid syndrome is characterized by recurrent thrombosis (arterial or venous) and/or pregnancy morbidity, and persistently raised levels of antibodies to phospholipid-related proteins.
3. There is a risk of malignancy in patients with dermatomyositis, particularly in the 2–3 years before and after the diagnosis of myositis is made.
4. Pulmonary hypertension is a complication of limited cutaneous scleroderma affecting 5–35% of patients.
5. Interstitial lung disease occurs in most patients with scleroderma, but progression to severe disease occurs in less than 20%.
6. Untreated multi-system vasculitis is fatal without potent cytotoxic or other immunosuppressive drugs and delay in diagnosis significantly affects morbidity and mortality.
7. Anti-neutrophil cytoplasm antibody testing is helpful in supporting a diagnosis in patients who have suggestive clinical and/or pathological features of vasculitis.

SYSTEMIC LUPUS ERYTHEMATOSUS

The autoimmune rheumatic diseases (formerly known as connective tissue diseases) represent a group of conditions that can be defined broadly as: multi-system inflammatory diseases of autoimmune origin associated with the anti-nuclear antibody (ANA) family of autoantibodies. A number of conditions fall within this family and autoimmune rheumatic diseases often show elements of overlap and similarity. These conditions have certain underlying pathological features that they share, but that occur relatively more frequently in some of the subgroups compared with others (Table 17.1). The four key pathological processes that underlie the autoimmune rheumatic diseases are inflammation, fibrosis or scarring, vasospasm and vascular thrombosis. The primary clinical features and many of the complications associated with these conditions can be deduced from these underlying pathological processes. Certain clinical/pathological features of these diseases are also more frequent with particular autoantibody subtypes. The presence of particular autoantibody subtypes may alert the clinician to investigate a particular organ or system for clinical features of relevance (Fig. 17.1).

Systemic lupus erythematosus (SLE) is the 'model' autoimmune rheumatic disorder. It presents

Table 17.1 Relative occurrence of specific pathological features that underlie the autoimmune rheumatic diseases

Pathology	SLE	DM/PM	Sjögren's Syndrome	Scleroderma	APS
Inflammation	+++	+++	++	+/–	–
Fibrosis	+	++	++	+++	–
Vasospasm	++	+	+	+++	–
Thrombosis	++	+/–	+/–	+	+++

These pathological features explain many of the clinical features of these conditions.
APS, antiphospholipid syndrome; DM/PM, dermatomyositis/polymyositis; SLE, systemic lupus erythematosus.

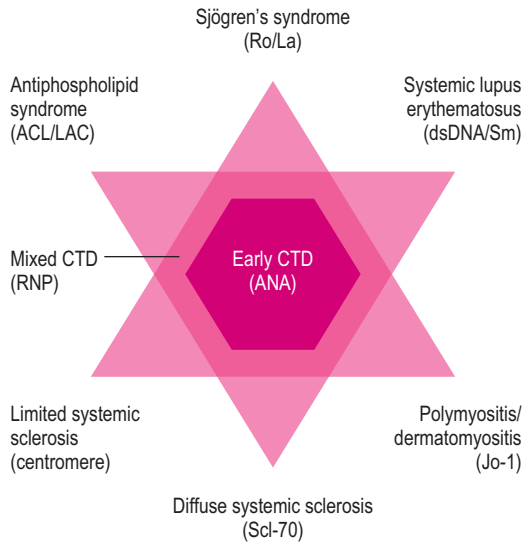


FIGURE 17.1 The spectrum of anti-nuclear antibody (ANA)-associated autoimmune rheumatic disease (ARD) showing the association of disease classification and autoantibody subtypes. The overlapping spectrum of autoimmune rheumatic disease and associated antibodies in serum are shown in parentheses. ACL, anti-cardiolipin antibody; LAC, lupus anticoagulant; RNP, anti-ribonucleoprotein antibody; dsDNA, double-stranded DNA antibody; Ro/La, anti-Ro/La antibodies; Scl-70, anti-Scl-70 antibody; Jo-1, anti-Jo-1 antibody; Sm, anti-Sm antibody. Remember that ANA can also be present in healthy individuals, especially the elderly, and has no clinical significance. (Adapted from Ahmad Y, Bruce IN 2000 Connective tissue disease and the role of the general practitioner. In Practice Series, Arc Publications.)

as a multi-system inflammatory disease with a wide range of clinical manifestations. Most of these manifestations can be explained on the basis of excess production of pathogenic autoantibodies. These autoantibodies, such as double-stranded DNA antibodies, either cause tissue injury directly or mediate the production of immune complexes that deposit in target organs to provoke tissue inflammation. However, SLE is associated with the production of a range of other autoantibodies whose significance is unclear.

EPIDEMIOLOGY

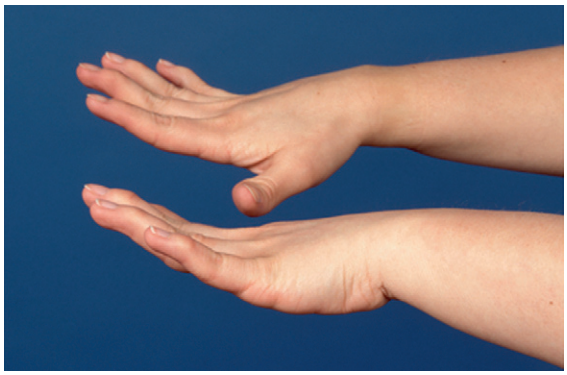
SLE, although uncommon, is not a rare condition. In UK studies the prevalence is approximately 1 in 4000 individuals, but there is a marked female preponderance with a female : male ratio of 9–13 : 1, meaning that SLE affects approximately 1 in 2000 females in the UK. There are also differences in prevalence according to ethnic background. Compared with white Caucasians, the prevalence is approximately 2–3 times higher in Asians from the Indian subcontinent and 5–10 times higher in Africans and African Caribbeans. SLE can present at any age from childhood through to older adulthood. The peak age at onset is in the late third – early fourth decade of life, with a second peak in the sixth decade.

AETIOLOGY

The cause of lupus remains unclear, but there is a strong genetic predisposition with first-degree family members being 50 times more likely to develop the disease than the background population. Additional factors known to cause or influence the development of lupus include ultraviolet (UV) light exposure, female sex hormones and certain drugs, e.g. chlorpromazine, hydralazine and isoniazid. It is known that anti-double-stranded DNA antibodies are directly toxic to the kidney, but it is not certain what role, if any, is played by the numerous other autoantibodies produced in SLE.

CLINICAL FEATURES

The symptoms and signs of SLE are diverse, but, as indicated in Table 17.1, inflammation is the predominant pathology associated with many of the key clinical features. Non-specific constitutional upset characterized by malaise, low-grade fever, fatigue and unexplained weight loss are common



A

B

FIGURE 17.2 Jaccoud's arthropathy in a patient with systemic lupus erythematosus. There are swan neck deformities on several digits (A). These are, however, fully reducible and the patient is still able to make a complete fist (B). This deformity is a result of ligamentous laxity rather that joint subluxation

in SLE. More specific inflammatory features include a malar or 'butterfly' rash, which is often light sensitive, and other cutaneous lesions including alopecia, mucosal ulceration and digital vascular changes such as nail-edge infarcts and splinter haemorrhages. Arthritis (small joint symmetrical polyarthritis) is also a common presenting feature. The arthritis is non-erosive, but in some cases ligamentous laxity can result in deformities similar to those seen in rheumatoid arthritis (RA) (Jaccoud's arthropathy; Fig. 17.2). In contrast to RA, however, these deformities are reducible. Importantly, SLE is also associated with inflammation in other organ systems, including serositis, nephritis and involvement of the central nervous system. Renal disease is often asymptomatic and can affect up to 25% of patients, although a higher occurrence is noted in African Caribbean, Chinese and Indo-Asian patients. Careful clinical assessment and regular urine examination is, therefore, necessary. A wide range of neuropsychiatric presentations have been described. Currently, the classification of SLE is based on a combination of clinical and laboratory investigations, and patients should have 4 of 11 criteria to confirm the classification of SLE (Box 17.1). However, it is important to remember that these criteria cannot be used as diagnostic criteria: they may assist in defining the spectrum of possible features but must be interpreted with common sense and clinical judgement and expertise.

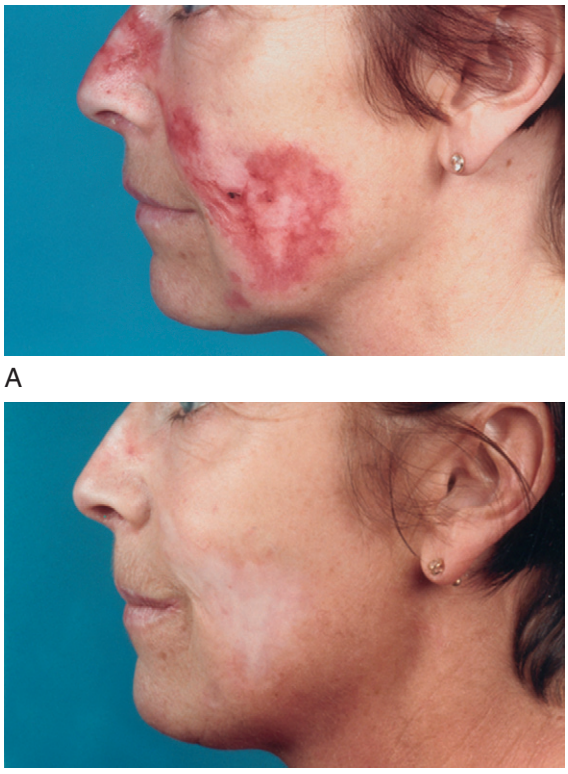
Box 17.1
American College of Rheumatology criteria for the classification of systemic lupus erythematosus (revised in 1997)

- Malar rash
- Oral ulceration
- Discoid rash
- Photosensitivity
- Arthritis
- Serositis
  - Pleurisy or pericarditis
- Neurological disorder
  - Seizures
  - Psychosis
- Renal disorder
  - Proteinuria (>0.5 g/day)
  - Cellular casts in urine
- Haematological disorder
  - Leucopenia (<4000/ml)
  - Lymphopenia (<15 000/ml)
  - Haemolytic anaemia
  - Thrombocytopenia (<100 000/ml)
- Immunological disorder
  - Positive antibodies to double-stranded DNA
  - Anti-Sm antibodies
  - Positive antiphospholipid antibodies: either IgG or IgM anticardiolipin OR a positive lupus anticoagulant OR a biological false-positive test for syphilis
- Anti-nuclear antibody positive

A person can be classified as having SLE if at least four criteria are present either serially or simultaneously. Note that having more than one of a particular subgroup counts as a single criterion, e.g. leucopenia and thrombocytopenia.

Thrombosis represents an important cause of clinical manifestations in lupus. The propensity to thrombosis is related to the presence of antiphospholipid antibodies, which reflect a pro-coagulant state. In addition, blood vessel inflammation can impair the normal anticoagulant properties of the endothelium. As a result, patients with SLE are at increased risk of venous thrombo-embolism, arterial thrombosis and adverse pregnancy outcomes (see antiphospholipid syndrome).

Up to 50% of patients with SLE also describe Raynaud's phenomenon, although this is usually less severe and less likely to cause digital ulceration compared with that in patients with scleroderma. Typical skin changes include scarring or fibrosis, and a subgroup of patients with SLE present with discoid lupus lesions (Fig. 17.3), which are often discrete areas, associated with scaling, hypo- or hyper-pigmentation and loss of associated skin appendages. If discoid lesions occur on the scalp, this results in scarring alopecia.



A

B

FIGURE 17.3 (A) Actively inflamed discoid lupus eruption on the light-exposed skin of the cheek and bridge of nose. (B) Even after successful treatment there is still residual atrophy and depigmentation of the affected area

OTHER COMPLICATIONS

Infection is a common complication in patients with SLE. Active disease is associated with complement consumption, relative hyposplenism, neutropenia and lymphopenia. In addition to low absolute counts, leucocyte function is also impaired. In addition, drugs such as corticosteroids and immunosuppressive agents increase the propensity to infection. It is also not unusual for infection to coexist with a flare-up of the underlying inflammatory disease and, therefore, sepsis needs to be considered carefully in most clinical settings. SLE is associated with an accelerated onset of atherosclerosis. The early development of atherosclerosis coupled with the increased thrombotic risk seen in SLE means that atherosclerosis should be considered in the differential diagnosis of relevant presentations, e.g. acute chest pain, acute focal neurological event.

LABORATORY ABNORMALITIES

Simple investigations can be extremely informative in patients with SLE. Anaemia may be present due to chronic disease, but haemolytic anaemia (positive Coombs' test) may also occur. Leucopenia, in particular lymphopenia, is characteristic and thrombocytopenia can occur either as a chronic, stable, low platelet count or as an acute profound thrombocytopenia, which is associated with bruising and bleeding complications. Urine abnormalities may be detected on dipstick (haematuria, pyuria and proteinuria). Any such abnormality requires further investigation to exclude infection or significant renal involvement. Patients can have significant glomerulonephritis requiring immunosuppressive therapy even when the serum creatinine level is within normal limits and, therefore, persistent microscopic haematuria/proteinuria usually requires a renal biopsy to determine further management. Serologically, patients with active lupus often have reduced C3 or C4 complement concentrations due to immune complex-driven consumption. Hypocomplementaemia may also be due to an underlying hereditary complement deficiency, which itself is a risk factor for developing SLE. ANA testing is positive in more than 90% of patients with SLE; however, the titre does not reflect underlying disease activity. In contrast,

antibodies to double-stranded DNA (dsDNA) are highly specific for SLE, although they may be positive in only 60% of all cases. In some patients, the titres of dsDNA antibodies do reflect underlying disease activity and in such cases rising titre may portend a future flare of clinical disease.

CLINICAL COURSE AND PROGNOSIS

SLE classically runs a relapsing and remitting course. With treatment, initial clinical manifestations are often suppressed; however, as treatment is tapered a further flare can occur. Certain triggers for flares can sometimes be recognized, such as psychosocial stress, intercurrent infection, UV light exposure or exposure to exogenous oestrogens. Although a clinical flare-up is often associated with recurrence of the previous clinical features, it is not unusual for new clinical features to develop or for a flare-up to be characterized by an entirely new organ/system involvement. Obviously, because the disease and its treatment can cause chronic morbidity, additional complications can also mimic a flare of the disease. For example, a patient with SLE presenting with acute chest pain may have an inflammatory serositis such as pericarditis. However, acute chest pain may also be caused by a pulmonary embolus, acute myocardial infarction or bacterial pneumonia, all of which are more common in patients with SLE.

The long-term survival for patients with SLE has improved considerably over the past 50 years. In the 1950s the 5-year mortality rate was 50%. Currently the 10-year survival rate is greater than 85% in most series. There is increased mortality in patients of African Caribbean or African American background. Mortality is also higher in patients who have renal or pulmonary involvement, as well as in patients with thrombocytopenia.

MANAGEMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS

The aim is to make a clear diagnosis and to determine the extent of involvement. It is also important to determine whether specific clinical features can be attributed to inflammation, thrombosis or other disease mechanisms, as well as to exclude specific complications such as infection. For mild non-life-threatening disease, topical therapies, non-steroidal anti-inflammatory drugs (NSAIDs) and general lifestyle advice, such as avoidance of sun exposure, may be sufficient. For mild-to-moderate disease, anti-malarial drugs (hydroxychloroquine or chloroquine phosphate), methotrexate, leflunomide, azathioprine and/or low-dose corticosteroids are frequently used. In patients with significant organ involvement, e.g. proliferative glomerulonephritis, severe neuropsychiatric involvement or uncontrolled generalized disease, immunosuppressive drugs, such as cyclophosphamide or mycophenolate mofetil, are indicated. Because of the risks of long-term toxicity from cyclophosphamide, most patients are switched to maintenance azathioprine or mycophenolate following successful initial disease control. More recently, novel therapies, such as anti-CD20 monoclonal antibodies, have shown limited efficacy in refractory disease. In addition to these therapies, other specific agents to control symptoms and/or to prevent complications are commonly required (Table 17.2). These therapies include anticonvulsants, anticoagulants, antihypertensives, lipid-lowering drugs and bone protective agents.

ANTIPHOSPHOLIPID SYNDROME

BACKGROUND

The antiphospholipid syndrome (APS) is defined as a clinical syndrome characterized by a tendency to recurrent thrombosis (arterial or venous) and/or pregnancy morbidity associated with persistently raised levels of antibodies to phospholipid-related proteins.

Antiphospholipid antibodies have been formally studied and delineated as recently as the early 1980s. However, an associated test for the lupus anticoagulant (LAC) was described in the early 1950s. This functional test is an *in vitro* assay in which a phospholipid-dependent coagulation test is prolonged (e.g. activated partial thromboplastin time, Russell's viper venom test, etc.). This prolongation cannot be corrected by the addition of normal plasma (which excludes a clotting factor deficiency). In contrast, however, adding phospholipid in excess to the mixture will normalize the test. Although the *in vitro* phenomenon is that of prolongation of a clotting time, the lupus anticoagulant test actually reflects a prothrombotic tendency. It was first described in the context of SLE, but the lupus anticoagulant can also be observed in patients who do not have SLE.

Table 17.2 Examples of drugs commonly used in the management of patients with systemic lupus erythematosus, including the indication and disease process being treated

Indication	Pathological Process	Drug Class	Examples
Disease process	Inflammation	Antimalarials	Hydroxychloroquine Chloroquine Mepacrine
		Steroids	Prednisolone Deflazacort
		Immunosuppressants Biologic therapies Anti-B-cell therapy, e.g. rituximab or belimumab	Azathioprine Methotrexate Cyclophosphamide Mycophenolate mofetil
	Raynaud's phenomenon	Vasodilators	Nifedipine Amlodipine Prostacyclin
	Clotting risk	Anti-platelet drugs	Aspirin Clopidogrel
		Anticoagulants	Warfarin Heparin
Associated symptoms	Depression	Antidepressants	Fluoxetine Paroxetine Amitriptyline
	Seizures/epilepsy	Anticonvulsants	Sodium valproate Phenytoin Carbamazepine
	Peptic ulceration	Ulcer healing drugs	Ranitidine Lansoprazole Omeprazole
Prevention of late complications	Osteoporosis	Bone protective agents	Calcium Vitamin D Risedronate Alendronate Calcitriol
	Hypercholesterolaemia	Lipid-lowering drugs	Simvastatin Pravastatin Fenofibrate
	Hypertension	Antihypertensives	Bendroflumethazide Captopril Losartan Amlodipine

CLINICAL FEATURES (TABLE 17.3)

VASCULAR THROMBOSIS

Thrombosis associated with APS can occur in any part of the circulation. The most important thrombotic complications include deep vein thrombosis and pulmonary embolism as well as stroke (Fig. 17.4), myocardial infarction and retinal artery occlusion. Untreated, there is a high risk of recurrent thrombotic events and, indeed, a careful clinical history may reveal previous unexplained thrombotic episodes in the distant past. Patients with APS can experience thrombosis on the venous and arterial side of the circulation, although it is more common for recurrent thrombosis to occur on the same side of the circulation as the previous thrombosis.

PREGNANCY MORBIDITY

APS often presents initially as a poor obstetric history. This can be either as unexplained spontaneous abortions before the 10th week of gestation or one or more unexplained deaths of a morphologically normal fetus after the 10th week of gestation. Other pregnancy morbidity, e.g. severe pre-eclampsia or severe placental insufficiency resulting in premature birth before 34 weeks' gestation, can also be part of this syndrome. The mechanism of pregnancy morbidity is believed to be thrombosis of the placental circulation resulting in failure of the placenta to develop adequately. In some cases frank placental infarction is seen.

OTHER CLINICAL FEATURES

Approximately one-third of patients with APS have thrombocytopenia, which is usually a chronic stable thrombocytopenia ($50–150\times10^9$/l). In addition, about 15% also have a Coombs-positive haemolytic anaemia. Cutaneous features associated with APS include livedo reticularis (Fig. 17.5), superficial thrombophlebitis and chronic leg ulcers. On careful screening, patients with APS frequently have thickening of cardiac valves, and 20–30% may have clinical evidence of mitral valve prolapse. In the central nervous system, clinical syndromes such as transverse myelitis, chorea and migraine may occur. It is, however, unclear whether

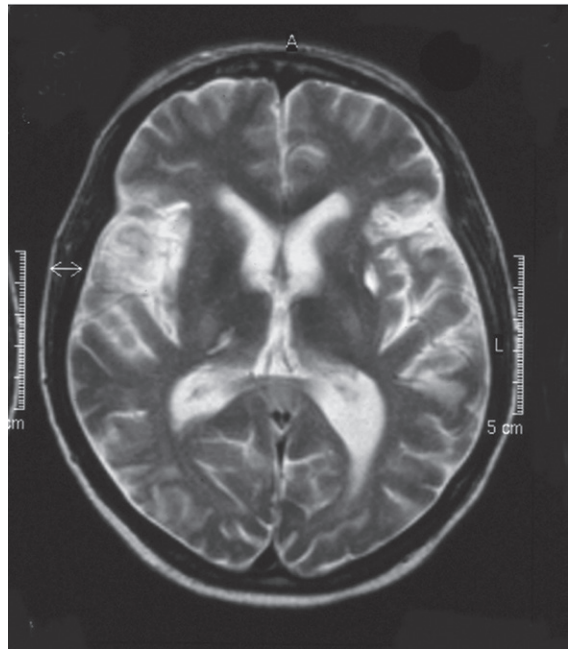


FIGURE 17.4 Magnetic resonance image of the brain in a patient with systemic lupus erythematosus and secondary antiphospholipid syndrome. The scan demonstrates significant cerebral atrophy as well as several areas of infarction from previous thrombotic episodes (strokes)

Table 17.3 Summary of the Sapporo criteria for the classification of antiphospholipid syndrome

Clinical Criteria	Laboratory Criteria*
Vascular thrombosis – objectively confirmed, single or recurrent episode(s) Arterial thrombosis OR Venous thrombosis	Anticardiolipin antibodies, IgG or IgM
Pregnancy morbidity (any of): • Three or more unexplained spontaneous abortions before 10 weeks' gestation • One or more unexplained death of a fetus after 10 weeks' gestation • One or more premature delivery due to pre-eclampsia/eclampsia before 34 weeks' gestation	Lupus anticoagulant

Antiphospholipid syndrome (APS) when one clinical criterion AND one laboratory criterion are fulfilled. Remember that these are classification criteria and not diagnostic criteria, which means that clinical judgement and common sense must be used (for example if there are alternative explanations for some of the findings).

*Need to be positive on two occasions at least 6 weeks apart.

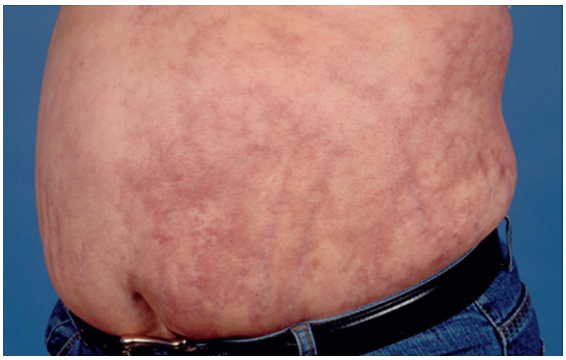


FIGURE 17.5 Livedo reticularis rash in a patient with antiphospholipid syndrome. The rash has a bluish purple reticular pattern, which does not improve in a warm environment

these are primarily thrombotic in nature or whether they represent a separate pathogenic mechanism. Occasionally patients can present with thrombosis in multiple vascular beds. This 'catastrophic' antiphospholipid syndrome is difficult to recognize clinically and is associated with a high mortality rate.

CLASSIFICATION

The initial descriptions of APS occurred in the context of SLE. APS may also be a complicating feature of other autoimmune diseases, such as rheumatoid arthritis and Sjögren syndrome. In this context the term secondary APS is usually employed. The majority of patients with APS do not have any other systemic autoimmune condition, and these are described as having primary APS.

MANAGEMENT

APS is only one cause of recurrent thrombosis or miscarriage. Careful evaluation should, therefore, be undertaken to identify other causes of thrombosis, e.g. Factor V Leiden, protein C and protein S deficiencies. Similarly, for recurrent miscarriage other causes, e.g. hormonal, anatomical and chromosomal causes, should be actively excluded. APS will constitute anything from 5% to 30% of such cases.

POSITIVE ANTIPHOSPHOLIPID ANTIBODIES WITHOUT CLINICAL THROMBOSIS OR PREGNANCY LOSS

There is no clear consensus as to how this group of patients should be managed. There is no high-quality clinical trial evidence on which to base any recommendations, but it is recognized that some of these patients are at increased risk of future thrombosis (this is estimated to be low at between 0% and 4% per annum) and many authorities would recommend general advice on stopping smoking, avoiding oestrogen-containing contraceptives, and maintaining good control of cholesterol and blood pressure. The use of long-term low-dose aspirin cannot be justified. Low-molecular-weight heparin is sometimes offered to patients undergoing surgery, long-haul flights (>4 hours in duration) and in patients who have a plaster cast applied. The use of low-dose aspirin cannot be justified.

RECURRENT PREGNANCY LOSS

In women who have had previous pregnancy morbidity associated with APS, randomized trials demonstrate that the optimum therapy is low-dose aspirin combined with low-molecular-weight heparin. This regimen can increase the live birth rate from less than 30% to approximately 80%. In view of the fact that the mother will also be at increased risk of venous thrombosis for up to 6 weeks postpartum, this treatment regimen may be continued until this point. Special planning for pregnancy is required for women who have had a previous vascular thrombosis and who are already taking warfarin outside of pregnancy. As warfarin is teratogenic, this will need to be stopped prior to 6 weeks' gestation and the mother transferred to a full therapeutic treatment regimen of heparin until after delivery.

MANAGEMENT OF THROMBOTIC COMPLICATIONS

Patients with APS who experience a thrombotic event have a significant risk of recurrent thrombosis if left untreated. As a result, for the majority of patients life-long anticoagulation with warfarin is recommended. The target international normalized ratio (prothrombin ratio) (INR) is usually kept at 2.0–3.0, although where further events occur a higher-intensity anticoagulation (INR >3.0) may be indicated. In patients who are fully anticoagulated there is little evidence that the addition of aspirin confers any further risk reduction. It is also useful to give general advice about maintaining good cardiovascular health. The use of oestrogen-containing contraceptives and hormone replacement therapies is contraindicated in these patients.

ADULT MUSCLE DISORDERS

Idiopathic inflammatory muscle disease comprises a group of conditions that are characterized by inflammation of striated muscle. These myositis syndromes fall within the family of autoimmune rheumatic diseases and they can occur on their own or overlap with other autoimmune rheumatic diseases, as outlined previously. Myositis is a rare condition with an annual incidence of approximately 5–7 new cases per million. The aetiology remains unknown.

CLASSIFICATION AND DIAGNOSTIC CRITERIA

The commonly described subtypes are outlined in Table 17.4. In addition, there are classic criteria for the diagnosis of the two most frequently described syndromes, polymyositis and dermatomyositis (Table 17.5). The commonest presenting feature is with proximal muscle weakness, which usually evolves over a 3–6-month period, but can be more insidious, or in some cases an acute presentation can be observed. In a small proportion of patients, the presenting feature is with the classic rash. The usual muscle groups involved include the proximal musculature of the upper and lower limbs, which will cause difficulty in functions requiring limb strength. Simple tasks, such as arising from a low chair, stepping into trousers as well as brushing hair, can become difficult. Patients sometimes walk with a 'waddling' gait. Other striated muscle is also involved and weakness of the neck flexors, as well as abdominal muscle weakness, can be observed causing difficulties getting out of bed, etc. As the upper oesophagus has significant amounts of striated muscle, dysphagia can occur. The myocardium may also be involved and involvement of the respiratory muscles can cause exertional dyspnoea.

CUTANEOUS INVOLVEMENT IN DERMATOMYOSITIS

The classical rash involves linear scaling papules on the dorsum of the hand (Gottron's papules), as well as a purple erythematous rash around the eyelid (heliotrope rash; Fig. 17.6). Patients with myositis may also experience photosensitivity with associated facial erythema and erythema of the 'V' of the neck. Nailfold capillaries can be extremely abnormal with giant capillary loops and a 'ragged nailfold' appearance.

OTHER CLINICAL FEATURES

Patients with myositis may also have a polyarthritis. In addition to involvement of the respiratory muscles, the lung parenchyma can be involved with a diffuse interstitial pneumonitis that can also result in dyspnoea. This is particularly common in patients with myositis specific antibodies to Jo-1 or PM-Scl. In a small number of cases, patients present with aggressive inflammatory lung disease only; muscle involvement may develop subsequently, but not always.

Table 17.4 Classification of common inflammatory myositis syndromes

Adult-Onset Syndromes	Childhood-Onset Syndromes
Polymyositis	Childhood-onset myositis
Dermatomyositis	
Cancer associated myositis (CAM)*	
Myositis overlapping with other autoimmune rheumatic disease	
Inclusion body myositis	

*Malignancy more frequently associated with dermatomyositis, especially in the presence of antibodies to transcriptional intermediary factor 1 γ (anti-TIF γ).

Table 17.5 Summary of Bohan and Peter criteria for the diagnosis of polymyositis and dermatomyositis

Criteria
Symmetrical proximal muscle weakness Biopsy evidence of myositis Electromyographic changes consistent with myositis Raised muscle enzymes on serum testing Typical rash of dermatomyositis
Diagnosis
Polymyositis (definite/probable): at least three of the first four criteria present Dermatomyositis (definite/probable): typical rash PLUS at least two of the first four criteria

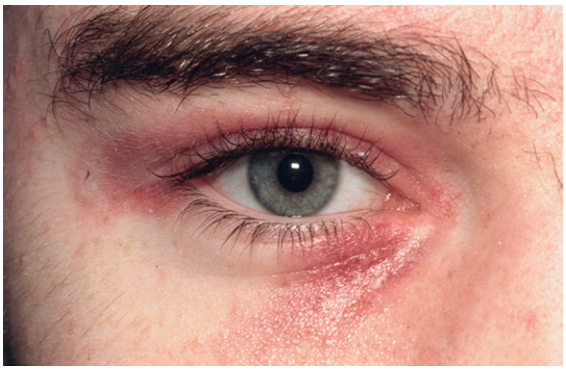


FIGURE 17.6 Heliotrope (sun-seeking) rash in a patient with dermatomyositis showing the typical erythematous periorbital rash. The name is derived from the heliotrope flower, which has a purple colour

CHRONIC COMPLICATIONS

The initial clinical features of myositis in the muscles, skin and lungs reflect an underlying inflammatory disorder. Secondary fibrosis/scarring can also occur. In the lungs this can result in pulmonary fibrosis, and in the muscle it can result in long-term weakness and failure to restore muscle strength to pre-morbid levels. Scarring and fibrosis within muscle is particularly disabling in childhood-onset dermatomyositis where areas of muscle damage can be complicated by soft-tissue calcinosis and failure of the muscle to grow adequately, resulting in flexion contractures.

MYOSITIS AND THE ASSOCIATION WITH MALIGNANCY

Patients with myositis, especially those with dermatomyositis, have been found to have an increased risk of developing an underlying malignancy (cancer associated myositis, or CAM). This increased risk of malignancy persists throughout the patient's lifetime, but the risk is particularly high in the 2–3 years before and after the diagnosis of myositis is made. Common sites of malignancy include the gastrointestinal tract, lungs, ovaries and the lymphatic system. As a general rule, the malignancies associated tend to be those of relevance to the age, sex and ethnicity of the patient. Vigilance is, therefore, required throughout the follow-up period for patients with dermatomyositis in particular, and initial screening for such cancers should be included in the management plan. The highest identifiable risk of cancer is associated with the presence of antibodies to transcriptional intermediary factor 1 γ (TIFγ), especially in the absence of any of the conventional myositis specific antibodies.

INVESTIGATIONS

Routine laboratory tests often reveal a low-grade anaemia of chronic disease associated with an increased erythrocyte sedimentation rate (ESR). Biochemical tests show raised creatine phosphokinase (CK) levels in the majority of patients, and in patients with extreme increases in CK concentration myoglobulinuria may occur that can lead to renal impairment. Electromyography (EMG) is a sensitive test for myositis. At the point of needle insertion spontaneous fibrillation can be observed, as can polyphasic potentials on muscle contraction. Muscle biopsy can provide important information by confirming the presence of an inflammatory cell infiltrate. The inflammatory pattern in polymyositis tends to be scattered throughout the muscle tissue. By contrast, dermatomyositis is frequently characterized by perivascular infiltration. The muscle biopsy is useful to exclude other non-inflammatory muscle diseases and to identify patients with inclusion body myositis, which is less responsive to conventional therapy. In addition to these investigations, magnetic resonance imaging (MRI) is increasingly being employed as a sensitive test to pick up muscle inflammation (Fig. 17.7). It can be a useful modality to decide on which muscle groups to biopsy.

MANAGEMENT

High-dose corticosteroids remain the mainstay of treatment in inflammatory myositis. Corticosteroids (1–2 mg/kg per day) can be used for the initial few weeks until significant clinical improvement occurs and the CK level has fallen to within the normal range. There is evidence that intravenous immunoglobulin may be effective.

Other immunosuppressive agents, such as azathioprine, methotrexate and cyclophosphamide, have also been used. Such agents can be used for their 'steroid-sparing' properties. This can be particularly useful in patients who require moderate to high doses of steroids to control their disease adequately. These agents are indicated in patients

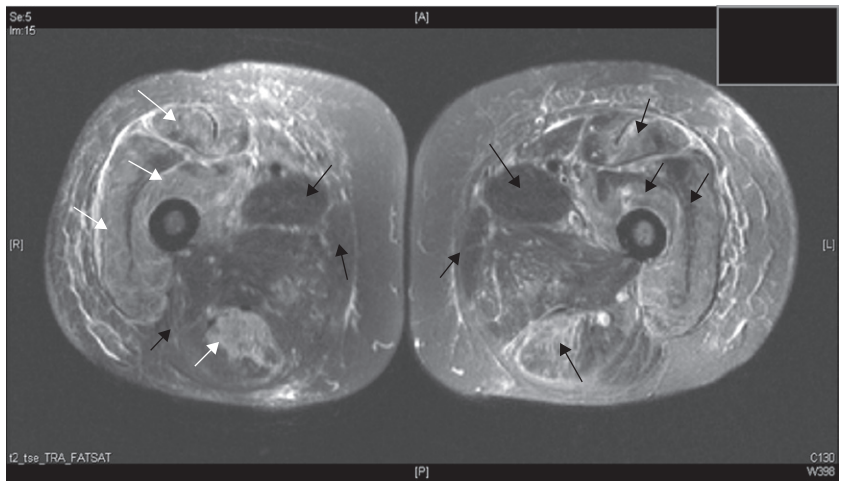


FIGURE 17.7 Cross-sectional T2-weighted scan through both thighs showing pale oedematous muscle groups with symmetrical involvement (white arrows) and characteristic sparing of adjacent muscle groups (black arrows)

who have an associated interstitial pneumonitis (note: methotrexate is relatively safe to use in these patients, despite potential concerns that it might be associated with the very rare complication of acute pneumonitis). In the medium term, management of these patients is often complicated by the development of steroid myopathy. This can be difficult to distinguish from the primary disease. In most cases, however, steroid myopathy will be associated with a normal CK concentration and EMG may be useful to distinguish ongoing chronic inflammation from simple mild myopathic changes. In some cases, however, a repeat muscle biopsy may be indicated to distinguish a flare from steroid myopathy.

In addition to medical management it is important to encourage patients to rehabilitate their muscles after an episode of myositis towards their pre-morbid levels. In addition, one should have a low threshold for re-evaluating the patient to rule out an underlying malignancy, should the clinical circumstances suggest this.

RAYNAUD'S PHENOMENON AND SCLERODERMA

Raynaud's phenomenon is a condition resulting from vasospasm, characterized by intermittent colour changes of pallor, cyanosis and subsequent hyperaemia in response to cold and/or emotional stress. Although noted most typically in the fingers, the circulation of the toes, ears, nose and tongue may be affected. Raynaud's phenomenon is more common in women than in men, with prevalence estimates ranging from 4% to 30%. Geographical variations in the prevalence relate to differences in climate. Raynaud's phenomenon may be a primary or a secondary process. In the primary form, attacks affect all digits in a symmetrical fashion, but do not result in tissue necrosis, ulceration or gangrene; no cause of Raynaud's can be detected, ANAs are not present, the nailfold capillaries look normal and the ESR is not raised. In the secondary form of the disease, symptoms commence at an older age (usually over 30 years), giving rise to painful and asymmetrical episodes, sometimes causing ischaemic skin lesions and typically associated with positive autoantibodies and capillaroscopic abnormalities, often with clinical features suggestive of autoimmune rheumatic diseases, especially systemic sclerosis.

Raynaud's is distinct from acrocyanosis, where there is continuous cyanosis of the hands or feet aggravated by cold temperature. Patients should be advised to stop smoking and to avoid medication that can induce vasospasm, such as β-blockers. Patients should avoid sudden changes in temperature where practical. This may mean wearing warm clothing, and gloves and socks, even in moderate weather. Medication used for Raynaud's includes calcium-channel blockers (such as nifedipine up to 80 mg daily). For more resistant or severe cases with digital ulcers, intravenous

prostacyclin infusions are effective. The role of phosphodiesterase-5 inhibitors, such as sildenafil, or endothelin-1 antagonists, such as bosentan (which is effective in treating pulmonary hypertension), for Raynaud's phenomenon and its complications remains uncertain, despite some promising evidence.

Systemic sclerosis, or scleroderma, is a systemic autoimmune disease that is mediated by vascular damage and fibrosis within the skin and visceral organs. The term scleroderma includes localized skin fibrosis (previously termed morphoea) and generalized forms with inflammatory, vascular and fibrotic pathology. The two main forms are limited cutaneous scleroderma and diffuse cutaneous scleroderma. Localized skin fibrosis may appear as an area of increased or reduced pigmentation, typically with some erythema and skin thickening. Over time, the central area of skin may become pale, whilst the edge of the lesion, representing the active area of fibrosis, may spread further. Patches of scleroderma can occur at any site, typically on the trunk and limbs. In childhood forms, the patches may be linear and can have a significant effect on growth of the affected area, leading to hemi-atrophy. Treatment is largely supportive.

Limited cutaneous scleroderma is typically associated with the presence of anti-centromere antibodies. It is defined by the extent of skin involvement (peripheral skin involvement distal to the elbows). There is a tendency to develop Calcinosis, Raynaud phenomenon, oEsophageal dysmotility, Sclerodactyly and Telangiectasia, leading to the previous description of CREST syndrome. Diffuse cutaneous scleroderma involves more widespread skin changes proximal to the elbows, and may, in advanced cases, cover almost the whole body surface. There is an association with the presence of anti-Scl-70 antibodies.

Although scleroderma has a significant mortality, there have been major improvements in the management of renal and pulmonary disease. With longer survival, we are increasingly aware of the effects of progressive fibrosis in many organs, such as the gastrointestinal tract, resulting in problems such as acid reflux, malabsorption and faecal incontinence. Angiotensin-converting enzyme inhibitors for scleroderma renal crisis, proton pump inhibitors for reflux oesophagitis, and advanced therapies for severe pulmonary arterial hypertension are now established. Better understanding of the underlying mechanisms means that, in future, cytokine-directed treatments may modify the course of the disease. At present, however, systemic sclerosis remains one of the least treatable of the autoimmune rheumatic diseases.

Pulmonary hypertension is a recognized complication of limited cutaneous scleroderma in 5–35% of patients. Regular screening, using echocardiography, should allow early detection and referral to an expert centre for consideration of endothelin-1 inhibition or sildenafil. Interstitial lung disease occurs in most patients with diffuse cutaneous scleroderma, but progression to severe restrictive lung disease occurs in less than 20%, many of whom will die. The histological changes are of non-specific interstitial pneumonia. The most effective initial treatment is with cyclophosphamide and low-dose corticosteroid therapy (preferably no more than 15 mg per day to avoid the risk of precipitating scleroderma renal crisis), but progression to lung fibrosis may be resistant to therapy.

SJÖGREN SYNDROME

Dry eyes and mouth are the main features of Sjögren syndrome, which may occur as a primary disease, typically in association with autoantibodies (anti-Ro or anti-SSA, and anti-La or anti-SSB). The exocrine glands are affected in a destructive, fibrosing process leading to failure of gland function. The pathological findings are of focal lymphocytic infiltration in the exocrine glands. Approximately 50% have arthralgia. Skin lesions may occur in up to 10% of patients, typically a cutaneous vasculitis, but patients may also develop photosensitive rashes identical to those seen in SLE, suggesting a common pathogenesis, but creating diagnostic confusion in some cases. Bronchial and bronchiolar dysfunction is the main lung manifestation rather than interstitial lung disease (more commonly seen in SLE and RA). Up to 13% of patients suffer from Raynaud's phenomenon. Both tubular interstitial nephritis and glomerulonephritis have been described. Neurological involvement is usually characterized by peripheral sensory neuropathy (not responsive to immunosuppression), and in some cases sensorineural hearing loss. Autonomic neuropathy is reported in patients with longstanding disease, but is rarely symptomatic. Sub-clinical myositis may occur in over 25% of patients, with histological abnormalities similar to those seen in

inflammatory myositis. Around 20% of patients have anaemia, cytopenias and a raised ESR, along with hypergammaglobulinaemia. The feared risk of transformation to lymphoma is lower than previously thought. Recent studies suggest that the incidence is around 5%; those at highest risk have neutropenia, cryoglobulinaemia, splenomegaly, persistent lymphadenopathy and low C4 levels. Overall, Sjögren syndrome is a slowly progressive condition with a much better prognosis than most inflammatory rheumatic diseases. Therapy is usually directed to supporting the failing exocrine glands (artificial tears and saliva) or stimulating residual gland function via muscarinic receptors (for example with pilocarpine or cevimeline). For those patients with extraglandular disease, which is mediated mainly by cryoglobulinaemia, immunosuppression with steroids and cytotoxic agents may be necessary. The role of anti-B-cell therapy is currently being explored. Female patients with anti-Ro and/or anti-La antibodies who are of childbearing age should be counselled with regard to the possible risks of congenital heart block (approximately 1–5% of anti-Ro-positive mothers) and the neonatal lupus syndrome.

SYSTEMIC VASCULITIS

Vasculitis means inflammation of blood vessel walls with narrowing and occlusion leading to tissue or organ damage. Primary vasculitis is diagnosed when there is no underlying autoimmune rheumatic disease; if vasculitis occurs in a patient with RA or SLE, for example, it is regarded as secondary. Vasculitis may be important in atherosclerosis where inflammation is responsible for plaque rupture and vessel occlusion. There are more than 100 new cases of primary vasculitis per million per year. Many patients have skin vasculitis only. The more serious forms of vasculitis, such as granulomatosis with polyangiitis (previously termed Wegener's granulomatosis) and microscopic polyangiitis, are less common; between 2.4 and 9.7 cases per million per year with a prevalence of between 30 and 53 per million per year.

AETIOLOGY

Most forms of vasculitis have no known cause. Table 17.6 summarizes factors known to cause vasculitis or associated with it. Infection can trigger episodes of disease (e.g. nasal carriage of

Table 17.6 Factors associated with the development or severity of vasculitis

Factor	Association	Effect
Hepatitis B virus	Definite	Previously a very common cause of polyarteritis nodosa, but now rarely implicated owing to widespread immunization
Hepatitis C virus	Definite	Most (>90%) patients with mixed essential cryoglobulinaemia
HIV virus	Definite	Undifferentiated vasculitis
Anti-thyroid drugs	Definite	Reversible forms of vasculitis similar to microscopic polyangiitis and granulomatosis with polyangiitis (GPA)
Cocaine	Definite	ANCA-positive vasculitis similar to GPA (Wegener's)
Staphylococcus aureus	Definite	Exacerbation of pre-existing GPA (Wegener's)
Levamisole	Definite	ANCA-positive vasculitis and thrombotic vasculopathy
Streptococcal pneumonia	Definite	Rheumatic fever and bacterial endocarditis
α_1-Antitrypsin deficiency	Probable	Increases the risk and severity of GPA (Wegener's)
Silica exposure	Possible	Increases risk of small vessel vasculitis
Farming and exposure to farm animals	Possible	Increases risk of Churg–Strauss syndrome

GPA, granulomatosis with polyangiitis.

Staphylococcus aureus increases risk of relapses of GPA). There is a seasonal variation in GPA (more cases are seen during spring and winter compared with autumn or summer). Hepatitis B is a well recognized and previously major cause of polyarteritis nodosa (PAN), but as a result of better public health and an immunization campaign the incidence of hepatitis B-related diseases is falling. Identifying a cause is a very important basis for treatment, and most patients with hepatitis B-related PAN can be cured by eradication of the virus. Unfortunately, it is more difficult to eradicate hepatitis C, a known cause of mixed essential cryoglobulinaemia. Other environmental factors that have been implicated are silica exposure, possibly by acting as a stimulant or adjuvant. Living in a farming or rural community has been linked to increasing risk of developing eosinophilic granulomatosis with polyangiitis (previously termed Churg–Strauss syndrome).

Genetic factors are important and may increase the risk or severity of disease. α_1-Antitrypsin deficiency increases the risk of developing GPA (Wegener's). α_1-Antitrypsin is the natural factor to neutralize proteinase-3, a toxic neutrophil enzyme that digests bacteria. One form of anti-neutrophil cytoplasm antibody (ANCA), often found in patients with GPA (Wegener's), is directed against proteinase-3 (see below).

PATHOLOGY

Some patients have intense inflammatory infiltration around blood vessels, invading through the vessel wall, causing necrosis of surrounding tissue. In other cases there is a granulomatous infiltrate, sometimes with giant cells (as seen in temporal arteritis or occasionally in GPA). Figure 17.8 shows a section from a temporal artery biopsy in a patient with temporal arteritis. In the kidney, pathological abnormalities are similar in different forms of vasculitis, suggesting that the kidney has a limited response to poor blood flow through its capillaries and venules. The typical renal lesion of a small-vessel vasculitis is focal segmental necrotizing glomerulonephritis (focal because it affects only a few glomeruli, not all of them; segmental because it may affect only a part of the glomerulus; and necrotizing implying tissue destruction). This may occur in GPA, microscopic polyangiitis, EGPA or other conditions such as SLE or bacterial endocarditis. The result is that you need to interpret the pathological findings together with the clinical and serological abnormalities.

CLASSIFYING DIFFERENT TYPES OF VASCULITIS

A precise diagnosis of vasculitis has implications for treatment and outcome. Patients with leucocytoclastic skin vasculitis often require no treatment apart from supportive management, and the outcome is very good. By contrast, patients with microscopic polyangiitis may present with lung haemorrhage and glomerulonephritis; they need aggressive chemotherapy and the outcome may be poor despite best management (mortality rate of 20–40% despite treatment). The pathology findings

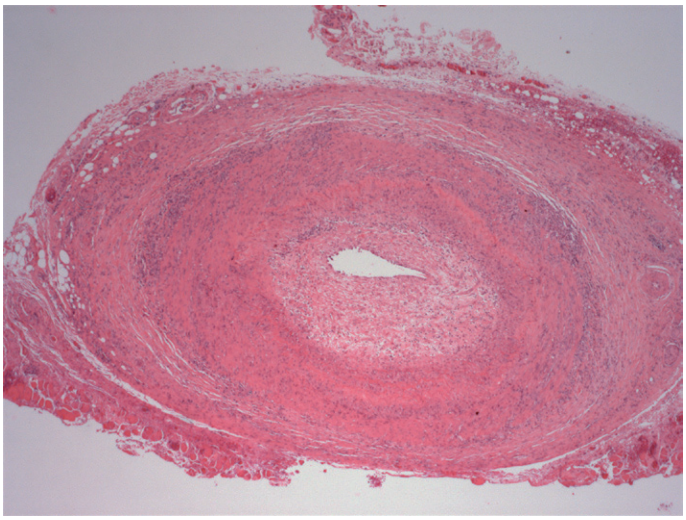


FIGURE 17.8 Low-power view of a temporal artery biopsy. The lumen is oedematous resulting in stenosis of the lumen. The internal elastic lamina has been destroyed by a cellular infiltrate, which extends through the media

in vasculitis can be helpful, but, because of greater awareness of vasculitis, patients increasingly present with less severe abnormalities. Patients should be investigated and treated at an early stage rather than let the condition develop into a full-blown form, by which time organ failure may have occurred. The pathological findings may be shared by different types of vasculitis. For example, granulomatous inflammation may be seen in patients with GPA (Wegener's) as well as patients with EGPA (Churg Strauss).

Classification of systemic vasculitis is based on the size of the smallest vessel to be affected by the vasculitic process. The distinction is between large-vessel disease, where large vessels alone are affected; medium-vessel disease, where medium-sized vessels such as small arterials are predominantly affected, although in some circumstances larger vessels may also be affected; and small-vessel vasculitis, where capillaries can be involved, although, confusingly, these patients can also have medium- and large-vessel disease. However arbitrary this system might seem, it is probably the most useful guide to therapy because often the smaller sized vessel involved determines which organs will be affected and, therefore, which treatment you will wish to give to patients. Table 17.7 summarizes the different forms of vasculitis according to vessel size.

ANCA defines a subgroup of patients with small-vessel vasculitis who have a predilection for renal disease (typically GPA and microscopic polyangiitis) and who require similar treatment.

AN APPROACH TO DIAGNOSIS

Making a diagnosis of vasculitis requires a thorough history and physical examination because many abnormalities are apparent from this simple basic clinical evaluation. Patients with multisystem disease should be assessed for the possible diagnosis of vasculitis. There are very few conditions that cause such widespread organ involvement. In fact, the more organ systems involved, the narrower the differential diagnosis becomes. Vasculitis may be secondary to an underlying autoimmune rheumatic disease. Infection and drugs can cause vasculitis; you need to take a full history and examination. Rarely, malignancy may cause vasculitis, but usually the primary tumour is obvious. The clinical presentations of some primary forms of vasculitis can overlap with one another.

In a patient with multi-organ disease, we need to look for raised inflammatory markers, abnormal serological tests such as ANCA, and try to confirm the diagnosis with a biopsy from an affected organ, or by imaging the vessels to show the abnormalities (usually smooth tapered narrowing or aneurysms, or both). However, investigating patients at an early stage of their disease may produce inconclusive results.

EVALUATION OF PATIENTS WITH AN ESTABLISHED DIAGNOSIS

A comprehensive assessment of patients with systemic vasculitis is essential as a basis for deciding appropriate therapy. Initial evaluation should include assessment of both active vasculitis and the presence of pre-existing damage, which may have occurred following episodes of previous vasculitis or even as a result of treatment of previous vasculitis. It is important to make this distinction, because treatment needs to be appropriate to the needs of the individual patient. For example, if the patient has established renal failure from previous episodes of disease activity then it is unlikely to respond to aggressive immunosuppression, whereas if renal failure has developed more rapidly and there are signs of active nephritis then there is every reason to act quickly and offer immunosuppressive treatment. A full history should be taken and peripheral vasculature examined. Typically such patients would have full examination of the upper airways; the eyes; skin; nail beds; chest and cardiovascular, abdominal, neurological and locomotor systems. Blood pressure must be measured in every patient and urine should be routinely tested for the presence of blood and protein. Weight is very useful as a baseline.

The initial blood test should measure renal function and liver function, haematology, acute-phase reactants and autoantibody screen. Viral studies may be relevant, especially for hepatitis B and C, and occasionally for HIV. Diagnostic imaging may be necessary or further assessment of organ function, such as lung function testing, may be helpful. In most instances, however, a chest X-ray is a useful part of the initial diagnostic workup (Fig. 17.9), mainly to exclude other pathologies, such as neoplastic disease or infection. Remember to consider previous episodes of treated or untreated tuberculosis (TB), which may have an important bearing on further management (if the patient

Table 17.7 Primary vasculitides

Disease	Epidemiology	Symptoms, Signs and Investigations	Treatment and Outcome
Giant cell arteritis or temporal arteritis (large-vessel vasculitis)	Elderly. Annual UK incidence 220 per million in older adults	Headaches, scalp tenderness, visual disturbance, jaw claudication often with polymyalgia High erythrocyte sedimentation rate (ESR), granulomatous inflammation on temporal artery biopsy	Corticosteroids. Relapse rates vary (30–80%). Steroid taper over 1–4 years Methotrexate may be useful additional therapy
Takayasu's arteritis (large-vessel vasculitis)	Females under 50 years, especially in Eastern countries. UK incidence 0.1 per million/year	Chronic ischaemia, new loss of pulses, bruits, systemic upset. Angiography – vessel narrowing or post-stenotic dilatation. MRA – wall oedema, carotid Doppler flow	Corticosteroids 5–10-year survival rate 80–90%, but 47% have permanent disability. Reconstructive surgery may be required for stenotic or aneurysmal lesions.
Polyarteritis nodosa (medium-vessel vasculitis)	Adults. UK incidence 0–4.6 per million/year	Multi-system organ involvement No glomerulonephritis Hepatitis B virus positive in some cases Biopsy of affected area or angiography, especially mesenteric, can show aneurysms or vessel narrowing	Corticosteroids plus antiviral agents (for hepatitis B-positive disease) or cyclophosphamide (for hepatitis B-negative disease) Mortality rate 23% (non-HBV PAN), 33% (HBV PAN); relapse rate 8% HBV PAN, 20% non-HBV PAN
Kawasaki disease (mucocutaneous lymph node syndrome) (medium-vessel vasculitis)	Endemic and epidemic forms with seasonal variation. UK incidence 34 per million/year in children under 5 years vs 900 per million/year in Japan	Fever, mucocutaneous inflammation; cervical lymphadenopathy; polymorphous exanthema Desquamation of skin 10 days after onset. Coronary arteries often involved Diagnosis on clinical findings plus coronary artery dilatation on echocardiography	High-dose aspirin and intravenous gammaglobulin Decreases incidence of coronary artery aneurysms Coronary artery lesions occur in 15–25% of untreated patients, but less than 10% of those given IVIG
Granulomatosis with polyangiitis (Wegener's) (small-vessel vasculitis)	Adults mainly, can occur in children. Annual incidence in UK 8.5 per million	Upper and lower airways, often with renal involvement Granulomatous inflammation in airways, focal segmental necrotizing glomerulonephritis in the kidney, C-ANCA positive in most cases against PR3	Localized upper airway disease cotrimoxazole plus or minus prednisolone or methotrexate with prednisolone Mupirocin useful for eradicating nasal staphylococcus Systemic disease requires prednisolone and cyclophosphamide (or rituximab) and plasma exchange for rapid progressive renal impairment Relapse rate of at least 50%
Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) (small-vessel vasculitis)	Adults mainly, although can occur in children. Annual UK incidence 1.3 per million	Respiratory tract features dominant – asthma, allergic rhinitis, pulmonary infiltrates Multiple drug allergies, mononeuritis multiplex; cardiac involvement is serious Eosinophilia; may be ANCA positive, usually P-ANCA (myeloperoxidase)	Corticosteroids; cyclophosphamide for serious disease (especially cardiac or renal involvement) Mortality low, but relapse and morbidity rates high

Continued

Table 17.7 Primary Vasculitides – cont'd

Disease	Epidemiology	Symptoms, Signs and Investigations	Treatment and Outcome
Microscopic polyangiitis (small-vessel vasculitis)	Adults mainly, but can occur in children. Annual UK incidence 8 per million	Haematuria, pulmonary haemorrhage, systemic upset with multi-system involvement Renal biopsy shows FSNGN P-ANCA usually positive (myeloperoxidase)	Corticosteroids and cyclophosphamide (or rituximab); plasmapheresis for renal failure Mortality rate 10–40%; relapse rate 20%
Henoch–Schönlein purpura (small-vessel vasculitis)	Predominantly in children but adults may be affected (they have worse prognosis). Annual UK incidence 1.2 per million in adults	Purpuric rash, flitting arthritis, abdominal pain, rectal bleeding, haematuria Skin biopsy or gastrointestinal tract biopsy may show IgA-dominant immune deposits, especially on basement membrane	Self-limiting in childhood, but if renal involvement present carries adverse prognosis Adults – more indolent course Steroids may be used for arthralgia and rash
Leucocytoclastic vasculitis (small-vessel vasculitis)	Adults and children	Skin involvement only with purpura or occasional ulcers or bullae	Symptomatic treatment with antihistamines; colchicine, steroids for resistant cases
Essential mixed cryoglobulinaemia (small-vessel vasculitis)	Adults mainly but can occur in children. Annual UK incidence 1.2 per million	Purpura, arthralgia, urticaria, ulcers and renal involvement Type II cryoglobulinaemia, strong association with hepatitis C virus	Antiviral therapy and steroids and plasmapheresis
Uncertain or unclassified	Annual UK incidence 4.8 per million	As above	May be any of the above

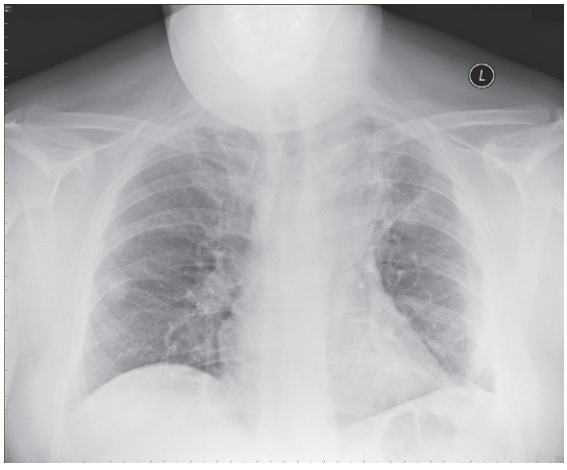


FIGURE 17.9 Lung involvement in a patient who has granulomatosis with polyangiitis. There is an extensive shadowing from granulomatous infiltration into the lungs

actually has TB as a cause of their vasculitis, you would want to treat the TB; if patients have active vasculitis and the presence of partially treated or previously untreated TB, you may need to consider anti-TB prophylaxis). Clinical evaluation of patients' progress remains the cornerstone of management and cannot be superseded by any routine blood monitoring. The same checklist of symptoms and signs of active vasculitis serves a useful role in monitoring patient disease state. It is also useful to document disease damage more formally and systems are available to record this. A useful checklist is shown in Table 17.8.

SEROLOGICAL MARKERS OF DISEASE ACTIVITY

Basic biochemical and haematological parameters and measurements of acute-phase response help

Table 17.8 Symptoms, signs and investigations that may occur in the context of active systemic vasculitis

Symptom	Sign/Investigation
Systemic	Malaise, myalgia, arthralgia/arthritis, headache, fever and weight loss
Cutaneous	Infarct, purpura, ulcer, gangrene and other skin vasculitis
Mucous membranes/eyes	Oral ulcers, genital ulcers, proptosis, conjunctivitis, episcleritis, scleritis, visual disturbances with visual loss, uveitis, retinal exudates and retinal haemorrhages
Ear, nose and throat	Nasal obstruction, bloody nasal discharge, crusting, sinus involvement, new deafness, hoarseness/stridor, subglottic stenosis and adnexal inflammation
Respiratory	Persistent cough, dyspnoea, wheeze, haemoptysis, pulmonary haemorrhage, nodules, cavities, infiltrate, pleurisy, pleural effusion and respiratory failure
Cardiovascular	Bruits, new loss of pulses with or without threatened loss of limbs, aortic incompetence, pericardial pain/rub, ischaemic cardiac pain and congestive cardiac failure
Gastrointestinal	Severe abdominal pain, bloody diarrhoea, intestinal perforation/infarct and acute pancreatitis
Renal	Hypertension (diastolic >95 mmHg), proteinuria >0.2 g/24 h, haematuria >10 red cells per high power field, renal impairment/failure, rise in creatinine >30% or fall in creatinine clearance >25%
Neurological	Organic confusion/dementia, seizures (not hypertensive), stroke, cord lesion, sensory peripheral neuropathy, cranial nerve palsy, motor mononeuritis multiplex

to differentiate active disease from irreversible damage. The ANCA test has improved our awareness of vasculitis by identifying patients who appear to have a vasculitis, but it is not a useful screening tool on its own. It must be used with clinical judgement in patients in whom there is a suspicion of vasculitis. Furthermore, ANCA testing is not useful as the sole guide to therapy, without clear evidence of clinical disease activity.

DIFFERENTIATING VASCULITIS FROM INFECTION

There is a close relationship between infection and vasculitis. Some infectious diseases cause certain types of vasculitis, for example hepatitis B and hepatitis C. *S. aureus* can exacerbate episodes of GPA, but has not been shown to cause the disease. In patients with an established diagnosis of vasculitis who become ill, it is important to differentiate the deterioration caused by intercurrent infection from that caused by vasculitis. This can be difficult because the clinical presentation may be exactly the same and it is very important to suspect infection, especially as most patients are on immunosuppressive drugs, which may mask obvious features of sepsis. In many cases it is necessary to start empirical antibiotic therapy at the same time as, or just prior to, introducing more immunosuppression, in case the problem is infection plus active vasculitis.

MANAGEMENT

Although there are different forms of vasculitis, there is a lot of overlap in organ involvement, and it is the organ involvement that primarily dictates the type of treatment that is most appropriate. For example, patients with ANCA-associated vasculitis involving the kidney will be given the same treatment whether the diagnosis happens to be granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis or microscopic polyangiitis. Drug treatments according to disease severity are summarized in Table 17.9.

The management of systemic vasculitis is very complex and we would strongly advise the involvement of physicians with experience in these diseases. Careful attention to important details, such as pre-treatment blood counts, renal function, and regular checks on haematology and biochemistry, can prevent inappropriate use of immunosuppression and limit toxicity from drug treatment. Supportive treatments alongside the standard

Table 17.9 Summary of therapies for systemic vasculitis

Therapy	Specific Drugs	Disease
Mild	None or colchicine or dapsone	Cutaneous leucocytoclastic vasculitis and some cases of Henoch–Schönlein purpura
Moderate	Prednisolone/prednisone	Giant cell arteritis, Takayasu's arteritis, resistant or severe cutaneous vasculitis
	Co-trimoxazole (trimethoprim–sulfamethoxazole)	Non-renal granulomatosis with polyangiitis
	Methotrexate + steroids	Non-renal granulomatosis with polyangiitis, resistant giant cell arteritis and resistant Takayasu's arteritis
	Azathioprine + steroids	Remission maintenance in microscopic polyangiitis, granulomatosis with polyangiitis, polyarteritis nodosa, eosinophilic granulomatosis with polyangiitis, resistant giant cell arteritis and resistant Takayasu's arteritis
	Mycophenolate mofetil and steroids	ANCA-associated systemic vasculitis
	Leflunomide with steroids	Granulomatosis with polyangiitis
	Ciclosporin A + steroids Ciclosporin A or azathioprine or α-interferon ± steroids	Resistant giant cell arteritis Behçet's syndrome
Standard	Cyclophosphamide and steroids or Rituximab and steroids for GPA and MPA.	Microscopic polyangiitis, granulomatosis with polyangiitis, polyarteritis nodosa (hepatitis B negative), necrotizing vasculitis, eosinophilic granulomatosis with polyangiitis with internal organ involvement (not just asthma)
Severe	Plasmapheresis + cyclophosphamide + steroids	Microscopic polyangiitis, granulomatosis with polyangiitis, polyarteritis nodosa, eosinophilic granulomatosis with polyangiitis with life-threatening or severe organ involvement
Specific	Intravenous gammaglobulin and aspirin	Kawasaki disease
	Antiviral drugs/plasmapheresis	Hepatitis B-related PAN, cryoglobulinaemic vasculitis related to hepatitis C
Experimental	Infliximab (but not etanercept)	Granulomatosis with polyangiitis
	Deoxyspergualin (gusperimus)	Granulomatosis with polyangiitis
	Mepolizumab (anti IL-5)	Eosinophilic granulomatosis with polyangiitis
	Immune ablation with autologous bone marrow transplantation	Severe granulomatosis with polyangiitis

immunosuppression outlined in the tables helps to prevent side-effects from the primary immunosuppressive therapy. Damage as a result of systemic vasculitis may need separate management, such as the management of hypertension from renal involvement or the use of bone protection for osteoporosis and fracture.

A rational basis for managing systemic vasculitis depends on appropriate diagnosis, accurate staging and assessment of disease activity prior to initiating treatment. In some patients specific therapy is available, but for the majority non-specific interference with the immune system is the most appropriate treatment. Small-vessel vasculitis with multi-system involvement requires intense immunosuppression with cyclophosphamide (or rituximab for MPA or GPA) and steroid, regardless of diagnosis. By contrast, larger-vessel vasculitis usually responds to steroids alone and many types of cutaneous vasculitis need no treatment at all.

Improvements in treatment will come only through better understanding of the underlying mechanisms of systemic vasculitis.

Drug toxicity remains a significant issue, as does the problem of relapsing disease, and this has been the basis for developing new strategies that are both more effective and less toxic for patients with systemic vasculitis. Rituximab, a monoclonal antibody directed against B cells, appears to be as effective as cyclophosphamide in ANCA-associated systemic vasculitis. We hope that new agents will be introduced within the next decade by linking a much better understanding of the pathogenesis of these diseases to the design or use of drugs with precise molecular targets.

SARCOIDOSIS

Sarcoidosis is a chronic inflammatory multi-system disease of unknown aetiology. It affects both sexes, all ages, all races and all geographical locations. The prevalence is 10–40 per 100,000. It is characterized by the presence of non-caseating granulomas.

CLINICAL FEATURES

(TABLE 17.10)

Sarcoidosis may be completely asymptomatic, or constitutional symptoms of fever, weight loss and fatigue may be prominent. Pulmonary manifestations are the most common feature. Musculoskeletal symptoms are varied, and can mimic many other rheumatological conditions. The onset is either acute or subacute and then follows either a self-limiting or chronic recurring course.

The acute arthritis typically affects the ankle joints; this is a combination of an arthritis, tenosynovitis and soft-tissue oedema. In other words, this is more typically a periarthritis than a true arthritis. This is usually non-erosive and self-limiting. The triad of arthritis, erythema nodosum (EN) and hilar lymphadenopathy is called Löfgren syndrome. Chronic arthritis is much less common and usually polyarticular. Bone involvement occurs in long-standing disease and is often asymptomatic.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis is wide and specific to the presentation. The most important differential diagnosis for the bilateral hilar lymphadenopthy (with and without EN) is tuberculosis.

PATHOGENESIS

The pathogenesis of sarcoidosis is due to stimulation of the host immune response to an unknown

Table 17.10 Clinical features of sarcoidosis

Organ	Frequency	Manifestation
Respiratory	90%	Hilar lymphadenopathy, pulmonary infiltrates and cor pulmonale
Bone and joints	13–38%	Arthralgia, periarthritis, acute arthritis, chronic arthritis, enthesitis, dactylitis, cystic bone lesions and periosteal reaction
Skin	30%	Erythema nodosum, hyperpigmented papules and lupus pernio
Eyes	20%	Uveitis, conjunctival granulomas and interstitial keratitis
Muscle	5–15%	Myopathy and, rarely, a raised creatine kinase
Neurological	5–10%	Headaches, cranial neuropathies, meningeal disease, mass, hypothalamic dysfunction, seizures and papilloedema
Salivary glands	3–9%	Sicca symptoms and parotid swelling
Liver	8%	Hepatomegaly
Spleen	6%	Splenomegaly
Kidney	5–10%	Nephrocalcinosis, hypertension, proteinuria, haematuria, renal failure
Cardiac	Reported	Conduction defects, arrhythmia, sudden death, cardiomyopathy and pericardial effusion
Vascular	Reported	Large- and medium-vessel vasculitis

foreign antigen. There is evidence of community, seasonal and geographical clustering.

INVESTIGATION

The typical pathological finding is the presence of non-caseating epithelioid and giant cell granulomas, combined with a compatible clinical and radiographic picture. Angiotensin converting enzyme (ACE) is produced by the epithelioid cells in granulomas. The serum ACE level may be raised, but the sensitivity and specificity of this test is only 47–55% and 77% respectively. Hypercalcaemia occurs in 5–7%, but is usually transient. The sarcoid macrophage is able to synthesize 1,25-dihydroxyvitamin D and parathyroid hormone-related protein.

TREATMENT

Drugs used in the treatment of sarcoidosis are shown in Table 17.11. Mild disease requires serial evaluation without treatment, or symptomatic treatment only. Progressive disease requires treatment to try to minimize end-organ damage.

RHEUMATIC FEVER

Rheumatic fever (RF) is a clinical syndrome in which inflammation of the skin, joints, heart and brain is attributed to cross-reaction with certain strains of group A streptococci. Today RF remains a leading cause of acquired heart disease in children and young adults in many parts of the world and, although uncommon in industrialized countries, there is evidence of a resurgence of RF activity, possibly due to changes in community strains of streptococci.

Table 17.11 Drugs used for sarcoidosis treatment

Drug	Indication
Non-steroidal anti-inflammatory drugs (NSAIDs), simple analgesics	Symptom control
Systemic corticosteroids	Parenchymal lung involvement, arthritis unresponsive to NSAIDs, extra-pulmonary disease
Topical corticosteroids	Eye disease
Hydroxychloroquine	Cutaneous disease
Methotrexate or azathioprine	Steroid-sparing agents for more severe disease
Ciclosporin or cyclophosphamide	Refractory and progressive disease
Anti-tumour necrosis factor	Case series only and variable results

Diagnosis of RF is based upon Jones' criteria (Table 17.12), a list of clinical manifestations compiled to avoid inaccurate diagnosis and now used to avoid morbidity from unnecessary antibiotic use and unwarranted anxiety. The probability of acute RF is high when there are *either* two major manifestations *or* one major and two minor manifestations *plus* laboratory evidence of antecedent group A streptococcal infection *sine qua non*. Suspicion arises at the presentation of an acutely inflamed joint, typically a flitting polyarthritis, or the presence of a new mitral or aortic regurgitant murmur at times of fever or sore throat. Other major criteria occur far less frequently; patients with Sydenham's chorea have involuntary, spasmodic, purposeless movements, are emotionally labile, and have changes in personality; erythema marginatum occurs typically on the trunk and has a pink serpigenous border, with central clearing, that changes shape before the observer's eyes; easily overlooked subcutaneous nodules are small, painless and localized over bony prominences (such as the spine) and in tendon sheaths. Evidence of streptococcal infection includes cultured growth from throat swabs, high antistreptolysin O titre (ASOT) (>800 Todd units), or raised anti-DNase B titre in the presence of a moderately raised ASOT. Patients with a high suspicion of RF should have a cardiological assessment including echocardiography.

Management of RF involves treatment of the acute inflammatory episode with NSAIDs (aspirin or ibuprofen) and antibiotics (penicillin), avoidance of recurrent episodes of RF with prophylactic antibiotics, and cardiac follow-up and intervention as required. The duration of prophylactic antibiotics is debated, but as a guide intramuscular benzathine penicillin (1.2 million units every 3 or 4 weeks) or oral penicillin (250–500 mg twice daily) may be given until the end of full-time education or for 5 years after the last acute attack. If carditis occurs, it is often mild and resolves spontaneously in about 80% of patients. If there is valvular involvement, prophylactic antibiotics

Table 17.12 Diagnosis of rheumatic fever using Jones' criteria requires laboratory evidence of group a streptococcal infection plus either two major manifestations or one major and two minor manifestations from:

Major Manifestations	Minor Manifestations	Evidence of Antecedent Streptococcal Infection
Carditis	Arthralgia	Positive throat culture
Polyarthritis	Fever	Positive rapid streptococcal antigen test
Chorea		Raised or rising ASOT ± antiDNase B
Erythema marginatum	Raised acute-phase reactants (erythrocyte sedimentation rate, C-reactive protein)	
Subcutaneous nodules	Prolonged PR interval	

are required at times of dental and surgical intervention to avoid bacterial endocarditis. The need for valve replacement is based upon the severity of cardiac failure.

IgG4 RELATED DISEASE

IgG4 related disease is a relatively newly recognized systemic inflammatory condition which is characterized by soft tissue swelling (also termed tumefaction), dense lymphoplasmacytic infiltrates containing significant numbers of IgG4-positive plasma cells, an irregularly whorled pattern of fibrosis (referred to as storiform fibrosis) and usually with an elevated serum IgG4 concentration. It particularly affects middle aged and elderly men. Although the dominant manifestation is sclerosing or autoimmune pancreatitis, extra-pancreatic features include thyroiditis, swollen salivary glands, lymph node enlargement, mediastinal and retroperitoneal fibrosis with associated periaortitis, aortitis, tubulointerstitial nephritis; in fact, almost any organ can be involved. Glucocorticoids are the main treatment, but some cases progress and the course can be relapsing and remitting.

FURTHER READING

Barbhaiya M, Erkan D. Primary thrombosis prophylaxis in antiphospholipid antibody-positive patients: where do we stand? Curr Rheumatol Rep 2011; 13:59–69.

Bertsias G, Ioannidis JP, Boletis J et al; Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. Ann Rheum Dis 2008; 67:195–205.

Dasgupta B, Borg FA, Hassan N et al; BSR and BHPR Standards, Guidelines and Audit Working Group. BSR and BHPR guidelines for the management of giant cell arteritis. Rheumatology (Oxford) 2010; 49:1594–1597.

Denton CP, Black CM. Scleroderma: clinical and pathological advances. Best Pract Res Clin Rheumatol 2004 18:271–290.

Dhillon R, Newton L, Rudd PT et al. Management of Kawasaki disease in the British Isles. Arch Dis Child 1993; 69:631–638.

Jennette JC, Falk RJ, Bacon PA et al. Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides Arthritis Rheumatism. Arthritis Rheum 2012 Oct 8. doi: 10.1002/art.37715.

Mukhtyar C, Guillevin L, Cid MC et al; European Vasculitis Study Group. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis 2009; 68:310–317.

Ramos-Casals M, Tzioufas AG, Font J. Primary Sjögren's syndrome: new clinical and therapeutic concepts. Ann Rheum Dis 2005; 64:347–354.

Umehara H, Okazaki K, Masaki Y et al. A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details. Mod Rheumatol 2012; 22:1–14.

Van der Woude FJ, Rasmussen N, Lobatto S et al. Autoantibodies against neutrophils and monocytes: tool for diagnosis and marker of disease activity in Wegener's granulomatosis. Lancet 1985; 1:425–429.

18

SYSTEMIC COMPLICATIONS OF RHEUMATIC DISEASES AND RARE ARTHROPATHIES

Raashid Luqmani, Nick Wilkinson and Benjamin Joseph

Cases relevant to this chapter

78, 89–90, 94

Essential facts

1. Many inflammatory rheumatic diseases are associated with systemic features, including weight loss, malaise, weakness and fever.
2. Lung alveolitis and fibrosis are common long-term complication of rheumatoid arthritis, systemic lupus erythematosus (SLE) and diffuse cutaneous scleroderma.
3. The risk of developing malignancy, especially non-Hodgkin's lymphoma, is five times greater in patients with inflammatory rheumatic disease, compared with that in healthy individuals.

The inflammatory arthritides, the autoimmune rheumatic diseases, and their treatment may have significant effects outside the bones and joints. Table 18.1 gives some examples and outlines the systems that might be affected. Some of this information is expanded on in other chapters of the book. This section provides a brief overview of problems to consider in everyday practice.

SYSTEMIC FEATURES

Many inflammatory rheumatic diseases are associated with significant systemic features, which may be responsible for weight loss, malaise, weakness and fever. This makes the differential diagnosis wider, with concerns over whether or not patients have malignancy, infection or drug toxicity.

CUTANEOUS PROBLEMS

The most common manifestations are drug reactions; typically they will resolve on discontinuing the offending agent. Patients with rheumatic disease are often treated with combinations of drugs for their main condition as well as associated co-morbidity. It may be necessary to find the offending drug by sequentially stopping the most recently prescribed drug, the next most recently prescribed drug, and so on. Some agents such as allopurinol are well known to cause a rash, if given in too high a dose, or in standard doses, for example the anti-tumour necrosis factor (TNF) agents commonly cause an injection-site reaction. For most drugs, however, the skin rash is unpredictable, and varies from trivial to life-threatening. Many rheumatic

Table 18.1 Summary of systemic complications of rheumatic diseases and their management

System	Problems	Examples
Systemic	Weight loss, fever, malaise	Many inflammatory diseases
Cutaneous	Drug reactions; rashes; vasculitis; Raynaud's; skin fibrosis	Most drugs; RA, SLE, psoriatic arthritis; scleroderma; autoimmune rheumatic disease; vasculitis
Neurological	Peripheral sensory and motor neuropathies; mononeuritis multiplex; compression of nerves or spinal cord; cerebral infarction; cranial nerve palsies	RA, SLE and autoimmune rheumatic diseases; vasculitis
Pulmonary	Pulmonary fibrosis/alveolitis; pleurisy and pleural effusions; pulmonary infiltrates/bleeding; nodules; bronchial ulceration; bronchial dryness	RA, SLE, autoimmune rheumatic diseases; vasculitis
Cardiovascular	Increased atherosclerosis leading to premature coronary artery disease and cerebrovascular disease; vascular inflammation of all sizes of blood vessel; valvular heart disease; thrombotic events in arteries or veins	SLE and RA; vasculitis; effect of NSAIDs; anti-phospholipid antibody syndrome
Gastrointestinal	Peptic ulcer disease; liver fibrosis; liver function abnormalities; overlap between inflammatory bowel disease and arthritis	NSAID use; methotrexate and sulfasalazine; Crohn's disease-related arthritis
Genitourinary problems	Renal impairment; nephritis; renal tract infections; dyspareunia; infertility; pregnancy loss	Vasculitis, SLE and other connective tissue diseases; drug effects; anti-phospholipid antibody syndrome
Eyes/mucous membranes	Oral/genital ulcers, dryness of mouth and eyes; uveitis; cataracts	Behçet syndrome; SLE, RA, Sjögren syndrome and other autoimmune rheumatic diseases; ankylosing spondylitis, juvenile arthritis; steroids
Haematological	Anaemia of chronic disease or gastrointestinal blood loss; neutropenia; thrombocytopenia; splenomegaly	RA, SLE and autoimmune rheumatic diseases; NSAID effects
Lymphoma risk/ cancer risk	Increased risk of lymphoma; autoimmune rheumatic diseases presenting with tumours; risk of immunosuppressive agents	RA, SLE and all autoimmune rheumatic diseases; all immunosuppressive agents
Infection	Joint infections usually derived from bacteraemia, local spread from osteomyelitis or direct trauma to the joint. Usually affects single joint. Patients with rheumatoid arthritis are more likely to suffer infections, especially if treated with immunosuppressive agents	Patients with pre-existing inflammatory joint disease are at greatest risk
Amyloid	Chronic inflammation leading to deposition of inert protein which interferes with affected organ function	Long-standing uncontrolled inflammation in juvenile arthritis, rheumatoid arthritis and spondyloarthritis

diseases are associated with rashes; systemic lupus erythematosus (SLE) is the most typical, resulting in a photosensitive eruption on light-exposed skin. Psoriatic rashes can be very obvious if present on the trunk or arms, but subtle and worth looking for in the hairline, natal cleft or umbilicus. The changes to skin in scleroderma are of thickening and discoloration, often accompanied by Raynaud's phenomenon. Vasculitic rashes are not specific for individual conditions; purpura is a common

manifestation, but nail-edge lesions and splinter haemorrhages can also occur.

NEUROLOGICAL PROBLEMS

Long-standing rheumatoid arthritis (RA) predisposes to sensory peripheral neuropathy (glove and stocking distribution). Chronic peripheral nerve injury may occur from synovitis in the wrist compressing the median nerve and resulting in carpal tunnel syndrome. Acute cord compression is a feature of long-standing RA with instability of the cervical spine, due to erosive disease of the odontoid peg, ischaemic pressure from pannus, and compounded by instability of the atlanto-axial articulation. Mononeuritis multiplex can arise as a result of different forms of vasculitis causing nerve injury. The brain may be at risk in SLE as a result of ischaemia through vasculitis, clotting of vessels by anti-cardiolipin antibody syndrome, or the vasculopathy of SLE. Mechanical problems in the spine may lead to nerve or cord compression depending on the level of injury and its severity. Careful evaluation of the nervous system is important in any patient with back pain, especially if they have a history of pain or numbness in a peripheral limb.

PULMONARY PROBLEMS

Lung alveolitis and fibrosis are common long-term complications of RA, SLE and scleroderma (especially diffuse cutaneous scleroderma). The pleural sac may be inflamed as part of a generalized polyserositis. In SLE and the vasculitides this is often acute with painful pleuritic pain, but in RA it is often more insidious leading to quite large pleural effusions and, eventually, to breathlessness on exertion. Rheumatoid lung nodules may be seen as isolated peripheral shadows on a chest radiograph, raising suspicion of tumour; they may even liquefy in the centre, giving rise to a fluid level and concern about possible abscess. Occasionally lung nodules occur prior to the onset of joint symptoms, causing considerable diagnostic confusion. Patients with systemic vasculitis affecting small vessels may develop alveolar inflammation and haemorrhage, typically in microscopic polyangiitis and anti-glomerular basement membrane disease (Goodpasture syndrome). Haemorrhage may also occur in granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome); however, diffuse infiltrates and/or nodules are more common. Bronchial and tracheal ulceration and inflammation leading to stenosis are characteristic findings in granulomatosis with polyangiitis. Patients with Sjögren syndrome can develop dryness in the trachea and bronchi, leading to cough, and predisposing to chest infections through impaired clearance of secretions.

CARDIOVASCULAR PROBLEMS

Cardiovascular risk of hypertension and cardiac failure on drug therapy, especially non-steroidal anti-inflammatory drugs (NSAIDs), is well recognized and has led to a re-evaluation of the role of NSAIDs in the long-term management of rheumatic diseases. Cardiovascular morbidity and mortality in all rheumatic diseases, especially SLE, is mediated via accelerated atherosclerosis. Atherosclerosis itself is recognized as an inflammatory condition. The risk of myocardial infarction in some patients with RA is similar to that for patients with type 2 diabetes mellitus.

GASTROINTESTINAL PROBLEMS

Gastrointestinal complications of NSAIDs and other drugs used to manage RA are common. Peptic ulcer, bleeding and perforation are highest in elderly patients or those also receiving steroid therapy, and NSAIDs should be avoided or used with caution in these patients. Liver function abnormalities are common in patients treated with methotrexate, leflunomide and sulfasalazine. Liver fibrosis is much less common. Small bowel inflammation may be caused by NSAIDs leading to abdominal pain, anaemia with an iron-deficient blood picture and normal upper gastrointestinal endoscopy. Small bowel examination of these patients may reveal ulcers or scarred areas with membrane formation (NSAID enteropathy).

GENITOURINARY PROBLEMS

Urinary tract infections are common in female patients with rheumatic diseases, especially if they are on immunosuppressive drugs. Dyspareunia due to dryness of the vagina is relatively common in patients with Sjögren syndrome, although patients may not raise the issue owing to embarrassment, or thinking that it is not connected to their rheumatic disease. It can be managed with simple lubricant creams. Small-vessel systemic vasculitides and

SLE can involve the glomeruli, leading to kidney inflammation and loss of function. All such patients should have their blood pressure checked, urine tested for blood and protein, and renal function assessed regularly. Unexplained haematuria should be investigated thoroughly in patients who have been treated with cyclophosphamide to look for evidence of urothelial cancer.

EYES/MUCOUS MEMBRANES

Oral and genital ulceration occurs as a result of disease, such as SLE or Behçet syndrome. Oral ulcers may also be caused by drug therapy such as methotrexate. Dry eyes and mouth are common in primary and secondary Sjögren syndrome. Patients with ankylosing spondylitis should be advised of the 20% risk of acute anterior uveitis; patients with juvenile idiopathic arthritis (JIA) (especially antinuclear antibody (ANA)-positive oligoarthritis) should be screened for chronic uveitis. Long-term steroid use predisposes to cataract formation.

HAEMATOLOGICAL PROBLEMS

A low haemoglobin level is often secondary to either bleeding due to NSAID therapy, or active inflammatory disease (in which case it will not respond to oral iron). Haemolysis may occur in connective tissue diseases especially SLE. SLE may induce neutropenia or thrombocytopenia. In some cases, resistant to systemic immunosuppression, splenectomy is justified, but patients will need pneumococcal vaccine prior to splenectomy followed by lifelong penicillin V administration. Thrombocytopenia typically occurs in primary anti-phospholipid antibody syndrome. A small number of patients with RA develop splenomegaly, thrombocytopenia and neutropenia (Felty syndrome).

LYMPHOMA RISK/CANCER RISK

All patients with inflammatory rheumatic disease have a 5-fold increased risk of developing a malignancy, especially non-Hodgkin's lymphoma, compared with controls. If patients are treated with immunosuppressive drugs, such as azathioprine, the risk may double (i.e. to 10 times normal). More potent immunosuppressive agents such as cyclophosphamide increase the risk of other tumours, especially bladder cancer, because one of the main metabolites of cyclophosphamide, acrolein, is excreted via the kidneys.

INFECTION RISK

Joint infection is more likely in patients with inflammatory joint disease than in patients with previously normal joints; it is important to consider the possibility of infection in patients with RA presenting with a "flare" of arthritis affecting a single joint. Immunosuppressive drugs used to treat rheumatic diseases carry a significant risk of infection, especially the more potent agents. Use of specific cytokine inhibitors, such as anti-TNF, is a particular concern, and has been associated with an increased incidence of tuberculosis (TB) in predisposed individuals.

AMYLOID RISK

Systemic amyloidosis is characterized by the production and deposition of inert insoluble protein in vessels and organs, eventually leading to failure. Primary (AL) amyloid (usually due to multiple myeloma, rarely congenital amyloidosis) is caused by excessive deposition of immunoglobulin light chains and is a form of monoclonal gammopathy. Secondary (AA) amyloid is produced from inflammatory (such as serum amyloid A protein) and non-inflammatory proteins, hormones or apolipoproteins (with genetic predisposition in Alzheimer's disease). AA amyloid previously accounted for organ failure and death in cases of juvenile idiopathic arthritis (JIA) and RA. Better management of arthritis has resulted in substantial improvement in overall survival, including a significant fall in the number of cases of amyloid. The most common cause (in 64%) of amyloid in Turkey is familial Mediterranean fever (FMF); 16% is due to infectious diseases, such as TB and other chronic lung infections (e.g. bronchiectasis), and RA accounts for 4% of cases and spondylo-arthropathy is the cause in 3%. Most patients present with peripheral oedema and proteinuria. Enlargement of the liver or spleen may be present in 11–17%. In 38% of cases there is progression to end-stage renal disease.

RARE ARTHROPATHIES

Adult Still's disease is a rare inflammatory disorder resulting in typical features of fever, arthralgia, rash and leucocytosis. Other clinical manifestations include sore throat, lymphadenopathy and/or

splenomegaly, and liver dysfunction. Patients do not have rheumatoid factor or ANA; systemic markers of inflammation are raised and ferritin levels are characteristically very high. Treatment is usually with steroids for systemic manifestations, and methotrexate or anti-TNF therapy for arthritis.

SYSTEMIC INFLAMMATORY CONDITIONS IN CHILDHOOD

Although individually many of the multi-system inflammatory diseases are rare in childhood, each with an incidence of 0.1–1 in 10 000, collectively they form a significant proportion of the paediatric rheumatology workload. This is attributable to complex presentation and, at times, a relentless progression requiring constant screening of renal, pulmonary, cardiovascular and cerebral function, along with complications from long-term therapy. Furthermore, as presentation may mimic other childhood diseases, both common (e.g. infectious diseases) and sinister (e.g. leukaemia and lymphoma), general physicians are frequently involved in the diagnostic challenge.

For ease of consideration, these diseases have been classified by a characteristic feature of pyrexia or rash. Overlap between these diseases is common, to such an extent that the diagnostic label may change with time as the true nature of the disease becomes apparent. As a result, it is essential to perform regular monitoring of symptoms, signs and laboratory screening tests to challenge early diagnoses and re-evaluate therapy. To avoid repetition, this section focuses on paediatric aspects of inflammatory disease and, where relevant, the reader is referred to other sections for a more general account of the disease.

PYREXIAL PRESENTATION

Differentiating this group of non-infectious inflammatory diseases, identified in Table 18.2, from self-limiting paediatric infectious disease relies upon awareness of inflammatory non-infective causes, and a detailed history and examination to identify characteristic features and symptom complexes.

Kawasaki disease should be considered early in any child with a high spiking pyrexial illness (39–40°C) with negative blood cultures and unresponsive to antibiotics. This is because timely treatment with intravenous immunoglobulins and aspirin will avert life-threatening coronary aneurysms. The diagnosis is made when there are four of five diagnostic criteria in addition to 5 days of fever: (i) conjunctivitis and (ii) oral mucosal changes each occur in 90% of cases, (iii) rash in 80%, and (iv) lymphadenopathy and (v) palmar erythema occur in 70%. In an infant, some criteria may be absent, but inconsolable irritability in the absence of meningitis should raise suspicion.

Other important diagnoses to consider are leukaemia, lymphoma and neuroblastoma, which may present with fever and constitutional disturbance. A blood count and film discussed with the haematologist may help in the diagnosis of leukaemia, the commonest childhood malignancy to result in musculoskeletal pain and arthritis, but a bone marrow aspirate is definitive.

In systemic-onset JIA there is a quotidian fever, which spikes to more than 39°C once or twice a day and always returns to normal. It may be accompanied by a salmon-pink or urticarial rash, and may precede the polyarthropathy by months. A rare and life-threatening association with systemic-onset JIA, SLE, and disorders of infectious and neoplastic origin is macrophage activation syndrome, characterized by abnormalities of liver function, a rapid fall in erythrocyte sedimentation rate (ESR) and bleeding diathesis. Periodic fever syndromes and vasculitic syndromes may also present with fever, rash and arthritis. They are often distinguished by the key features and investigations identified in Table 18.2, although many such diagnoses remain undifferentiated. Of the microbiological investigations the throat swab is important in determining the presence of streptococcus.

The periodic fever syndromes are rare, but important, systemic conditions that cause intermittent episodes of systemic inflammation, with organ involvement, especially in the abdomen, joints and skin. They occur predominantly in children and young adults. They are inherited disorders of the immune system, due to defects in the genes that control cytokine function. Familial Mediterranean Fever (FMF) is the most common variant; others in this group include hypergammaglobulinaemia D and periodic fever syndrome (HIDS), TNF receptor-associated periodic syndrome (TRAPS), and the family of cryopyrin-associated periodic syndromes: Muckle–Wells syndrome, familial cold autoinflammatory syndrome (FCAS), and neonatal onset multisystem inflammatory disease (NOMID).

Table 18.2 Pyrexial presentation of multi-system inflammatory disease in childhood

Diagnosis	Characteristic features	Investigation
Kawasaki disease	High spiking fever (39–40°C) > 5 days 4 of 5 criteria (*see text*) (± irritability in infant) Coronary artery aneurysms if untreated	Suspicion Platelets, echocardiogram
Systemic-onset juvenile idiopathic arthritis (JIA)	Quotidian fever and evanescent rash may precede polyarthritis by months (*see text and Chapter 27*). Serositis, hepato-splenomegaly, lymphadenopathy	Platelets, echocardiogram
Neoplasia (leukaemia, lymphoma, neuroblastoma)	Always consider if multi-system disease of indeterminate cause, and if normal/low platelets	Blood film; bone marrow aspirate; abdominal USS/CT
Post-infectious illnesses • Arthritis and eye disease • Rheumatic fever • Lyme disease	 Preceding enteric infection Jones' criteria (*see Chapter 17*) Rash and arthritis following a tick bite (*see Chapter 16*)	Stool culture Throat swab, ASOT Anti-DNAse b *Borrelia*
Other vasculitides • Polyarteritis nodosa • Granlulomatosis with polyangiitis • Microscopic polyangiitis • Churg–Strauss syndrome • Takayasu's arteritis • Behçet's disease	} Fever, weight loss, fatigue, *plus one or more of:* – skin or mucosal lesions – focal neurological deficit – myositis and arthritis – nephritis/hypertension – breathlessness with abnormal chest radiograph – limb claudication	Renal angiography MRI/MRA Tissue biopsy ANCA
Periodic fever syndromes • Familial Mediterranean fever • Hyper-IgD syndrome • TNF associated periodic syndrome • Muckle–Wells syndrome • PFAPA • Deficiency of the interleukin-1 receptor antagonist (DIRA)	*60% of periodic fevers are unclassifiable* 1–3 days of fever, peritoneal/pleuropericardial pain, arthritis 3–7 days of fever, erythema, aggressive arthritis >7 days of fever and ocular signs Prolonged fever, urticaria and deafness **P**eriodic **F**ever, **A**phthous ulcer, **P**haryngitis, **A**denitis Sterile osteomyelitis, periostitis and pustulosis	Genetic analysis IgD; *MVK* analysis TNFα receptor study Hearing test
Macrophage activation syndrome (haemophagocytic lymphohistiocytosis)	Life-threatening complication of systemic onset JIA, SLE, virus Persistent fever, lymphadenopathy, hepatic failure and purpura; with sudden fall in ESR and platelet count and marked rise in LFTs and ferritin	Bone marrow aspiration

SKIN PRESENTATION

Diagnoses typically associated with a characteristic rash (Table 18.3), such as Henoch–Schönlein purpura, SLE and juvenile dermatomyositis (JDM), also present with constitutional symptoms of sustained fever, fatigue, anorexia and weight loss.

The onset of SLE occurs in childhood in 20% of patients, and in the young has similar clinical features and management to those in adults (see Chapter 17). A malar rash is also seen in JDM, but the violaceous heliotrope of the upper eyelid, Gottron's papules and peri-ungual erythema are classical. MRI of the thigh is used to confirm the inflammatory myopathy. A recurrent polycyclic course is observed in 60% of patients with JDM and may involve the joints, gastrointestinal tract, lungs and central nervous system. Treatment includes steroids and methotrexate, but in severe cases cyclophosphamide is used.

The rash of juvenile sarcoid, distinct from sarcoid in adolescents and adults, is described as 'sago', and localized scleroderma, more common in children than adults, is typically of a linear

Table 18.3 Skin presentation of multi-system inflammatory disease in childhood

Diagnosis	Characteristic features	Investigation
Henoch–Schönlein Purpura	Palpable purpura of classical distribution (*see* Chapter 17). Possible intussusception, arthralgia, nephritis	Urinalysis, blood pressure
Post-streptococcal vasculitis (cutaneous polyarteritis)	Palpable purpura with palmar involvement; may be associated with arthritis and transient neuropathy	Throat swab, ASOT, anti-DNase b
Systemic Lupus Erythematosus	Rash in 75% of patients; malar rash in 50% of patients Lupus nephritis and CNS disorder determine outcome	ANA, dsDNA, complement, ESR, lymphocyte count, urinary protein
Juvenile Dermatomyositis	Violaceous heliotrope on upper eyelids, Gottron's papules, peri-ungual erythema and proximal inflammatory myopathy. Also synovitis; GI ulceration; pulmonary fibrosis; CNS disease (rare)	MRI/USS of thigh Muscle enzymes (Endoscopy, CT chest)
Juvenile Sarcoid	'Sago' rash, boggy arthritis, eye disease	Biopsy
Scleroderma	Linear waxy thickened skin resulting in limb deformity Also morphoea; systemic sclerosis very rare	Thermography Capillaroscopy
Mixed Connective Tissue Disease	Raynaud's and arthropathy	Anti-RNP
Neonatal Lupus Erythematosus	Inflammation of skin, liver and haematological complications. Heart block permanent	ECG, ECHO
NOMID (Neonatal onset multisystem inflammatory disease)	Onset in infancy of triad of rash, symmetrical arthropathy and chronic meningitis	MRI, lumbar puncture

rather than morphoea form of distribution. Sarcoid and scleroderma may respond to steroids and methotrexate.

Of the two inflammatory illnesses peculiar to the first few months of life, inflammation in NOMID (see Table 18.3) is progressive, whereas in neonatal lupus, attributable to transplacental passage of maternal autoantibodies, it is transient. However, the heart block from neonatal lupus can be permanent.

FURTHER READING

Clarke JT, Werth VP. Rheumatic manifestations of skin disease. Curr Opin Rheumatol 2010; 22:78–84.

Grateau G. Musculoskeletal disorders in secondary amyloidosis and hereditary fevers. Best Pract Res Clin Rheumatol 2003; 17:929–944.

Grateau G. Clinical and genetic aspects of the hereditary periodic fever syndromes. Rheumatology 2004; 43:410–415.

Moreland LW, Curtis JR. Systemic nonarticular manifestations of rheumatoid arthritis: focus on inflammatory mechanisms. Semin Arthritis Rheum 2009; 39:132–143.

Tuglular S, Yalcinkaya F, Paydas S et al. A retrospective analysis for aetiology and clinical findings of 287 secondary amyloidosis cases in Turkey. Nephrol Dial Transplant 2002; 17:2003–2005.

19

BONE DISORDERS

M. Kassim Javaid, Julia L. Newton and Raashid Luqmani

Cases relevant to this chapter

37, 41, 45, 53, 63, 73, 82, 92, 95, 98

Essential facts

1. Osteoporosis is the most common metabolic bone disorder.
2. It is important to look for underlying causes of osteoporosis.
3. Osteomalacia is under-diagnosed in the UK.
4. The commonest cause of osteomalacia is vitamin D deficiency.
5. Paget's disease is due to overactivity of the osteoclast.
6. Osteonecrosis typically presents with pain and causes morbidity in young active people.
7. Causes of osteonecrosis include increased intra-osseous pressure, fat emboli, external compression of blood supply, direct osteocyte death, mechanical stress and increased thrombotic tendency.
8. Magnetic resonance imaging is the most sensitive investigation for early osteonecrosis.

OSTEOPOROSIS

Osteoporosis is the most common bone disorder and the pathophysiology is discussed in detail in Chapter 2. It is a significant cause of morbidity, increased disability and mortality, and imposes a major economic burden on the NHS. There is a 10–30% increase in mortality in the 12 months following a hip fracture. Osteoporosis is defined as a condition of skeletal fragility characterized by reduced bone mass and microarchitectural deterioration predisposing a person to an increased risk of fracture. The following mechanisms are responsible either alone or in combination: a failure to achieve adequate peak bone mass, an increase in bone resorption and a reduction in bone formation. It is more common in women and in the Caucasian population. Post-menopausal bone loss is the most significant cause of osteoporosis (Box 19.1).

CLINICAL FEATURES

Osteoporosis is asymptomatic. Fragility fractures are the main consequence of osteoporosis, and can present either with fracture or with pain or loss of height with development of a thoracic kyphosis (Fig. 19.1). If the osteoporosis is secondary to another disorder, for example Cushing syndrome, features of the underlying disease may be the initial presenting complaint. The bones most frequently affected by a fragility fracture are the hip, vertebra and wrist. The risk is related directly to age, and is due to a combination of age-related bone loss and an increased rate of falls (Box 19.2).

AETIOLOGY

As described in Chapter 2, bone remodelling is a dynamic process, and the resorption and laying down of new bone are tightly coupled processes.

Box 19.1
Causes of osteoporosis

- Post-menopausal oestrogen deficiency
- Corticosteroid excess (iatrogenic or Cushing's disease)
- Hyperparathyroidism
- Malabsorption, e.g. coeliac disease
- Osteomalacia
- Hyperthyroidism
- Anorexia nervosa
- Hypopituitarism, hypogonadism
- Multiple myeloma
- Osteogenesis imperfecta

Box 19.2
Risk factors for the development of osteoporosis

- Previous fracture
- Family history of fragility fracture
- Excess alcohol
- Smoking
- Corticosteroid treatment
- Amenorrhoea for 6 months (excluding pregnancy)
- Late menarche
- Early menopause including surgical menopause
- Low body weight
- Immobility/physical inactivity
- Drugs – heparin, phenytoin
- Inflammatory diseases – rheumatoid arthritis, ankylosing spondylitis, Crohn's disease
- Diabetes, stroke

In osteoporosis there is an imbalance of osteoclast and osteoblast activity. There may also be an increase in the initiation of new bone remodelling cycles (activation frequency). The resorption phase is faster than the formation phase, which can further contribute to osteoporosis when the activation frequency is high. Genetic factors contribute strongly to peak bone mass and to the rate of bone loss after peak mass has been achieved. Oestrogen has a central role in both men and women, but men do not have the same dramatic changes in sex hormone levels during middle age as women do (Table 19.1).

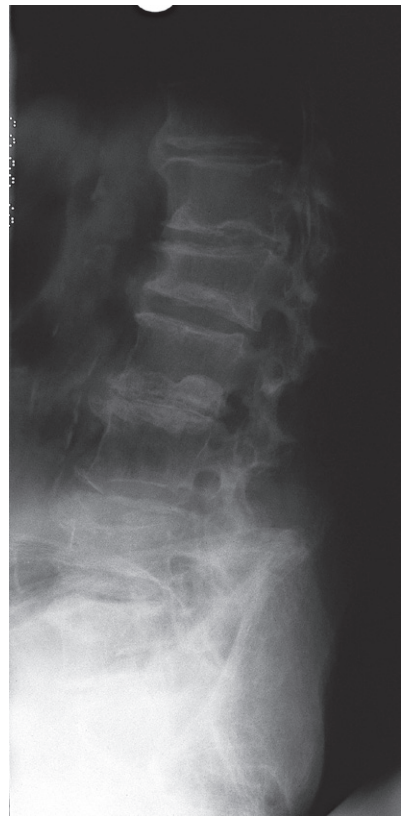


FIGURE 19.1 Osteoporotic fracture of the spine showing vertebral collapse

DIAGNOSIS

Bone mineral density (BMD) is measured at the lumbar spine (L1–L4) and proximal femur (femoral neck and total hip) using dual-energy X-ray absorptiometry (DEXA) scanning. A T score of less than –2.5 indicates osteoporosis and a T score of between –1.0 and –2.5 indicates osteopenia.

INVESTIGATIONS

Box 19.3 outlines the investigations for osteoporosis.

BONE TURNOVER MARKERS

Bone turnover marker levels (Table 19.2) are affected by a number of factors:

- Significant inter- and intra-individual variation
- Turnover parallels growth velocity during childhood and fracture healing
- Circadian rhythm
- Seasonal variation (follows vitamin D levels through seasons)
- Medication (bisphosphonates, corticosteroids)

Table 19.1 Underlying mechanisms of osteoporosis

Disease	Mechanism
Post-menopausal osteoporosis	Increased rate of remodelling, uncoupling of bone formation and resorption, increased osteocyte apoptosis, low oestrogen increases T-cell production of IL-1 and TNFα (both are osteoclastogenic), low oestrogen reduces osteoprotegerin (a regulator of bone turnover)
Hyperparathyroidism	Increased bone turnover
Hyperthyroidism	Increased bone turnover
Cushing's disease	Uncoupling of bone resorption and formation
Corticosteroid treatment	Uncoupling of bone resorption and formation; increased osteocyte apoptosis, renal calcium loss and secondary hyperparathyroidism
Vitamin D deficiency	Direct and secondary hyperparathyroidism
Calcium deficiency	Secondary hyperparathyroidism

Table 19.2 Bone turnover markers

Resorption	Serum *C*- and *N*-telopeptides of type I collagen crosslinks (urine)
Formation	Pro-collagen type I peptide (PINP), bone-specific alkaline phosphatase, osteocalcin, *C*- and *N*-terminal pro-peptides of type I collagen

Box 19.3
Investigations for osteoporosis

- Bone profile (calcium, phosphate, alkaline phosphatase, parathyroid hormone)
- 25-Hydroxyvitamin D and PTH
- Renal function
- Thyroid and liver function
- Multiple myeloma screen (erythrocyte sedimentation rate, serum immunoglobulins and protein electrophoresis, urinary Bence Jones protein)
- Consider thyroid function tests, coeliac screen, urinary cortisol, testosterone, oestradiol, luteinizing hormone, follicle stimulating hormone, prolactin

- The presence of other disease, overt or subclinical, that affects bone turnover (Paget's disease, thyroid disease, hyperparathyroidism, osteomalacia)
- Renal failure causes a false increase in bone turnover markers.

TREATMENT

The aim of treatment is to reduce the incidence of fragility fractures. A readily available on-line calculator can be used to establish absolute risk of future fracture (FRAX™), which is an improvement over the T score, but there are still limitations. Lifestyle modification measures should be discussed with all patients, including improving calcium intake (equivalent of 1 pint of milk a day or 600 mg/day), supplemental vitamin D (50–75 nmol/l), weight-bearing exercise, healthy body mass index, smoking cessation and reduction of alcohol consumption if excessive. Balance and exercise classes promote increased bone density, but also help in fall prevention. Hip protectors have been advocated, but compliance is poor and effectiveness has been questioned. Current drug options are shown in Table 19.3, but fracture still occurs despite appropriate treatment.

Monitoring treatment includes the use of bone turnover markers to assess whether remodelling rates have been significantly suppressed by anti-resorptive medication. In a minority of patients treated with bisphosphonates, atypical subtrochanteric fractures occur, and in patients undergoing cancer therapy with intravenous zoledronate, osteonecrosis of the jaw has occurred. Hence therapy is usually recommended for 5 years, after which the need for future treatment is reviewed.

OSTEOMALACIA

Osteomalacia and rickets are due to vitamin D deficiency, which causes an accumulation of osteoid and poor mineralization of bone. The clinical picture is called rickets or osteomalacia, depending upon whether it is before or after cessation of growth respectively.

VITAMIN D METABOLISM

Vitamin D is a pro-hormone formed by the action of ultraviolet radiation on its precursor (7-dehydrocholesterol) in the skin. It undergoes

Table 19.3 Drugs for osteoporosis, with mechanism of action and side effects

Drug	Mechanism of Action	Side Effects
Calcium and vitamin D	Reduces hyperparathyroidism of increasing age	Hypercalcaemia
Bisphosphonates	Inhibition of osteoclast activity, increased osteoclast programmed cell death, slowing of the remodelling cycle allowing full mineralization of new bone to occur	Oesophagitis
PTH (teriparatide) – synthetic *N*-terminal portion of PTH	Large increase in bone formation (anabolic) and a modest increase in resorption; increased periosteal apposition (deposition of bone on the surface to increase strength)	Headaches, rarely; hypercalcaemia, nausea, leg cramps
Strontium ranelate	Mechanism is not fully understood. Has anti-resorptive and anabolic effects	Diarrhoea, headache, nausea, deep vein thrombosis (DVT)
HRT (hormone replacement therapy)	Reduces bone resorption by blocking cytokine signalling to the osteoclast	Risk of breast cancer, DVT, increased cardiovascular risk
SERMs (selective (o)estrogen receptor modulators)	Reduces bone resorption	Increased DVT risk and hot flushes (reduction in breast cancer risk)
Denosumab	Inactivates RANKL and so inhibits osteoclast maturation	Usually well tolerated, but may cause diarrhoea, headache, nausea and tiredness.

two hydroxylation steps to become an active hormone. The first, the 25-hydroxylation step to become 25-hydroxycholecalciferol, occurs in the liver, and the second, in which the 25-hydroxycholecalciferol is converted to 1,25-dihydroxycholecalciferol (calcitriol), takes place in the kidney for endocrine function but in most body tissues for autocrine/paracrine actions.

CLINICAL FEATURES

In rickets, the areas of bone most severely affected are the metaphyses of long bones leading to a characteristic clinical and radiological picture (Box 19.4).

The signs and symptoms of osteomalacia are often vague and the diagnosis may be missed unless considered specifically (Fig. 19.2). These clinical features and the typical radiological findings are listed in Table 19.4. There is a considerable differential diagnosis for osteomalacia (Box 19.5).

Box 19.4
Clinical features of rickets

- Craniotabes of the skull
- Enlarged epiphyses of wrists
- 'Rickety rosary' of osteochondral junctions
- Harrison's sulcus in the rib cage
- Bow, knock knee or windswept leg deformities
- Floppy baby
- Dental abnormalities
- Delayed growth

INVESTIGATIONS

The typical biochemical findings for osteomalacia and other disorders of bone are shown for comparison in Table 19.5. As well as a bone profile (calcium, phosphate, parathyroid hormone, alkaline phosphatase), urea and electrolytes, and serum ferritin will identify any evidence of renal failure or malabsorption as an underlying cause for osteomalacia.

AETIOLOGY

Osteomalacia is usually caused by vitamin D deficiency, but there are other rarer causes to consider (Table 19.6). The main cause of hypovitaminosis D is a lack of sun exposure; the two largest at-risk groups are women and children screened from the

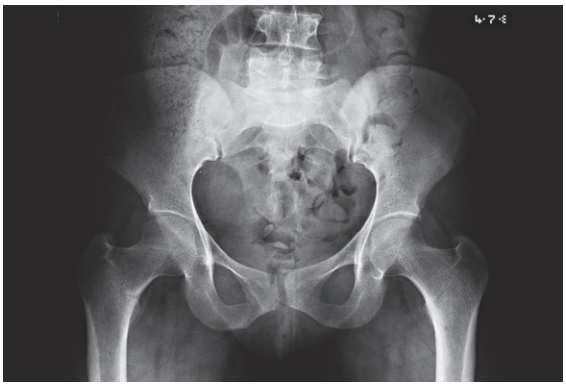


FIGURE 19.2 Osteomalacia in a young Asian woman complaining of pain in the hips – note the Looser's zone in the right femoral neck

Box 19.5
Differential diagnosis of osteomalacia

- Osteoporosis
- Fibromyalgia
- Polymyalgia rheumatica
- Polymyositis
- Rheumatoid arthritis
- Multiple myeloma
- Metastatic bone disease

Table 19.4 Features of osteomalacia

Symptoms	Bone pain, proximal myopathy with normal creatine kinase, pain from a pathological fracture, polyarthralgia
Signs	Bone tenderness, waddling gait, proximal weakness, tetany (hypocalcaemia)
Radiology	Looser's zone (cortical fractures on the compression side of the bone), pathological fractures, demineralization, features of hyperparathyroidism – chondrocalcinosis, subperiosteal erosions
Biochemistry	Calcium – normal or low; phosphate – normal or low; bone-specific alkaline phosphatase – normal or increased; 25-hydroxyvitamin D – low; 1,25-hydroxyvitamin D – normal or low; PTH – high
Histology	Excessive osteoid and reduced mineralization. Caution as similar picture in disorders with increased bone turnover (hyperparathyroidism, Paget's disease, hyperthyroidism)

Table 19.5 Typical biochemical findings in common bone diseases

	Ca^{2}+	PO_4	ALP	PTH	eGFR	25-(OH) Vit D	1,25-$(OH)_2$ Vit D
Osteomalacia	ln/↓	ln/↓	↑	hn/↑	n	↓	n/hn/ln
Osteoporosis	n	n	n	n	n	n	n
Primary hyperparathyroidism	↑	ln/↓	hn/↑	↑	n/↑	n	n
Renal osteodystrophy	ln/↓	hn/↑	↑	↑	↑	ln/↓	ln/↓
Paget's disease	n*	n	↑	n	n	n	n

n, Normal; ln, low normal; hn, high normal; ALP, alkaline phosphatase; PTH, parathyroid hormone; eGFR, estimated glomerular filtration rate; 25-(OH) Vit D, 25-hydroxyvitamin D; 1,25-$(OH)_2$ Vit D, 1,25-hydroxyvitamin D.
*High if immobility or secondary osteosarcoma.

sun because of skin colour, cultural clothing habits and/or the elderly in institutions.

Renal osteodystrophy encompasses the spectrum of bone disease in association with chronic renal failure. The main components are hyperparathyroidism, adynamic bone disease and osteomalacia.

MANAGEMENT

Management consists of education to prevent osteomalacia, particularly in at-risk populations, e.g. the elderly, and replacement therapy. Vitamin D is abundant in oily fish and supplemented in certain cereals. Fifteen minutes of sunshine to the

Table 19.6 Causes of vitamin D deficiency

Hypovitaminosis D	Lack of sun exposure, poor dietary intake
Malabsorption	Coeliac disease, gastrectomy, pancreatic insufficiency
Renal disease	Hypophosphataemic renal disease (hereditary and acquired forms), Fanconi syndromes (hereditary and acquired forms), distal renal tubular acidosis, renal osteodystrophy
Other	Anticonvulsants – phenytoin, carbamazepine (catabolize vitamin D to inactive metabolites), aluminium, heavy metal poisoning, bisphosphonates

face and hands/forearms three times a week between April and September is sufficient sun exposure. Darker skin requires longer sun exposure to generate the same amount of vitamin D. Protocols for vitamin D replacement depend upon the severity of the deficiency and the compliance of the patient. Mild deficiency can be replaced with 800 IU orally per day; more severe deficiency should be treated with high-dose oral bolus therapy (200 000–300 000 IU loading dose of oral D_3 given as divided doses over weeks or days) and then 800 IU daily maintenance. Rarely, parenteral vitamin D is given. Calcium supplementation of up to 800 mg a day should be given routinely. All pregnant women at risk of low vitamin status are encouraged to take at least 400 IU D_3 per day throughout pregnancy.

PAGET'S DISEASE

Paget's disease of bone (PD) is the second most common bone disorder after osteoporosis, affecting 5.4% of the population over 55 years of age in the UK. The prevalence is highly variable between races and countries. The highest rate is in the UK, and the condition is rare in Japan, China, India and Scandinavia. The normal, highly regulated, process of bone remodelling is disturbed. There is excessive bone resorption and, due to the tightly coupled nature of osteoclast and osteoblast activity, this is followed by the rapid laying down of disorganized, weak, abnormal bone. For a review of the normal bone remodelling cycle, see Chapter 2.

Table 19.7 Clinical features of Paget's disease

Common	Rare
Bone pain	Osteosarcoma
Osteoarthritis	Vascular steal phenomenon
Pathological fractures	High-output cardiac failure
Bone deformity	
Headache	
Nerve root compression (deafness)	

Box 19.6
Most frequently affected bones in Paget's disease (descending order of frequency)

- Pelvis
- Lumbar spine
- Femur
- Thoracic spine
- Sacrum
- Skull
- Tibia
- Humerus

CLINICAL FEATURES

The frequency of PD increases with age. It is rare at less than 50 years of age and affects both sexes, with a slight predominance in men. It is often asymptomatic and discovered incidentally from a raised alkaline phosphatase (ALP) level in the blood or an X-ray performed for an unrelated reason. Only 10–30% of people with PD are symptomatic and the commonest presentation is pain (Table 19.7). Osteosarcoma is a frequently quoted complication of PD, but it is becoming rarer and occurs in less than 1% of patients. PD has a predilection for certain bones, but may affect anywhere in the skeleton (Box 19.6).

Some 17% of patients have a single site of PD. Once diagnosed, new sites do not develop during a patient's lifetime. The lesions are highly localized and progress slowly, but relentlessly, once present without treatment.

AETIOLOGY

The aetiology is incompletely understood. There is a genetic and an environmental component to the disease. Current hypotheses are based around an environmental insult in a genetically predisposed individual. The primary abnormality lies within the osteoclast. Osteoclasts in PD are increased in number and size, and multi-nucleated. Osteoclast precursors are also abnormal and are hypersensitive to factors that stimulate their differentiation into mature osteoclasts, including RANKL and 1,25-$(OH)_2D_3$. Osteoblasts are normal, but have increased activity due to increased stimulation from factors released by the osteoclasts. The initial lesion is, therefore, osteolytic followed by the rapid laying down of weak disorganized bone.

INVESTIGATIONS

A raised bone-specific ALP, a marker of bone formation, is often the first clue. Other markers of bone turnover are increased including PINP (formation) and *N*-telopeptide of type 1 collagen in the urine (resorption). Calcium levels are usually normal unless there has been a recent fracture or prolonged immobility. X-ray will show the typical appearances of thickened, coarse cortical bone (Fig. 19.3) and in some cases, during phases of highly increased osteoclast activity, the appearance of localized osteoporosis, called osteoporosis circumscripta (Fig. 19.4). An isotope bone scan is indicated to distinguish monostotic from polyostotic disease. Radiographic imaging of weight-bearing areas is essential to exclude occult partial fractures. In patients with high ALP levels and localized bone pain in the setting of long-standing disease, MRI and CT may help differentiate malignant transformation. In patients with a sudden increase in pain, MRI is indicated to investigate for fractures through the abnormal bone.

TREATMENT

Treatment is not always indicated. Pain is the most common reason for treating. Other reasons for medical treatment include sequelae of the disease: fractures and nerve root compression from the expanded bone. Prior to surgery, treatment may be indicated because pagetic bone is more vascular and consequently bleeds more. Bisphosphonates inhibit osteoclast activity and promote osteoclast apoptosis, and are the mainstay of treatment. A single infusion of 5 mg zoledronate is sufficient to control disease for many years. However, this should not be used in those with partial fractures in weight-bearing areas because of the risk of fracture completion. In these patients, oral therapy with risedronate and correction of occult vitamin D deficiency are indicated. Orthopaedic intervention may also be needed.

OSTEONECROSIS (AKA AVASCULAR NECROSIS, ASEPTIC NECROSIS, BONE INFARCTION OR OSTEOCHONDRITIS DISSECANS)

Osteonecrosis (ON) is the final common pathway of a number of conditions that result in bone death. The pathophysiology of ON is discussed in Chapter 2.

AETIOLOGY

The aetiology is multifactorial, but the final stage of ON is bone death due to a compromised blood

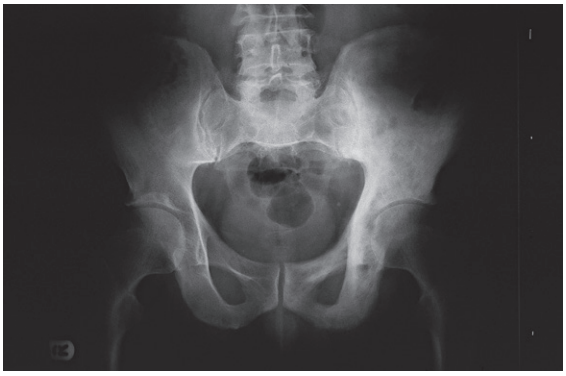


FIGURE 19.3 Paget's disease of the left hemi-pelvis

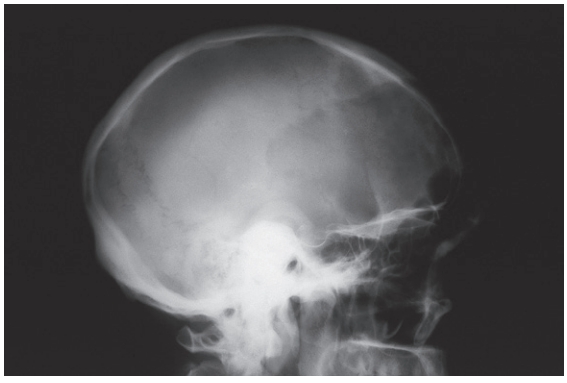


FIGURE 19.4 Paget's disease of the skull showing the phenomenon of osteoporosis circumscripta

Table 19.8 Risk factors for osteonecrosis and conditions associated with osteonecrosis

Risk Factor/Associated Condition	Mechanism*
Trauma	Interruption to blood supply
Corticosteroid treatment, Cushing's disease	Increased intra-osseous pressure, fat emboli, inhibition of angiogenesis, increased osteoporosis and microfracture, direct osteocyte death; cumulative dose of corticosteroids is more predictive of increased risk than daily dose
Haemoglobinopathies – sickle cell disease, thalassaemia	Sludging of abnormal red blood cells, marrow hyperplasia and increased intra-osseous pressure
Hyperlipidaemia	Increased intra-osseous pressure, fat emboli, intravascular coagulation
Alcohol	Fatty liver and fat emboli, direct osteocyte death, secondary Cushing's syndrome
Autoimmune conditions – SLE, ALPS**	Increased thrombotic tendency
Inherited clotting cascade abnormalities – factor V Leiden, protein C and S deficiency	Increased thrombotic tendency
Marrow infiltration	Increased intra-osseous pressure, increased thrombotic tendency
Infection ± disseminated intravascular coagulation	Increased thrombotic tendency
Malignancy	Corticosteroid treatment, marrow infiltration, increased thrombotic tendency
Polycythaemia rubra vera	Sluggish blood flow, increased thrombotic tendency
Hyperbaric exposure (Caisson's disease)	Intra-medullary nitrogen bubbles
Pregnancy	Impaired venous drainage by gravid uterus, mechanical stress from increased weight, increased endogenous steroids
Haemophilia	External arterial compression from recurrent haemarthroses
Gaucher's disease	Sludging of abnormal red blood cells, fat emboli, increased intra-osseous pressure
Radiation therapy	Dose-dependent osteocyte death, aetiology unclear
HIV infection	Unknown
Bisphosphonates	Unknown aetiology, affects the jaw

*These are proposed mechanisms; not all are proven.
**SLE Systemic lupus erythematosus, APLS Anti-phospholipid syndrome.

supply. Trauma and sickle cell disease are the two most common causes of ON worldwide. There are many identified risk factors and associated conditions (Table 19.8) for atraumatic ON, but there is still a significant number of idiopathic cases. Many of the idiopathic cases occur in children, adolescents and young adults.

CLINICAL PRESENTATION

Many of the patients affected by ON are young and active with a predilection for certain bones (Box 19.7). Pain is usually the presenting complaint and may be accompanied by a limited range of movement. Up to one-third of patients are asymptomatic. There is a high incidence of bilateral involvement in atraumatic cases involving the femoral head, femoral condyles and humeral head. Premature degenerative disease is a common consequence of ON and a major cause of disability.

METHODS OF DIAGNOSIS

MRI is the most sensitive method and may detect pathology before collapse is seen radiographically (Figs 19.5 & 19.6). Once ON is well established,

Box 19.7
Bones commonly affected by osteonecrosis

- Femoral head
- Femoral condyles
- Humeral head
- Proximal tibia
- Talus
- Scaphoid
- Lunate (Kienbock's disease)
- Navicular (Köhler's disease)
- Lesser metatarsals (Freiberg's disease)
- Cuboid
- Vertebra

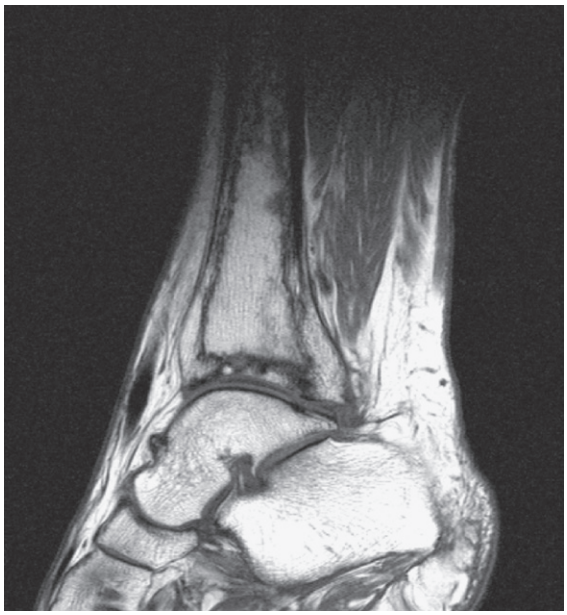


FIGURE 19.6 The corresponding MRI scan showing an extensive bone infarct within the distal tibia. There is some linear high signal within the longitudinal axis of the Achilles tendon. This may represent an area of longitudinal tearing

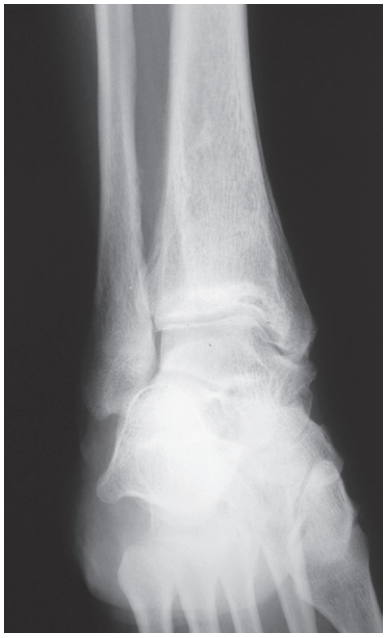


FIGURE 19.5 Plain radiograph of osteonecrosis showing an unusual osteonecrosis of the distal tibial shaft of a 41-year-old woman with an inflammatory arthritis for 2 years. Changes include subchondral sclerosis in the distal tibia at the ankle joint. Some periosteal reaction is noted along the distal aspect of the tibia. There is some narrowing of the joint space medially with sclerosis

every imaging method, such as standard plain film, CT and isotope bone scan, will reveal it. Table 19.9 lists the various methods of imaging and their characteristic findings in ON.

MANAGEMENT

Treatment may include avoidance of weight-bearing, analgesia and surgery, such as bone decompression and joint replacement. There are published case series using bisphosphonates and iloprost in the management of ON, but these are still experimental.

Prevention by the recognition and management of treatable disorders such as hyperlipidaemia and alcoholism is crucial. Early diagnosis and intervention improves outcome, so a high index of suspicion is important. ON is an irreversible process. Management includes conservative treatment to reduce the use of the affected joint and simple analgesics. Surgery is often required and the commonest procedures are core decompression and joint replacement. Prognosis is dependent upon the location and stage of the disease. There is the potential for biologic therapies in the future.

Table 19.9 Methods of imaging patients with suspected osteonecrosis

Imaging Method	Time of Diagnosis	Findings	Characteristics
MRI	Days to weeks	Decreased signal in a segmental pattern	Excellent sensitivity Good specificity
Isotope Bone Scan	Weeks	Early decreased uptake, late increased uptake	Good sensitivity Poor specificity
Plain X-Ray	Weeks to months	Radiolucency, osteonecrosis, microfractures, subchondral collapse	Poor sensitivity Good specificity
CT	Months	Reactive sclerosis, subchondral collapse	Poor sensitivity Good specificity

OSTEOCHONDRITIS DISSECANS

This condition usually affects children and adolescents, and is discussed in Chapter 25.

PERTHES' DISEASE

This condition usually affects children and adolescents, and is discussed in Chapter 25.

FURTHER READING

Kanis JA, Burlet N, Cooper C et al; European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 2008; 19:399–428.

Michou L, Brown JP. Emerging strategies and therapies for treatment of Paget's disease of bone. Drug Des Devel Ther 2011; 5:225–239.

Papaioannou A, Morin S, Cheung AM et al; Scientific Advisory Council of Osteoporosis Canada. 2010 Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ 2010; 182:1864–1873.

Shane E, Burr D, Ebeling PR et al; American Society for Bone and Mineral Research. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 2010; 25:2267–2294.

Thacher TD, Clarke BL. Vitamin D insufficiency. Mayo Clin Proc 2011; 86:50–60.