Pathogenesis, diagnosis and management of Paget’s disease of the bone


Abstract

Paget’s disease of the bone is a chronic condition that affects bone remodelling in focal areas of the skeleton. The disease may affect one or several sites and can cause a variety of subsequent complications such as pain, bony deformity, osteoarthritis, fracture or nerve compression. Understanding the disease and how it affects patients enables nurses to understand patient needs and improve the quality of care delivered.

Aims and intended learning outcomes

The aim of this article is to familiarise readers with the pathophysiology of Paget’s disease of the bone (PDB) and identify how it is diagnosed and managed, including complications.

After reading the article you should be able to:

- Identify factors associated with the development of PDB.
- Discuss how the complications of PDB affect activities of daily living.
- Outline the management strategies that may be used.
- Discuss the role of the nurse in caring for people with the disease.

Introduction

PDB is a chronic progressive disorder of bone remodelling (resorption and formation) (Bolland and Cundy 2013, Rea et al 2013). It is characterised by focal areas of increased and disorganised bone remodelling that affect one or more bones (Ralston 2013). In PDB the rate of bone formation may be six times above normal levels (Cundy and Reid 2012), with the new bone abnormal in shape and structure and weaker than normal bone.

The disease was first described by Sir James Paget in the 19th century and was referred to as osteitis deformans (Colina et al 2008). Unlike other metabolic bone diseases such as osteoporosis or osteomalacia, PDB can affect one or several bones in a focal, but random, manner (Corral-Gudino et al 2013). Disease affecting one bone is termed monostotic, whereas disease affecting several bones is referred to as polyostotic (Colina et al 2008). PDB classically affects the axial skeleton with the pelvis, femur, lumbar spine, skull and tibia being the most commonly affected sites (Ralston 2013) (Figure 1). It can be present without significant clinical findings (Colina et al 2008).

Incidence and prevalence

PDB is the second most common metabolic bone disease after osteoporosis. It is common in older people, and more common in men than women (Corral-Gudino et al 2013). It is rare for PDB to be diagnosed before the age of 40 years (Colina et al 2008), although incidence increases gradually after this age and affects approximately 5% of women and 8% of men by the age of 80 (van Staa et al 2002), and approximately 10% of people after 90 years (Colina et al 2008).

Radiological survey is the most common method for determining prevalence. As most patients have involvement of either the pelvis, lumbar spine or proximal femur, assessing consecutive abdominal X-rays allows an approximation of prevalence (Bolland and Cundy 2013).

The prevalence of PDB varies between countries studied, with the highest prevalence being in the UK at 5.4% and the lowest being in Japan (0.00028%) (Corral-Gudino et al 2013). Other areas of higher prevalence include Australia, New Zealand, North America and Western Europe, and areas of low prevalence include Scandinavian countries, the Indian subcontinent, China and the Middle East (Colina et al 2008).
Incidence and prevalence have decreased in most regions over the past 25-30 years as has the severity of cases seen (Corral-Gudino et al. 2013, Rea et al. 2013). The reasons for these changes remain unclear, although they are likely to be as a result of genetic and environmental factors that may vary between regions (Corral-Gudino et al. 2013). Approximately 15% of patients with PDB have a family history of the disease, with the disease being inherited in an autosomal dominant manner (Ralston 2013).

Now do time out 1.

**Activity**

Before moving on to the next section, visit the Paget’s Association website and download its simple facts leaflet (www.paget.org.uk/simplefacts.pdf) or go to www.arthritisresearchuk.org/arthritis-information/conditions/pagets.aspx to familiarise yourself with the disease and how it affects bone.

**Pathogenesis**

PDB is of unknown aetiology, although evidence suggests genetic and environmental factors may be involved (Colina et al. 2008). Griz et al. (2006) noted that patients with polyostotic disease have more frequent involvement of the pelvis, skull and femur than those with monostotic disease. The mechanisms responsible for the focal nature of PDB are unclear, as are the factors that determine which bones are affected.

**Remodelling** The normal adult skeleton undergoes constant remodelling with osteoclasts removing bone (resorption) and osteoblasts forming bone. In PDB the pace of remodelling is considerably enhanced. PDB goes through different stages of bone remodelling followed by a quiescent phase (Colina et al. 2008). Initially there is an increase in bone resorption, which is mediated by large multinucleated osteoclasts. In PDB osteoblasts have been shown to have an increased expression of genes such as receptor activator of nuclear factor k B (RANK), RANK-Ligand, interleukin-1, interleukin-6 and Dickkopf-1 (Ralston et al. 2008, Rea et al. 2013). All of these can contribute to localised increases in bone turnover (Rea et al. 2013), which is the main feature of Paget’s disease.

The initial osteoclast resorption phase is followed by the osteoblastic response where there is excessive and disorganised new bone formation (Colina et al. 2008) (Figure 2). The chaotic and disorganised deposition of lamellar and woven bone produces the characteristic mosaic pattern of Pagetic bone. Bone that is deposited in a chaotic fashion with a disorganised structure can be of poor quality and consequently account for some of the complications seen in PDB, such as structural deformity and fracture. In advanced disease bone marrow is replaced with new vascular structures and thickening of the bone (Roodman and Windle 2005).

**Genetics** Genes are important in the development of PDB. Mutations have been found in four genes (Ralston et al. 2008). Mutations in the sequestosome 1 (SQSTM1) gene occur in up to 50% of patients with
a family history of PDB. The SQSTM1 gene encodes a protein, p62, which regulates osteoclast function (Ralston and Layfield 2012).

Changes have also been observed in the tumour necrosis factor receptor superfamily, member 11a (TNFRSF11A) gene, which encodes receptor activators of RANK that have an important role in osteoclast differentiation and function (Ralston et al 2008). It is thought that PDB develops at an earlier age and is more extensive in people with specific gene mutations than in those who do not have characteristic genetic changes (Hocking et al 2004). The TNFRSF11B gene and the valosin-containing protein (VCP) gene are also being studied in relation to the development of PDB (Ralston et al 2008).

Environmental and other factors Reductions in the prevalence and severity of the disease have been reported in some countries, although remained stable in other areas (Ralston et al 2008). This may be due to changes in the environment and environmental triggers, or changes in the ethnic makeup of the population due to migration from low prevalence areas (Ralston 2008).

Viral infection has been suggested as playing a part in the pathogenesis of PDB as antigens and nucleic acid sequences of measles, canine distemper and the respiratory syncytial virus have been identified in the nuclei and cytoplasm of Pagetic osteoclasts (Whyte 2006). This theory is controversial as the prevalence of PDB is often inconsistent with measles and canine distemper and evidence of viral sequences in bone cells has not always been identified in samples analysed (Bolland and Cundy 2013).

It is most plausible that people with a genetic susceptibility develop the disease when exposed to an environmental stimulus such as infection (Selby 2009). Other factors that have been implicated as possible disease triggers include repetitive mechanical loading of the skeleton, deficiency of dietary calcium or vitamin D deficiency during childhood, zoonotic infections and exposure to environmental toxins (Ralston et al 2008).

Clinical features For most patients, PDB is asymptomatic, with approximately 30% experiencing symptoms (Colina et al 2008). Clinical presentation is variable depending on how many areas are affected and their location (Rea et al 2013). Abnormal bone remodelling can cause pain, deformity, osteoarthritis and neurological compression (van Staa et al 2002). As Pagetic bone is brittle it may fracture spontaneously. This is known as a pathological fracture and occurs most commonly in the femur, tibia, humerus and forearm (Colina et al 2008).

There is also an increased risk of hearing loss, tinnitus, dizziness and back pain (Ralston et al 2008). Some patients report erythema and increased temperature at the affected sites due to increased vascularity and blood flow (Nivens 2004). Potential complications of PDB are summarised in Box 1.

Bone pain Up to 40% of patients who come to medical attention will present with bone pain (Ralston 2013). This is the most common symptom and may be caused by increased bone turnover (Ralston 2013). Pagetic pain is typically described as a deep aching bone pain, which can be present at rest and persist through the night (Ralston 2013). It is often worse on weight bearing on affected bones, for example, in the femur or tibia.

Pain is also commonly associated with deformities such as bending of the long bones (Figure 2) or enlargement of the skull. Long bone deformities may predispose to secondary osteoarthritis (Colina et al 2008) as a result of altered joint dynamics (Bolland and Cundy 2013). Involvement of subchondral bone can compromise the joint and predispose to osteoarthritis developing in the joint. This may be termed Pagetic arthropathy (Ralston and McInnes 2014). On assessing the nature of the pain, it is important to establish if it is localised to the bone (PDB), rather than to the joint (arthropathy) (Ralston et al 2008).

Enlargement of the bones is often noted by patients, particularly when it affects the skull, as patients notice, for example, that their hats no longer fit. Cranial enlargement may result in cranial nerve defects due to compression of the nerves. Loss of hearing does not commonly occur due to compression of the auditory nerve but is more likely to be due to osteosclerosis of the temporal bone that affects conduction (Ralston and McInnes 2014).

Pagetic changes to facial bones may cause dentures to no longer fit comfortably and dental procedures such as tooth extraction can be problematic (Colina et al 2008). Compression of the spinal cord and spinal nerves

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**Box 1: Potential complications of Paget’s disease of the bone**

**Skeletal**
- Bone pain.
- Back pain.
- Bone and joint deformities.
- Fractures.
- Secondary osteoarthritis.

**Neurological**
- Basilar invagination (where the top of the odontoid process projects through the foramen magnum).
- Nerve entrapment.
- Spinal stenosis.

(Whyte 2006, Seton et al 2011)

**Cardiac**
- High-output congestive cardiac failure due to increased Pagetic bone vascularity.
- Hypertension.

**Other**
- Malignancy – osteosarcoma.
- Metabolic – hypercalcaemia.
may occur due to remodelling and deformity of the skeletal structures. This can result in back pain, spinal stenosis or nerve compression. In clinical practice it can be difficult to distinguish between pain from co-existing musculoskeletal disorders such as degenerative intervertebral discs and stenosis.

Now do time out 2.

### Activities of daily living

Consider the musculoskeletal and neurological changes that may occur due to PDB. Write a list of the ways that these can affect activities of daily living and consider what can be done to help maintain independence.

High-output cardiac failure is considered a rare complication of PDB, along with obstructive hydrocephalus (abnormal accumulation of cerebrospinal fluid in the brain), headaches, dizziness and hypercalcaemia in immobilised patients (Whyte 2006, Ralston 2013). Pagetoid obstructive hydrocephalus mainly results from flattening of the skull base (platybasia) and consequent basilar invagination (Ferraz-de-Souza et al 2013). Symptoms of hydrocephalus may include memory loss, gait disturbance and urinary incontinence. Treatment is typically by surgical insertion of a shunt to drain the fluid and reduce the pressure on the brain (Ferraz-de-Souza et al 2013).

**Osteosarcoma** This rare complication is a malignant tumour that produces osteoid (Brigman 2004), which develops in less than 1% of people with PDB (Rea et al 2013). Osteosarcomas typically present with local pain and tenderness or occasionally with pathological fractures. Although rare, they should be suspected in patients who have a sudden increase in bone pain, swelling, pathological fracture or involvement of a new skeletal area (Colina et al 2008, Ralston 2013). X-rays may show expansion of the bone with cortical destruction and areas of elevated periosteum. The surrounding soft tissue mass may contain areas of calcification (Brigman 2004).

Diagnosis is often confirmed by computerised tomography (CT) scan or magnetic resonance imaging (MRI) to determine the extent of the growth and bone biopsy for histology. Treatment of patients with osteosarcoma should be by a specialist team, although it typically involves surgical removal of the tumour and chemotherapy and/or radiotherapy. Unfortunately, the prognosis of osteosarcoma is often poor in older people with PDB (Ralston and McInnes 2014). Sharma et al (2005) reported a survival time of 17 months for patients with sarcoma.

**Figure 3** X-ray showing old and new spongy bone of lower femur

Wellcome Images
Biochemistry allows measurement of bone turnover and provides an objective assessment of disease activity and response to treatment (Colina et al 2008). It should include assessment of liver and renal function as well as calcium, alkaline phosphatase and 25-hydroxy vitamin D (Ralston 2013).

Alkaline phosphatase is an enzyme produced by bone cells and can be measured to assess the level of bone activity (Nivens 2004). As increased alkaline phosphatase levels reflect the spreading of osseus involvement (Colina et al 2008), they can be used to monitor disease activity. Measuring serum calcium and 25-hydroxy vitamin D levels provides useful clinical information that can exclude hyperparathyroidism and vitamin D deficiency as a cause of elevated alkaline phosphatase levels. Patients with PDB typically have elevated alkaline phosphatase levels, and otherwise normal results (Ralston 2013). During resorption osteoclasts release bone collagen and minerals that can also be measured by serum markers such as N-telopeptide (Nivens 2004). A summary of biochemical markers is included in Box 2.

Management

The aim of treatment is to relieve symptoms and prevent complications. Bone pain caused by increased bone turnover can be difficult to differentiate from pain caused by complications such as osteoarthritis, deformity or nerve compression (Ralston and McInnes 2014), or other co-existing musculoskeletal conditions. Careful evaluation with a methodical history of the pain and thorough clinical examination will help determine if pain is due to increased metabolic activity, a new complication of PDB, or a co-existing musculoskeletal condition and will influence management (Ralston 2013). Patients who are asymptomatic and who are not at risk of secondary complications do not need any specific treatment and can be monitored with regular clinical reviews and a measurement of alkaline phosphatase (Bolland and Cundy 2013). Patients with symptomatic PDB also require regular reviews to assess changes in disease activity, symptoms and need for intervention.

Bisphosphonates

Oral bisphosphonates are the first choice of treatment, although intravenous (IV) administration is an alternative if the oral route is contraindicated or if there is rapid progression of complications such as neurological compression. Amino bisphosphonates such as pamidronate, zoledronate and risendronate are more effective at suppressing bone turnover than simple bisphosphonates such as etidronate (Ralston and McInnes 2014). Bisphosphonates work by inhibiting osteoclastic activity and therefore reduce bone resorption. Calcitonin is not commonly used for PDB because of its short duration of action, and reduced antiresorptive effects compared with bisphosphonates, although it is effective in controlling bone pain (Ralston et al 2008).

Alkaline phosphatase levels start to fall approximately ten days after starting bisphosphonate therapy and symptoms usually start to improve while alkaline phosphatase levels are falling (Ralston 2013). When potent bisphosphonates are given at correct doses, the disease process can be suppressed for prolonged periods (Cundy and Reid 2012). The patient is considered to be in remission when normal levels of biochemical markers such as alkaline phosphatase have been reached (Griz et al 2006). People with more extensive disease tend to relapse earlier than those with limited disease, particularly when less potent medications or lower doses are used (Cundy and Reid 2012). Repeated courses of bisphosphonates can be given if symptoms return (Ralston and McInnes 2014).

Oral bisphosphonates have poor gastrointestinal absorption and therefore medication needs to be taken on an empty stomach to achieve adequate absorption, which is why it is often recommended that medications are taken first thing in the morning (Ralston 2013). Common side effects include dyspepsia and diarrhoea (Ralston et al 2008). Rarer side effects include uveitis, rashes, atrial fibrillation and osteonecrosis of the jaw (Ralston 2013). IV administration of bisphosphonates can provoke an acute phase response with patients experiencing transient flu-like symptoms (Ralston et al 2008). This acute phase response is often reduced on the second and subsequent infusions.

Hypocalcaemia after bisphosphonate therapy in PDB has been noted, especially when serum calcium and 25-hydroxy vitamin D were not at optimum levels before treatment (Ferraz-de-Souza et al 2013). Calcium and vitamin D deficiencies are common in older people, and it is important that they are corrected before starting bisphosphonate therapy to avoid complications such as hypocalcaemia.
as hypocalcaemia. This is particularly important when bisphosphonates are prescribed intravenously as effects are increased with IV treatment (Ralston et al 2008).

As pain, osteoarthritis, stenosis and hearing loss are common in many older people without PDB, it can be challenging to determine which symptoms are due to the disease (Bolland and Cundy 2013). A course of bisphosphonates can be helpful in eliminating increased bone activity as the cause of pain (Bolland and Cundy 2013). If symptoms do not respond to antiresorptive therapy it may be that the pain experienced is due to a complication of the disease such as spinal stenosis or osteoarthritis and therefore will require appropriate management. There is some debate as to whether bisphosphonates can prevent complications of PDB, although there is little evidence to support or disprove this (Bolland and Cundy 2013). Similarly, there is no evidence to suggest that asymptomatic patients benefit from antiresorptive therapy (Ralston 2013).

**Pain control** Simple analgesics and non-pharmacologic interventions such as weight loss and exercise programmes can be helpful in treating secondary complications such as osteoarthritis (Bolland and Cundy 2013). The use of analgesics such as paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and anti-neuropathic drugs such as gabapentin may help treat pain, however, care should be taken to avoid long-term use of NSAIDs due to the increased health risks associated with prolonged use. Non-pharmacologic approaches to pain control should also be considered as part of a holisitic approach to management. Strategies may include hydrotherapy, acupuncture and transcutaneous electrical nerve stimulation (Ralston 2008).

Now do time out 3.

**Analgesia**

Write a list of analgesics that may be suitable for older people with PDB. What type of pain are they most suited for, under what circumstances may they be used, for example, daily pain due to bony changes, after fractures and nerve compression, and what are their side effects? Use the British National Formulary or equivalent reference source to determine whether any of these drugs should be avoided in specific groups of patients, for example, those with reduced liver or kidney function.

Orthotic devices and walking aids can help to reduce pain caused by musculoskeletal changes and deformities (Ralston 2013). Aids and devices such as shoe raises and walking sticks can help specific problems such as limb shortening and substantially improve health-related quality of life. Advice on weight control and healthy eating may also help to reduce unnecessary loading of joints that are already painful (Whyte 2006).

Physiotherapy can be helpful in improving strength and function as well as increasing musculoskeletal range of movement and flexibility (Nivens 2004). This is of particular importance when considering mobility and the potential problems that may occur due to changes associated with PDB. As the disease progresses and musculoskeletal changes become more advanced, it is important to consider how these changes affect mobility and potentially the increased risk of falling. A falls assessment may help identify and minimise potential hazards or risks.

Now do time out 4.

**Falls risk**

Consider some of the patients that you care for. Write down the different factors that may be involved with patients falling. Now look around and see if you can spot any of these falls risk factors and see how you can address them.

**Surgery** Surgical intervention may be required to manage complications, such as joint replacement for osteoarthritis, fracture fixation, osteotomy to correct bone deformity or decompression surgery to relieve pain and symptoms from spinal stenosis. Surgery can improve quality of life, especially for those with advanced osteoarthritis. Pagetic changes to the bones and joints mean that people with PDB are more likely to need a hip or knee replacement than others of the same age who do not have PDB (van Staa et al 2002). However, surgery is often challenging due to enlarged bones and osteosclerosis (Ralston 2013). The increased vascularity of Pagetic bone also makes surgical procedures more complex and may precipitate high-output cardiac failure in older patients with limited cardiac reserve (Ralston and McInnes 2014).

It is important to assess how changes have influenced activities of daily living and quality of life. For example, changes to physical function may lead to increased social isolation and loneliness and can subsequently affect quality of life. Psychological aspects of chronic disease include low self-esteem, depression and altered body image. These can affect a person’s quality of life as much as the physical effects of the disease, therefore each patient should be assessed for the psychological, social and cultural dimensions of illness to ensure holistic care.

Changes in appearance or function of any part of the body due to chronic illness such as PDB can alter the perception of body image (Green 2008). This altered...
body image can cause personal distress and can affect self-esteem, which in turn may limit social engagement and interaction with others (Price 1990).

It is important that healthcare professionals assess the effect that altered body image or social isolation has on daily activities and quality of life, so that appropriate action can be taken to address problem areas. Mild depression and hopelessness are also commonly experienced by people with chronic disease and can reduce the ability to cope with pain and daily challenges (Turner and Kelly 2000). Healthcare professionals should adopt a positive attitude towards psychological aspects of chronic illness and address these in as much detail as physical aspects in order to maximise the patient’s health-related quality of life.

Now do time out 5.

Psychological effects

Consider the psychological effects of PDB on older patients. Find out what services or activities are available locally to help reduce social isolation. Make a list of their contact details so that these are readily to hand when you support patients.

Nurses can educate patients about the nature of the disease, potential complications and medication side effects. It is often helpful to provide written information to supplement any advice given verbally as this allows people to return to the information and refresh any parts they may need clarifying.

Resources are available to support patients (Box 3).

References


Box 3 Resources and information

- Arthritis Research UK: Paget’s Disease of Bone
  www.arthritisresearchuk.org/arthritis-information/conditions/pagets.aspx
- Paget’s Association: www.paget.org.uk
- UpToDate Patient Information: Paget Disease of Bone (osteitis deformans) (Beyond the Basics): www.uptodate.com/contents/paget-disease-of-bone-osteitis-deformans-beyond-the-basics

Conclusion

PDB is a common condition in older people. The disease is characterised by abnormal bone remodelling, which may result in pain and complications such as deformity, osteoarthritis and nerve compression. Bisphosphonates can be used to slow bone turnover and reduce pain, although other interventions such as orthotic devices and physiotherapy can help maintain independence and quality of life. To ensure that patients are able to maintain optimum function and a good health-related quality of life, a multidisciplinary and holistic approach to care is important.

Now that you have completed the article you might like to write a reflective account. Guidelines to help you are on page 39.