Paget's disease: a clinical review

Paget's disease was first described more than 150 years ago, but the exact cause is still unknown – genes and the environment are both important. This article explores the basic science and clinical aspects of this intriguing condition.

Sir James Paget first described Paget's disease in 1876. His name is eponymously associated with several conditions including Paget's disease of the nipple and Paget's disease of the bone (Coppes-Zantiga and Coppes, 2000). He described five cases of a slowly progressive disorder, leading to enlargement and deformity of the bones, at the Medical and Chirurgical Society of London. He called this disorder osteitis deformans, which we now refer to as Paget's disease of the bone (Paget, 1877).

Several theories exist as to the pathogenesis of the disease but the exact cause remains an enigma. The absence of a definite pathophysiological model contributes to the generally poor understanding of this deforming bony disease. The main theories of causation will be discussed.

Epidemiology

UK

The UK had the highest prevalence of Paget's disease in the world according to a 1992 study which suggested that up to 8% of males and 5% of females in the UK would be affected by the age of 80 years (Kaplan and Singer, 1992). More recently, the Paget's Association (2010) has quoted that the disease occurs in up to 2% of white adults over 55 years in the UK. A radiological study in the UK undertaken in the 1970s suggested that the prevalence at that time might be around 5.4% of the population over the age of 55 years. There has since been a sharp downturn in the prevalence of Paget's disease in the UK (Dr Adrian J Crisp, personal communication, 2013) which has not been the case in other European countries. The exact reason for this anomaly is unclear, but immigration from low risk countries must be taken into account.

European and global

Paget's disease appears to be particularly prevalent in temperate climates and in populations of northern European ancestry. A prevalence of 3–4% in those over 50 years of age and 10% in those over 80 years of age is documented (Kaplan and Singer, 1992). Prevalence is lower in more sub-continental and Far Eastern countries

Environmental triggers

Dietary factors such as low levels of calcium and vitamin D during adolescence may contribute to the future dynamics of one's bone profile and hence predisposition to Paget's disease (Mirra, 1987), although this is unlikely. The evidence regarding a viral trigger remains unproven but cannot be dismissed. It is unlikely that Paget's disease can be explained by either one hypothesis or another and it is almost certainly caused by both genetic susceptibility and an environmental component.

Pathophysiology

Bone remodelling is an important process both throughout growth and in adult life. The homeostasis of bone tissue is maintained by the balanced processes of bone formation (osteoblastogenesis) and resorption (osteoclastogenesis) (*Figure 1*).

The slow viral hypothesis

The slow viral theory is based on the concept that a paramyxovirus infection remains quiescent in the bone for many years and becomes active at a later age. Several researchers, both in the UK and abroad (Mills and Singer, 1976), have reported finding inclusion bodies in Pagetic osteoclasts resembling viral material. Mills and Singer (1976) described nuclear inclusion bodies in the osteoclasts of all their patients with Paget's disease. According to the slow viral hypothesis, the virus infects the osteoclasts which then become hyperactive and uncontrollably break down bone. Compensatory osteoblastic activity is then seen, resulting in the deposition of immature Pagetic bone.

More recent reviews argue that the role of these viruses is questionable. Matthews et al (2008) sourced samples from 22 patients with Paget's disease of the bone and 31 controls. Using reverse transcriptase polymerase chain reaction (a genetic test used to detect RNA expression levels), they attempted to detect genes for measles nucleocapsid and matrix proteins. They did not find measles virus sequence in any of the Pagetic or control samples but identified these in samples of a measles virus culture isolate included as a positive control.

Genetic explanation

The genetic predisposition to Paget's disease is clear from the literature. Environmental components as emphasized by the viral theory have some role, but there is strong

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Figure 1. Relationship between the possible mechanisms that cause Paget's disease and their clinical effects. Rogue osteoclasts formed from varying mechanisms (shown in brown) begin to reabsorb bone – when mutated these can be targeted for Paget's disease. Osteoblasts are summoned to fill the voids, this occurs at a rapid rate and the osteoblasts are unable to form normal structured mineralized bone resulting in the clinical and radiological features of Paget's disease (shown in green). PTH = parathyroid hormone; RANKL = receptor activator of nuclear factor κB ligand; RANKR = receptor activator of nuclear factor κB ligand.

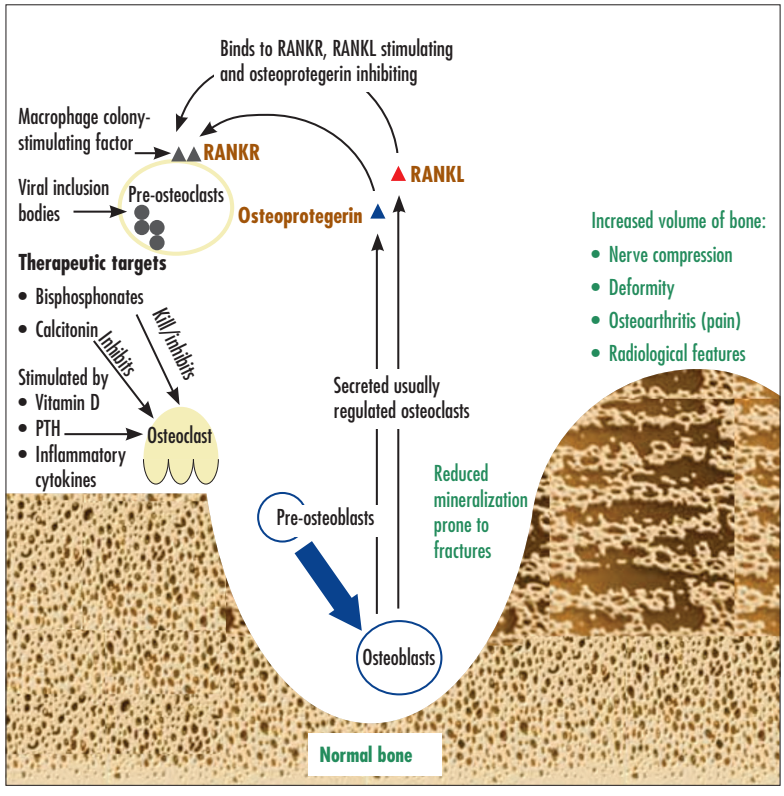
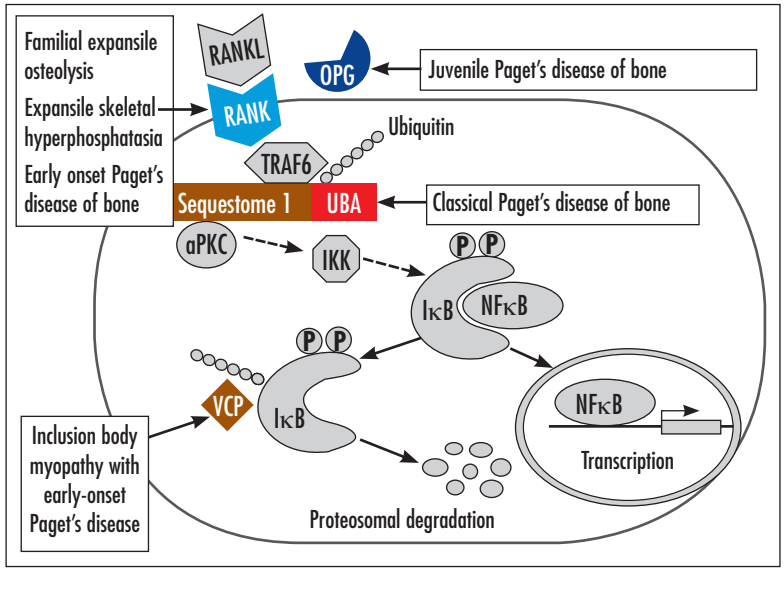


Figure 2. Some genetic defects implicated in Paget's disease. From Daroszewska and Ralston (2006). aPKC = atypical protein kinase C; IkB = inhibitor of nuclear factor κB; IKK = inhibitor of nuclear factor κB kinase; NFκB = nuclear factor κB; OPG = osteoprotogerin; P = phosphate; RANK = receptor activator of nuclear factor κB; RANKL = receptor activator of nuclear factor κB ligand; TRAF6 = TNF receptor associated factor 6; UBA = ubiquitin associated; VCP = valosin-containing protein.



evidence that genetic factors are also key to the aetiology of Paget's disease. Siris et al (1991) found that 12.3% of those with Paget's disease had a positive family history as opposed to 2.3% of controls. They found a higher predisposition in relatives of cases (having a 7-fold increased risk of developing Paget's disease *vs* controls). Morales-Piga et al (1995) found that 40% of cases had a family member with the disease. Migrant studies have shown that people who migrate from high to low prevalence areas retain a higher risk of developing Paget's disease, supporting a genetic link (Gardner et al, 1978).

Figure 2 shows some genetic defects involved in Paget's disease. Downstream of TRAF6 (tumour necrosis factor (TNF) receptor-associated factor 6), p62 normally recruits ubiquitin carboxyl-terminal hydrolase which helps inhibit receptor activator of nuclear factor κB (NFκB) (RANK) signalling and osteoclast activation. The main gene implicated is *SQSTM1* (p62) and seven other susceptibility loci for Paget's disease of the bone have been identified by genomewide association studies (Ralston and Layfield, 2012).

SQSTM1 (p62) – chromosome 5q35

The protein produced by *SQSTM1* is important in interleukin 6 (IL-6), TNF and receptor activator of nuclear factor κB ligand (RANKL) signalling pathways. These all help regulate osteoclast function. Research in families with prevalent Paget's disease found a strong susceptibility locus on chromosome 5q35 via linkage analysis (e.g. proline to leucine switch at position 392 of the p62 gene). Not all people with relevant gene mutations go on to develop Paget's disease, suggesting a contribution of environmental triggers to offset the genetic susceptibility (Ralston and Layfield, 2012). At present evidence suggests that *SQSTMI* mutations account for approximately 40–50% of patients with familial Paget's disease and 2.5–10% of sporadic cases (Siris et al, 1991; Daroszewska and Ralston, 2006).

TNFRSF11A gene – chromosome 18

The RANK ligand is an established osteoclastogenic factor. *TNFRSF11A,* a gene on chromosome 18, encodes RANK, which plays an essential role in osteoclast differentiation and bone resorption (Daroszewska and Ralston, 2006). The gene responsible for familial expansile osteolysis (an autosomal dominant familial bone dysplasia that has phenotypic overlap with Paget's disease) was mapped to a locus on chromosome 18q21–22 by Hughes et al (1994). The maximum logarithm of the odds score for genetic linkage of chromosome 18q to familial expansile osteolysis was found to be over 11. (Logarithm of the odds score greater than 3.0 signifies a 1000:1 chance that linkage did not occur by chance.)

TNFRSF11B gene – chromosome 8q24

TNFRSF11B is the third gene that has been implicated in Paget's disease. This is especially associated with juvenile

Paget's disease but there is also some evidence of a link with classical late onset Paget's disease. The common mechanism in all the described mutations is loss of osteoprotegerin function. By binding RANKL, osteoprotegerin inhibits NFκB, which in turn inhibits osteoclast differentiation and bone resorption. Most severely affected individuals have mutations in the cysteine-rich ligand-binding domain, disrupting binding between osteoprotegerin and RANKL (Chong et al, 2003). Daroszewska et al (2004), in an association study of 690 UK and 66 worldwide cases, found that the G1181 allele of *TNFRSF11B* predisposes to both sporadic and familial Paget's disease (when *SQSTM1* is not implicated). Other genes have also been implicated in rare syndromic forms of Paget's disease as shown in *Figure 2* (e.g. valosin-containing protein).

Clinical aspects of Paget's disease

The clinical features of Paget's disease are caused by the abnormally fast bone remodelling that leads to destruction and subsequent formation of excessive and abnormal bone. A common manifestation of Paget's disease is skeletal deformity. This occurs in most bony areas but is most visible over the skull and the lower extremities. The cranium enlarges asymmetrically in patients with Paget's disease, with greater enlargement over the frontal and occipital areas. Bowing of the upper extremity long bones is much less common than in the lower extremity, possibly because weight-bearing forces are minimal. Hearing loss is a common feature in those with cranial enlargement. A dull persistent pain is common and may be skeletal, neurological or muscular in origin (Langston and Ralston, 2004).

Presentation

The majority of patients with Paget's disease are asymptomatic and when symptoms do arise they are caused by the overgrowth and deformity of the affected bone. The two main clinical manifestations of Paget's disease are pain as a consequence of bone overgrowth (e.g. nerve impingement) and deformities in affected areas. The pain experienced in Paget's disease usually presents late in the progression of the disease and is often a dull ache that is present throughout the day, worsening at night and on weight-bearing joints (Whyte, 2006). *Table 1* highlights clinical manifestations of Paget's disease (Langston and Ralston, 2004; Whyte, 2006).

Complications of Paget's disease

Complications of Paget's disease include peripheral nerve entrapment, pathological fractures, secondary osteoarthritis, malignant transformation of the Pagetic bone into osteosarcoma and high output cardiac failure (Whyte, 2006).

Osteosarcoma

Osteosarcoma is an uncommon but well-recognized complication of Paget's disease. Price (1962) found that those with Paget's disease had a 0.15% chance of developing osteosarcoma – 30 times higher risk than the general population. Osteosarcoma secondary to Paget's disease has a bad prognosis, with a 5-year survival rate of 5% (Shaylor et al, 1999).

Diagnosis of Paget's disease

The diagnosis of Paget's disease can be biochemical and radiological.

Biochemical

Biochemical tests are a good screening tool. Since Paget's is a disease of increased bone turnover, markers of bone turnover are increased in active disease. Many people with X-ray evidence of Paget's disease of the bone have normal alkaline phosphatase activity but most people are referred to clinic for undiagnosed elevation of alkaline phosphatase (Eekhoff et al, 2004). Measuring bone-specific alkaline phosphatase levels can be a good way of assessing radiologically confirmed Paget's disease (Selby et al, 2002). Since Paget's is not a disease of bone mineralization, the calcium, phosphate and parathyroid hormone levels are generally normal. This helps distinguish it from other causes of a raised alkaline phosphatase level. The characteristic blood investigation results in Paget's disease are shown in *Table 2*.

Radiological

Diagnosis is often confirmed by radiological investigations such as X-rays and isotope bone scintigram. X-ray findings of Paget's disease can be divided into an early (primarily lytic), combined (lytic and sclerotic) and a late phase (primarily sclerotic). The descriptions below list the key radiological features found at each stage of Paget's disease.

Early phase (lytic)

The characteristic radiological feature of the osteolytic phase in the skull had been named osteoporosis circumscripta. Osteolytic lesions are the earliest that form and are most visible on the skull. They are a sign of the primary pathology within Paget's disease – excessively fast osteoclastic resorption of bone.

Table 1. Common associations with Paget's disease of the bone

Common associations with Paget's disease	Arthritis (40–50%)
	Pain (40–45%)
	Bone deformity (12–36%)
	Fracture (4–16%)
Less frequent associations with Paget's disease	Radiculopathy and platybasia leading to spastic paraparesis
	Chronic back pain
	Impaired functional status
	Hearing loss and angioid streaks in the retina
	Headache
	Depression

Combined phase (lytic and sclerotic)
In this stage, accentuated trabecular markings, cortical thickening and loss of corticomedullary distinction are seen.

Late phase (primarily sclerotic)
Bone enlargement, sclerosis and long bone thickening (*Figure 3*) are seen in this phase.

Isotope bone scanning
Isotope bone scanning using technetium-labelled bisphosphonates can detect up to 50% more Pagetic lesions than seen on plain radiography alone. It is only done when Pagetic lesions have been confirmed from at least one classic skeletal site and is useful in determining the extent of polyostotic disease. It is less specific than plain X-rays and hence may still need to be confirmed by the former. Isotope bone scanning is more sensitive than plain X-rays and can detect widespread disease (as one can see the whole skeleton). For this reason the UK guidelines on the management of Paget's disease recommend bone scintigraphy be undertaken in all patients to determine the extent, site and total burden of disease (Selby et al, 2002). *Figure 4* shows a diagnostic algorithm for Paget's disease.

Therapeutics
Conservative management
In overweight patients, weight loss helps reduce pressure and stress on already weakened bones. Increasing the amount of exercise the patient does and optimizing the diet helps to achieve this. Exercise strengthens muscles that support bones. Occupational therapy and physiotherapy also help a great deal. If bowing of a leg bone interferes with walking, a shoe lift or walking sticks can help. If the patient's hearing has been affected, a special hearing aid may help. Exercises can be prescribed to help strengthen muscles that support the bones.

Analgesia
Anti-inflammatory agents (e.g. ibuprofen) and analgesics (e.g. paracetamol) are most commonly used to treat pain.

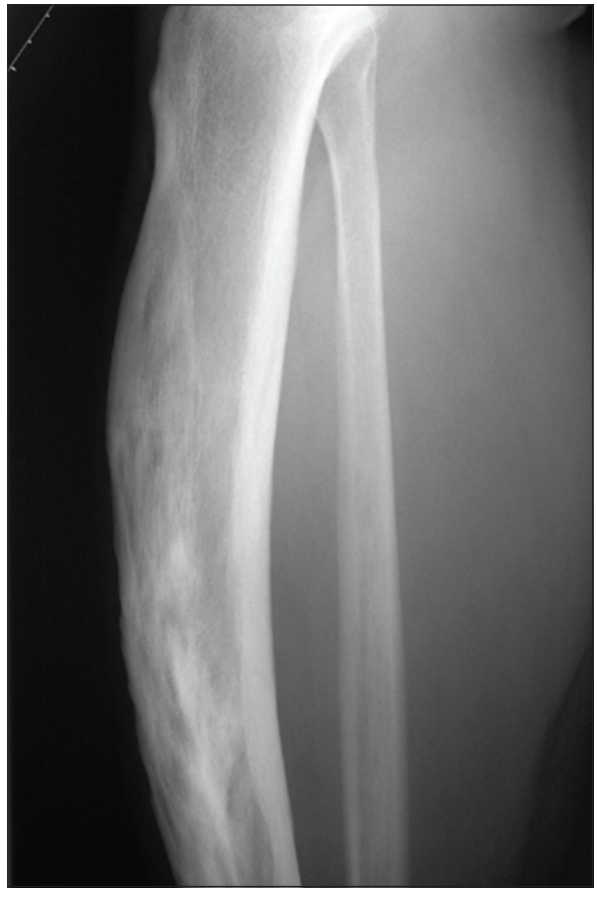
Table 2. Conditions where the alkaline phosphatase level is raised

	Calcium	Phosphate	Parathyroid hormone
Sarcoidosis	↑	↑	←→
Renal failure	↓	↑	↑
Primary hyperparathyroidism	↑	↓	↑
Osteomalacia	↓	↓	↑
Rickets	↓	↓	↑
Paget's disease	←→	←→	←→
Hyperthyroidism	↑	←→	←→

Bisphosphonates
There is no evidence from randomized controlled trials that treatment with bisphosphonates prevents any complication. Bisphosphonates are useful in relieving Pagetic pain (Selby et al, 2002). Risedronate is the most recently approved oral bisphosphonate. Reid et al (2005) reported the results of two studies comparing zoledronic acid to risedronate in the treatment of Paget's disease. Intravenous zoledronate produced a better response and should now be considered first-line treatment as it produces better and longer term symptom reduction. The single infusion regimen also makes zoledronate an attractive and cost-effective treatment.

When to start treatment with bisphosphonates
Bone pain is the primary indication for treatment. Many drugs have been developed for treatment over the years, with the most effective being bisphosphonates. The PRISM study, a large multicentre trial involving 1331 patients in 42 hospitals, compared the effects of intensive bisphosphonate treatment with symptomatic only treatment. Patients allocated to symptomatic therapy were untreated unless they had bone pain at which point they were given non-steroidal anti-inflammatory drugs, analgesia and, if unresponsive, bisphosphonates. Patients allocated to intensive therapy received repeated courses of bisphosphonates with the aim of normalizing the

Figure 3. Thickening of long bones.



alkaline phosphatase level. While the patients who received intensive bisphosphonate therapy achieved better normalization of alkaline phosphatase levels, there was no significant difference in terms of fractures, joint replacement, pain or quality of life (Langston et al, 2010).

One criticism of the PRISM study was that oral risedronate was used as first line for patients with an elevated alkaline phosphatase rather than intravenous pamidronate or zoledronic acid (Reid et al, 2010).

The PRISM authors are currently conducting an extension of the original study called PRISM-EZ to investigate whether the greater suppression of alkaline phosphatase levels by zoledronic acid causes clinical benefit (Goodman et al, 2013). Preliminary results suggest not but further results are awaited.

The PRISM study has certainly highlighted the need for further clinical trials and studies to see if the significant effects of bisphosphonates on bone turnover can be translated into clinical benefit for patients.

UK national guidelines for treatment of Paget's disease of the bone

A working party derived from the Bone and Joint Society as well as the National Association for the Relief of Paget's Disease has published UK national guidelines for the treatment of Paget's disease of the bone (Selby et al, 2002). These guidelines reiterate the indications for treatment. Bone pain is the only clear indication for treatment, although deafness and hypercalcaemia are relative indications. Asymptomatic patients with disease in areas that suggest a higher degree of progression can be offered bisphosphonate treatment (Selby et al, 2002).

In patients with no evidence of significant bone turnover, pain control is the first-line treatment. The ability of bisphosphonates to initiate apoptosis and inhibit cellular metabolic pathways leads to an improved biochemical profile of patients with Paget's disease, evidenced by a relative reduction in alkaline phosphatase levels. Intravenous infusion is the preferred route of administration as a result of the gastrointestinal side effects experienced by patients if given via the oral route. The biochemical improvement noted with treatment is mirrored by radiological improvement (Selby et al, 2002). Although bisphosphonates hold promise in helping in the remission of patients with Paget's disease, in cases where patients relapse despite treatment, evidence is lacking as to whether they would benefit from re-treatment with bisphosphonates. However, expert consensus opinion is that those with symptomatic or biochemical evidence of relapse should be treated with bisphosphonates again (Selby et al, 2002). Evidence suggests a definite role for bisphosphonate treatment in hypercalcaemia associated with Paget's disease and metabolically active symptomatic disease (Langston et al, 2010).

The role of surgery

Surgery may be needed if the disease has caused deformity or damaged a joint. For example, joint replacement surgery may be an option if a bone near to a joint is affected and has caused bad osteoarthritis. In practice surgery is very uncommon, primarily as a result of the surgical difficulties posed by the brittle nature of Pagetic bone. By its very pathophysiological nature Paget's disease is a hypervascular condition. Elective surgery would inevitably lead to major blood loss in patients with Pagetic bone. These patients are given bisphosphonate cover to try to minimize this blood loss, but there is no evidence that bisphosphonates can reduce blood loss after surgery as this has never been studied. BJHM

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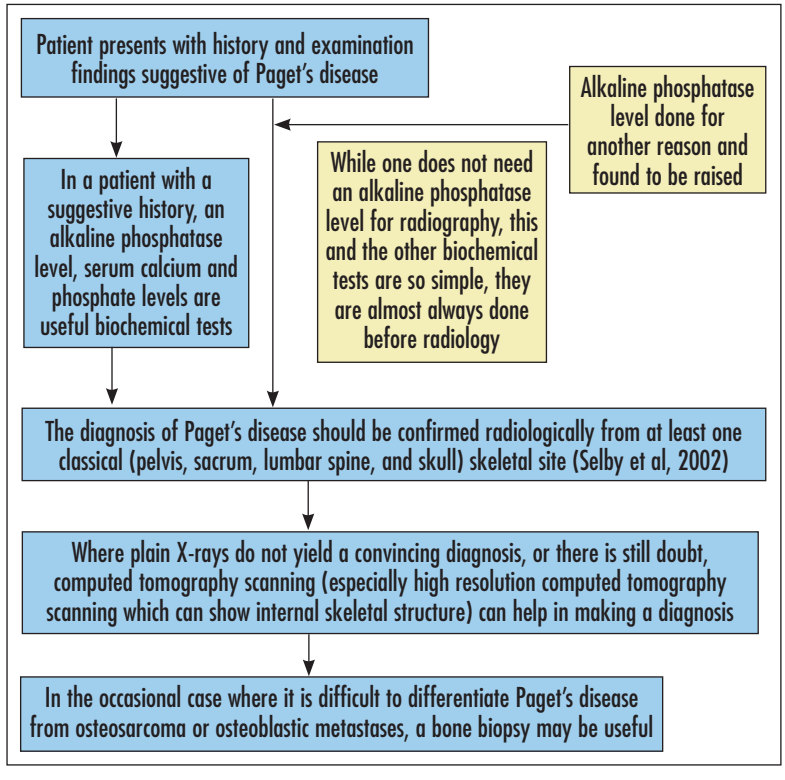
Figure 4. Diagnostic algorithm.



KEY POINTS

- Paget's disease of the bone can cause significant bone pain and disability, requiring early detection and intervention.
- Although biochemical screening is often used as a tool for the diagnosis, it is important to be aware that the screen can be normal in patients with inactive disease. Imaging may be more helpful in such cases.
- The associations with bone and other neoplastic lesions need to be remembered, particularly in patients with grossly elevated serum calcium levels.

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