Paget's Association

Paget's Disease of Bone

Information for

Healthcare Professionals

Version 1: 2020

Paget's Disease of Bone

Introduction

This information booklet presents an overview of Paget's Disease of Bone, for all healthcare professionals who care for patients affected by the condition.

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Paget's Disease of Bone

A Disorder of Bone Remodelling

Characterised by focal abnormalities in bone remodelling at one (monostotic) or several (polyostotic) skeletal sites, Paget's Disease of Bone (PDB) is initiated by enhanced resorption by abnormal multinucleated osteoclasts, followed by disorganised bone formation by osteoblasts. This dysregulation of bone turnover in Paget's disease results in abnormalities of the bone structure, weakening of the bone and enlargement or deformity of the affected bones. Pagetic bone often appears misshapen and enlarged. The focal increases in osteoclast and osteoblast activity in PDB are also accompanied by marrow fibrosis and increased vascularity of bone.

PDB can affect almost any bone, but there is a predilection for the pelvis, spine, femur, tibia, and skull. It is often asymmetrical, and it is unclear why only certain bones are affected. It is possible that it may be related to mechanical stresses, which are placed on the skeleton at specific sites, or differences in the blood supply to these bones.

Incidence

In the UK, PDB is the second most common metabolic bone disease after osteoporosis. It has been estimated to affect around 1% of people, over the age of 55 years, in the UK. In general, it is declining in incidence and severity.

The condition is also common in other European countries such as France, Spain and Italy, and in people of European descent who have emigrated to other regions of the world, such as Australia, New Zealand, the United States of America and Canada.

Aetiology

The pathogenesis of PDB is not completely understood, but genetic factors play a key role. The most important susceptibility gene for PDB is *SQSTM1,* which encodes p62, a protein involved in the nuclear factor kappa B (NF-kB) signalling pathway. Mutations in *SQSMT1* have been identified in 40% - 50% of familial cases and in 5% - 10% of patients who do not report a family history.

Environmental factors also play a role in PDB, as evidenced by the fact that reductions in prevalence and severity have been observed in many countries over the past 25 years. Researchers have yet to discover which environmental factors influence the development of Paget's disease.

Assessment of Patients

When Paget's disease is suspected, there must be a detailed assessment process, including any family history of the condition.

The Paget's Association's Centres of Excellence

Most UK hospitals have a specialist who can deal with the condition. If there is no specialist locally, then referral to one of the Paget's Association Centres of Excellence might be beneficial. The Centre of Excellence Award recognises hospital (NHS) and university departments, within the UK, which demonstrate excellence, in both the care of patients, and research into Paget's disease. Further information can be found on our website **paget.org.uk**

Clinical Features

Many clinical features and complications of PDB are thought to be due to the abnormalities of bone remodelling. In many cases, individuals are unaware that they have the condition and may never develop symptoms.

- In those that present clinically, bone pain is the most common symptom.
- The blood flow to active areas of Paget's disease increases due to the high rate of bone remodelling. This can sometimes lead to a feeling of warmth over the affected bone.
- The affected bone may become enlarged and misshapen.

Diagnosis

The most widely used biochemical marker to aid diagnosis of PDB is serum total alkaline phosphatase (ALP), which is typically elevated in active PDB.

The condition has characteristic features on x-ray (summarised in Box 1). Individually, these features are not specific, but when they occur in combination, they are usually diagnostic.

Radionuclide bone scintigraphy is widely considered to be a valuable technique for the diagnosis of PDB and to assess the extent of the disease.

Box 1
X-ray features of PDB

- *Osteolytic areas*
- *Cortical thickening*
- *Loss of distinction between cortex and medulla*
- *Trabecular thickening*
- *Osteosclerosis*
- *Bone expansion*
- *Bone deformity*

Management

It is recognised that not everyone with Paget's disease requires treatment, because, in many cases, it causes no symptoms nor complications. Decisions to treat Paget's disease should be made by a specialist, on an individual basis.

Specific anti-pagetic treatment involves the use of osteoclast inhibitors to reduce the elevation in bone turnover that is characteristic of active disease. In addition, analgesics, non-steroidal anti-inflammatory drugs, and anti-neuropathic pain agents can be used for symptom control.

FIRST-LINE

Zoledronic Acid

For those who require treatment, the current first-line bisphosphonate, due to its potency and prolonged duration of action, is zoledronic acid. It is the bisphosphonate most likely to relieve pain from active Paget's disease. A single infusion of 5mg can be effective for many years.

Risedronate

Risedronate is also an effective treatment and is given orally once a day, 30mg for 2 months. Risedronate also helps relieve pain from active Paget's disease with effects that can last for 2 years or more. The duration of effect is not as long as that of zoledronic acid.

Pamidronate

Pamidronate is an effective treatment but has largely been superseded by zoledronic acid. Pamidronate is given in several doses, intravenously and repeated when necessary, depending on symptoms. Doses can vary, but commonly 60mg is given by an infusion and this is repeated on 3 consecutive days.

Calcitonin

In cases where bisphosphonates are not recommended, calcitonin injections may be considered to treat bone pain in Paget's disease.

Follow up

An assessment of the response to treatment should take place between 3 and 6 months after treatment has been completed.

Clinical Guideline

Commissioned by the Paget's Association, a clinical Guideline*, for the Diagnosis and Management of Paget's Disease of Bone in Adults, was published in 2019, on behalf of the Paget's Association, the European Calcified Tissue Society (ECTS), and the International Osteoporosis Foundation (IOF).

The Guideline is a result of work carried out by a Guideline Development Group (GDG), which comprised of a group of experts in the field, with patient involvement. The Guideline was endorsed by the ECTS, the IOF, the American Society of Bone and Mineral Research, the Bone Research Society (UK), and the British Geriatric Society.

Recommendations

Several recommendations are made in the Guideline. The following were highlighted by the Guideline Development Group as the most important.

1) Radionuclide bone scans, in addition to targeted radiographs, are recommended as a means of defining, fully and accurately, the extent of the metabolically active disease in patients with Paget's Disease of Bone.

2) Serum total alkaline phosphatase (ALP) is recommended as a first-line biochemical screening test, in combination with liver function tests, in screening for the presence of metabolically active Paget's Disease of Bone.

3) Bisphosphonates are recommended for the treatment of bone pain associated with Paget's disease. Zoledronic acid is recommended as the bisphosphonate most likely to give a favourable pain response.

4) Treatment aimed at improving symptoms is recommended over a treat-to-target strategy, aimed at normalising total ALP in Paget's disease.

5) Total hip or knee replacements are recommended for patients with Paget's Disease of Bone who develop osteoarthritis, for whom medical treatment is inadequate. There is insufficient information to recommend one type of surgical approach over another.

Further Research Needed

The GDG found that there was a lack of research on patient-focused clinical outcomes and so they were able to identify several areas where further research is needed. This will assist the Paget's Association when consideration is given to applications for research funds.

Open Access

The Guideline was published in 2019, in the Journal of Bone and Mineral Research* and has open access. The full Guideline is available to download from our website **paget.org.uk**

*__Guideline Reference__

Ralston, S. H., Corral-Gudino, L., Cooper, C., Francis, R. M., Fraser, W. D., Gennari, L., Guañabens, N., Javaid, M. K., Layfield, R., O'Neill, T. W., Russell, R. G., Stone, M. D., Simpson, K., Wilkinson, D., Wills, R., Zillikens, M. C. and Tuck, S. P. (2019), Diagnosis and Management of Paget's Disease of Bone in Adults: Journal of Bone Mineral Research. Vol. 34, p 579-604.

Complications

The overall frequency with which complications occur in PDB is unknown but when they occur, surgical treatment is often required. Medical treatment with bisphosphonates is seldom effective at treating complications of Paget's disease when they are established.

Bone Deformity

Paget's disease can cause bone to become enlarged and misshapen. Long-standing disease may cause the weight-bearing bones of the leg to bow *(see Figure 1)*.

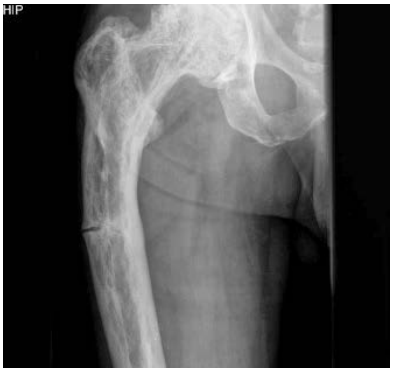


Figure 1
PDB and an incomplete fracture of the femur

Osteoarthritis

Paget's disease can predispose to the development of osteoarthritis at adjacent joints. Joint replacement is common in those with Paget's disease *(Figure 2)*. The changes of Paget's disease usually affect only one side of a joint and are not present in both bones that make up the joint.

Fracture

There is an increased risk of fracture *(Figure 1),* particularly in the weight-bearing bones of the legs. Fractures may initially be incomplete, (stress fractures or fissure fractures), which are at high risk of complete fracture. Fissure fractures predominantly, but not exclusively, affect weight-bearing bones, such as the thigh bone (femur).

Hearing Loss

If the skull is involved, hearing loss can occur.

Nerve Entrapment

Enlarged bones may cause nerve compression. Complications can therefore include basilar invagination of the skull, obstructive hydrocephalus, spinal canal stenosis, and paraplegia. It has been suggested that, in some cases, paraplegia may be due to a vascular "steal" phenomenon, rather than direct compression of the spinal cord.

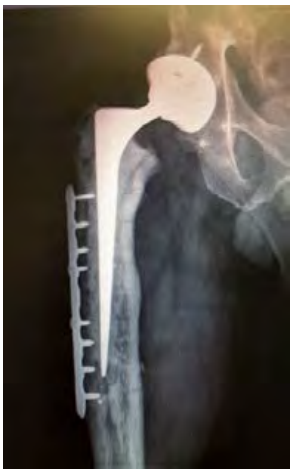


Figure 2
The same femur as in Figure 1, taken some years later after the hip was replaced

Excessive Blood Loss During Surgery

Owing to the increased blood flow to areas of active PDB, were the bone to fracture or surgery be undertaken, active disease would have the potential to result in excessive blood loss in patients undergoing surgery.

Cardiac Failure

In severe cases, high-output cardiac failure, due to increased bone blood flow, has been reported but is extremely rare, especially as Paget's disease is decreasing in severity.

Paget's Associated Osteosarcoma

Osteosarcoma associated with Paget's disease is a rare primary bone cancer. It should be suspected in any patient with Paget's disease, where there is a sudden increase in bone pain, or there is enlargement of the affected bone. Patients suspected to have osteosarcoma should undergo urgent imaging with a CT scan or MRI and be referred for a surgical opinion.

Diagnosis and Monitoring of Paget's Disease of Bone

Main clinical presentation of PDB

Symptomatic patient

- "Bone" pain
- Bone deformity or pathological fracture

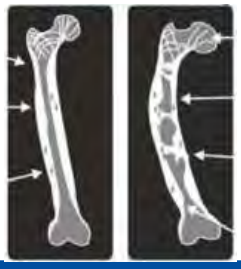
Asymptomatic patient

- Raised serum total alkaline phosphatase (ALP) with normal liver function test.
- PDB detected on imaging conducted for investigation of another disorder

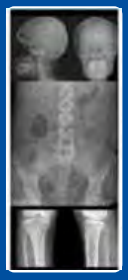
PDB diagnosis

Targeted X-ray of site

Characteristic X-ray features of PDB



Plain X-ray of

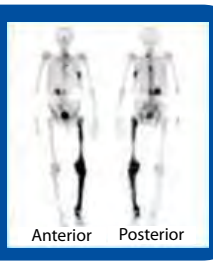


1. Skull and facial bones
2. Abdomen
3. Tibiae

are recommended as initial screening in patients suspected to have PDB

Diagnosis and defining extent of PDB

Radionuclide bone scintigraphy (RBS)
RBS in addition to targeted X-ray, are recommended as a means of fully and accurately defining the extent of metabolically active PDB.



Other imaging

Magnetic resonance imaging (MRI)
or computed tomography (CT)
– Not recommended for the diagnosis of PDB.
– Recommended to assess disease complications.

Assessment of metabolic activity

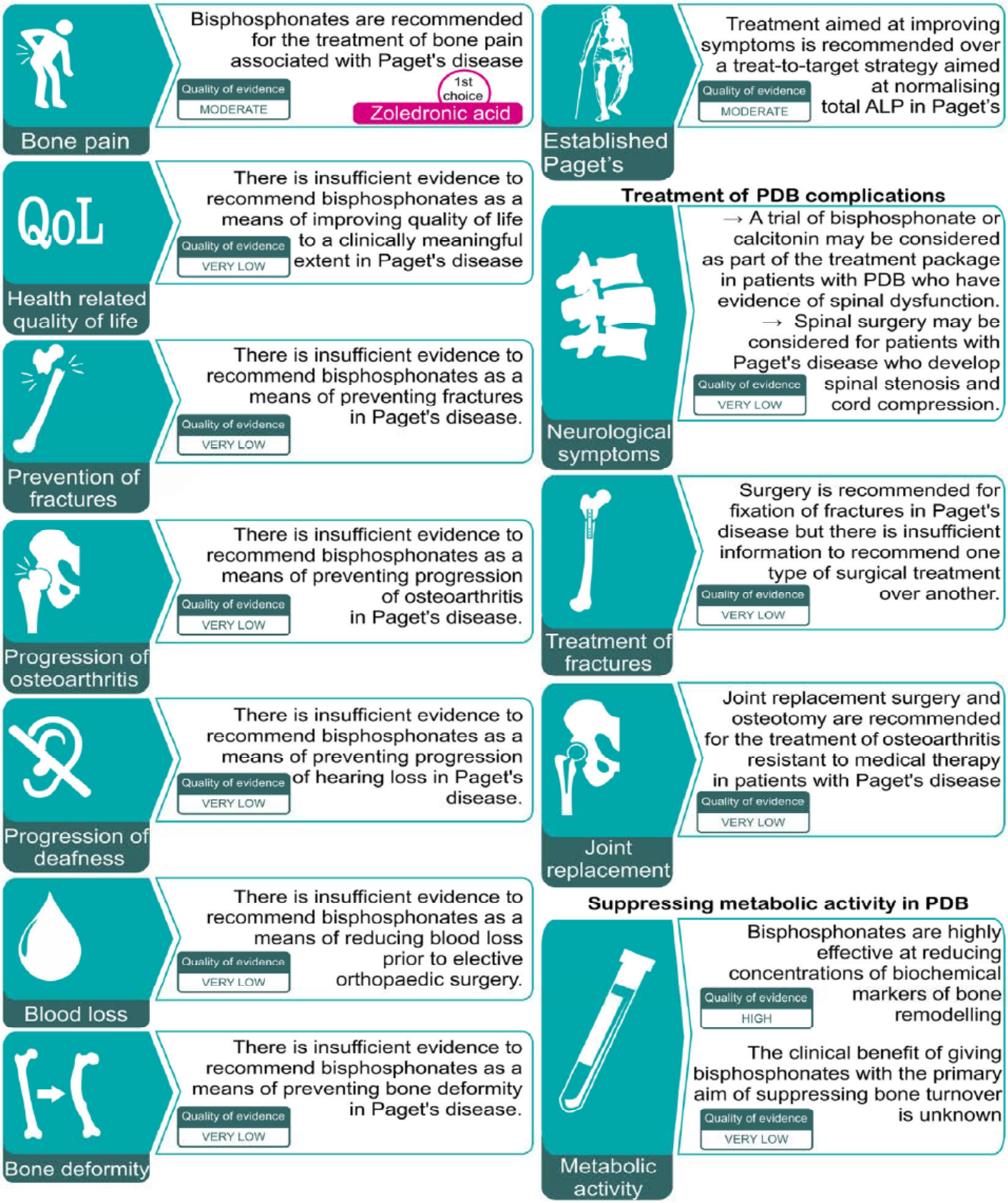
Serum total ALP is recommended as a first line biochemical test in combination with liver function tests in screening for the presence of metabolically active PDB:

If total ALP values are normal and clinical suspicion of metabolically active PDB is high, measurement of BALP, PINP or uNTX may be considered.

ALP: alkaline phosphatase, BALP: bone specific alkaline phosphatase, GGT: gamma-glutamyl transferase, PDB: Paget's disease of bone; PINP: procollagen type 1 amino-terminal propeptide; uNTX: urine N-terminal telopeptide.

Reproduced from Ralston, S. H. et al, (2019), Diagnosis and Management of Paget's Disease of Bone in Adults: A Clinical Guideline. Journal of Bone Mineral Research. Vol. 34, p 579-604.

Management of Paget's Disease of Bone



Reproduced from Ralston, S. H. et al, (2019), Diagnosis and Management of Paget's Disease of Bone in Adults: A Clinical Guideline. Journal of Bone Mineral Research. Vol. 34, p 579-604.

Case Studies

The following cases are examples of patients who were referred to their local rheumatology service.

Case 1

Long-standing, undiagnosed PDB with subsequent osteosarcoma

Presenting Complaint
A 90-year-old man was referred for treatment of presumed osteoarthritis, which had reached the point that he could no longer cope.

For 30 years he had had a painful lower left leg and had been forced to retire at the age of 60 due to the pain. His tibia was bowed with consequent leg shortening.

Investigations
Isolated raised alkaline phosphatase.

X-rays revealed Paget's disease, *(Figure 3)* with some secondary osteoarthritis in the knee.

Isotope bone scan showed Paget's in the tibia. No other areas involved.

Management
He was treated with risedronate, 30mg daily for 2 months and provided with a raised shoe.

Outcome
There was considerable improvement in his pain.

On subsequent review, he developed worsening pain in his tibia and he was found to have osteosarcoma. This was confirmed after referral to the specialist sarcoma service and he sadly passed away a few months later.

Comment
This is a rare case of malignant transformation in bone affected by Paget's. New symptoms arising from involved bones need investigation as to the cause, especially when the disease has previously been asymptomatic or well treated and brought under biochemical control. Possible explanations include fissure fractures, secondary osteoarthritis in adjacent joints and nerve entrapment.

Osteosarcoma is a rare cause, but one not to miss as it requires urgent referral to centres specialising in this type of tumour for investigation and treatment. As an aside, risedronate was used in this individual because the case predated the availability of zoledronate.

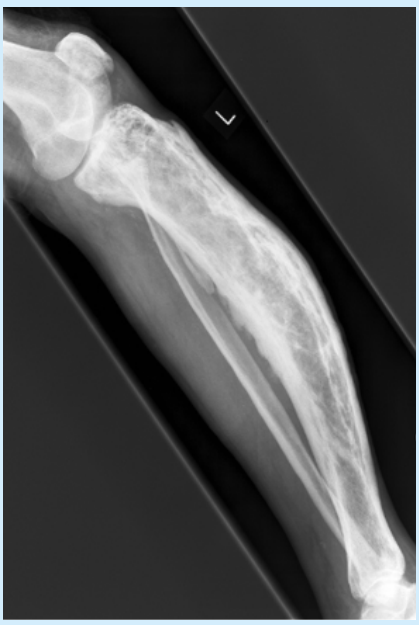


Figure 3

Case 2

A 67-year-old man with pain in his right hip

Presenting Complaint
A 67-year-old man attended his GP complaining of pain in his right hip. It was present at rest and became slightly worse on walking. His general health was good.

He was taking lisinopril 10mg daily for hypertension; atorvastatin 10mg daily for high cholesterol; and paracetamol 1-2g daily for pain.

Investigations
Routine bloods showed normal renal function, normal calcium biochemistry and normal LFT, apart from a raised serum total alkaline phosphatase at 350 U/L (reference range 40-125). Serum 25(OH) vitamin D was low at 24nmol/L (reference range 25-160).

An x-ray of the pelvis showed changes typical of Paget's disease in the right upper femur *(Figure 4)*.

Management
The patient was referred to secondary care.

A radionuclide bone scan showed Paget's disease in the right upper femur with a stress fracture on the lateral femoral cortex, but no other affected sites.

Following discussion of treatment options, he was given vitamin D supplements and went on to have a single infusion of zoledronic acid 5mg, as a day case in his local hospital.

Outcome
On review 4 months later, the pain had improved, and repeat bloods showed that the ALP had fallen to 76 U/L.

On follow up 2 years later, his pain had remained well controlled with intermittent paracetamol and his ALP remained within the normal range.

Comment
The patient had pain localised to an affected site and biochemical evidence of increased metabolic activity of Paget's disease, on biochemistry and bone scan. His symptoms responded well to zoledronic acid, which is considered the treatment of first choice in Paget's disease because of its beneficial effects on pain and long duration of action, which in many cases can extend for up to 5 years or more.

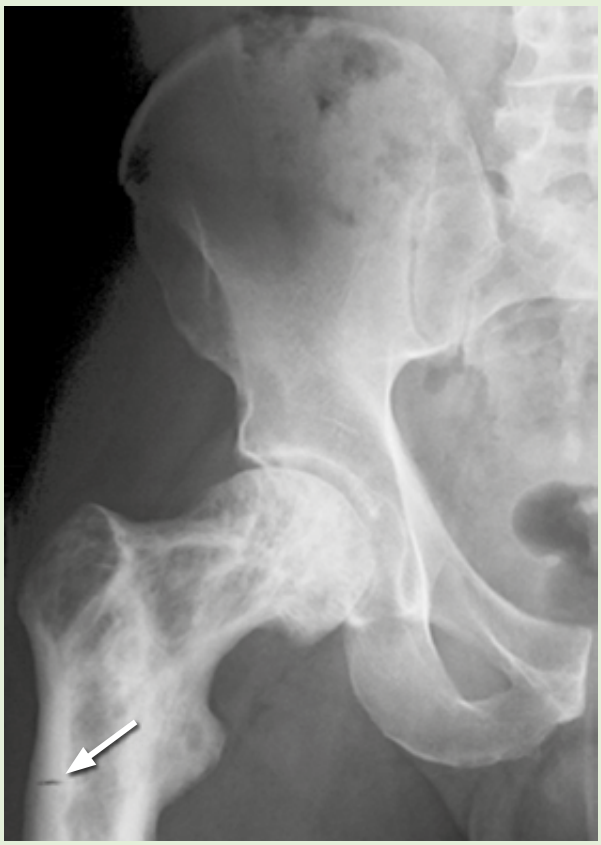


Figure 4
X-ray showing bone expansion, accompanied by osteosclerosis and osteolysis in the upper right femur. The stress fracture is indicated by the white arrow.

Case 3

A 72-year-old man with back and leg pain

Presenting Complaint
A 72-year-old man attended his GP complaining of pain in the lower back region with radiation to both legs, which had been gradually worsening over the previous 2-3 years. He had a history of ischaemic heart disease.

He was being treated with atorvastatin 10mg daily, bisoprolol 10mg daily, vitamin D 800 units daily and co-codamol up to 8 tablets daily.

Investigations
Routine bloods showed normal renal function, and normal calcium biochemistry. Liver function tests showed a raised serum total alkaline phosphatase at 245 U/L (reference range 40-125). Serum 25(OH) vitamin D was 55nmol/L (reference range 25-160).

An x-ray of the pelvis showed evidence of Paget's disease and osteoarthritis in the lumbar spine *(Figure 5)*.

Management
The patient was referred to secondary care for further evaluation.

A radionuclide bone scan showed Paget's disease of L1-L3 with widespread OA change and MRI scan showed evidence of lumbar stenosis at L2-L3.

Following discussion of treatment options, he was offered a therapeutic trial of zoledronic acid, but the possible need for spinal surgery was also discussed.

Outcome
He had a severe reaction to zoledronic acid with fever, bone pain and gastrointestinal upset for a week after the infusion.

On subsequent review 6 months later, his ALP had fallen to 56 U/L, but his pain had not improved. He was referred for spinal decompression surgery which markedly improved his symptoms.

He remained well on follow up 3 years later with some back pain, which is well controlled with co-codamol.

Comment
The patient had pain localised to an affected site, but the lack of response to zoledronic acid indicated that this was most likely due to spinal stenosis and osteoarthritis, both of which can complicate Paget's disease. Imaging with MRI is not generally required to make a diagnosis of Paget's disease, but as this case illustrates, it can help assess the presence of complications such as spinal stenosis.

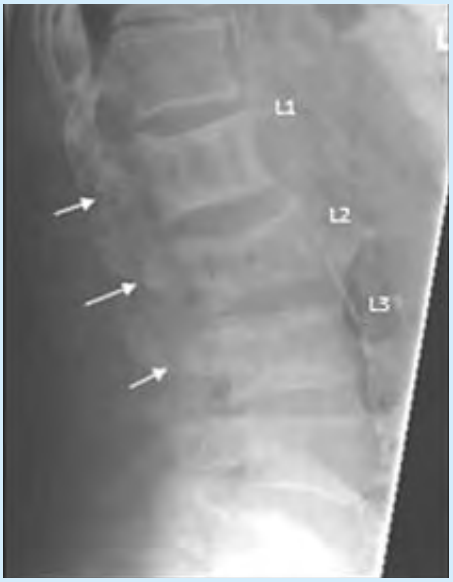


Figure 5
X-ray showing osteosclerosis and osteolysis of L1, L2 and L3 with superadded OA change and osteophyte formation in the posterior vertebral elements (arrows).

Case 4

A 62-year-old man with right hip and knee pain on walking

Presenting Complaint
A 62-year-old man attended his GP complaining of pain in the right hip and right knee on walking, which had been gradually worsening over the previous 2-3 years. He was previously well with no significant past medical history and was taking diclofenac 50mg three times daily for the pain and co-codamol up to 8 tablets daily.

Investigations
An x-ray of the pelvis showed Paget's disease in the upper femur, but OA change in the right hip joint *(Figure 6)*.

Routine bloods showed normal renal function, and normal calcium biochemistry. Liver function tests showed a raised serum total alkaline phosphatase (ALP) at 175 U/L (reference range 40-125). Serum 25(OH) vitamin D was 75nmol/L (reference range 25-160).

Management
The patient was referred to the department of orthopaedic surgery for further evaluation, considering that the pain was most likely due to OA and he was listed for a hip replacement. He underwent a right total hip replacement and was then referred to the metabolic bone clinic for follow up of the Paget's disease. Treatment options were discussed, but he declined to have bisphosphonate therapy as his pain had disappeared.

Outcome
He remained well about 12 months after the right hip arthroplasty, with no pain and serum ALP remained elevated at 168 U/L.

He is being kept under annual review to monitor his symptoms.

Comment
The patient had pain localised to the right hip, but the radiation to the knee is characteristic of osteoarthritis. Although there is Paget's of the right upper femur, the pain responded fully to arthroplasty indicating that OA was the likely cause. Clinical experience indicates that the outcome of arthroplasty in patients with Paget's is excellent. There isn't any evidence so far to suggest that normalization of ALP in patients with PDB is of clinical benefit, but this is an area of ongoing research.

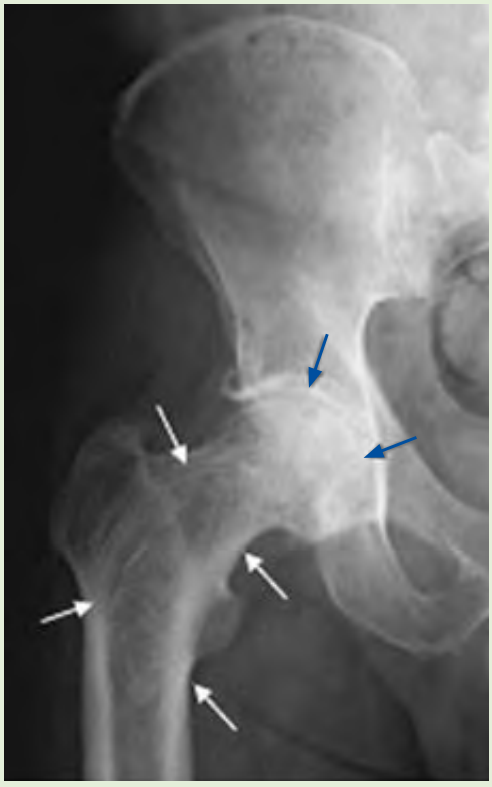


Figure 6
X-ray showing trabecular coarsening and bone expansion of the upper right femur, consistent with Paget's disease (white arrows), and loss of joint space in the right hip joint, consistent with advanced osteoarthritis (blue arrows).

The Paget's Association

The Paget's Association is the only UK charity to focus solely on Paget's Disease of Bone in adults.

The Association:

- acts as a resource for patients, carers and professionals, offering high-quality information and support
- funds and encourages quality research projects
- provides educational awards
- promotes excellence in care and research, through the Paget's Association Centre of Excellence (PACE) Award
- raises awareness of the condition

Booklets and Leaflets

Free booklets and leaflets are available for you to give to your patients.

Free Professional Membership

- Professional membership of the Paget's Association is free of charge
- We welcome both UK and overseas members
- Our membership pack includes a summary of the clinical Guideline, information booklets, copies of our magazine, Paget's Passport, information sheets on various aspects of Paget's disease and a complete list of the UK Centres of Excellence

Health professionals, researchers, patients and carers can join the Paget's Association online or request a membership application form using the contact details below.

For full details and a complete list of current membership benefits, please visit our website

paget.org.uk

Get in Touch

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