

# Bone Quality in Paget's Disease of Bone

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**Abstract** Paget's disease of bone is produced by a localized increase in osteoclastic and osteoblastic activity which can progress slowly to involve an entire bone if untreated. A common feature is enlarged bones which are deformed, particularly in weight-bearing regions of the skeleton such as the lower extremity. Pathologic fractures may be a consequence, and nonunion of femoral fractures is not uncommon. Analyses of bone biopsies from patients with Paget's disease indicate that there is a lower, heterogeneous degree of bone mineralization and a younger tissue age than that found in control bone. Pagetic bone also has less resistance to plastic deformation and a straighter crack path than control bone.

## Introduction

Paget's disease of bone is a chronic disorder of bone which develops in one or several bones of the skeleton and usually is not diagnosed before the age of 50 [1•]. It is found nearly equally in men and women. It may affect multiple members of a family in 20–30 % of cases with an autosomal dominant pattern of inheritance albeit with incomplete penetrance. The highest incidence has been in the UK and in the countries where there are large numbers of individuals whose ancestors

have come from the UK. It is also relatively frequent in countries of Western Europe and much less common in Scandinavia and Asia. In recent years, the incidence has diminished in many countries [2], particularly in countries where measles vaccination was instituted about 50 years ago [3].

## Pathology

The disorder evolves from osteolytic foci induced by a localized increase in osteoclasts which often contain many more nuclei than are found in normal bone, and harbor nuclear and cytoplasmic inclusions which resemble paramyxovirus nucleocapsids [3]. The lesion spreads to adjacent bone at a slow rate, and osteoblasts become prominent in areas where osteoclasts previously resorbed bone. The bone formation produced by the osteoblasts is greater than normal but the bone produced is primarily woven in nature rather than lamellar (Fig. 1). Over time, there may be an increase in the size of bone as well as an increase in bone mass. This has been termed the osteosclerotic phase. The bone marrow in these lesions loses its hematopoietic constituents and has a fibrovascular structure with increased blood vessels and numerous bone cell precursors.

## Skeletal Deformity

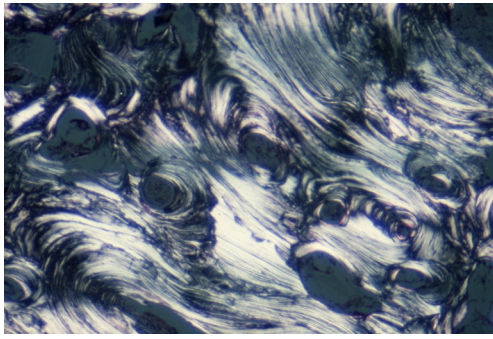
Many patients with Paget's disease have no symptoms. They may be discovered to have the disorder by chance from radiographs taken for other problems, or from elevated serum alkaline phosphatase levels or other markers of bone metabolism. Some individuals develop skeletal deformities which lead to a diagnosis.

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**Fig. 1** Iliac crest bone biopsy from a patient with Paget's disease demonstrating chaotic lamellar bone interspersed with woven bone,  $\times 16$

In the later stages of the disease, deformity may be a striking feature. The skull and facial bones may become asymmetrically enlarged (Fig. 2), the spine may exhibit kyphosis, and long bones, particularly in the lower extremities, may develop a marked degree of lateral and anterior bowing (Fig. 3). The deformity may place great stress on the adjacent joints and produce symptomatic degenerative arthritis.

Although early treatment with calcitonin or bisphosphonates can suppress disease activity and stop the progression of the osteolytic front, there is no evidence that deformity of a pagetic bone can be reversed to any extent.

## Fractures

Patients with Paget's disease have an increased incidence of fractures [4••], predominantly in the lower extremity. Although in the osteolytic phase where there is a localized reduction in bone mass, fractures are not common. The osteosclerotic bone in the femur and tibia is more prone to fracture. There is no evidence that suppressing disease activity reduces the incidence of fractures in patients with Paget's disease. The nature of the fractures is different than those associated with osteoporosis. They



**Fig. 2** Marked enlargement of facial bones and skull in a 73-year-old woman



**Fig. 3** Severe bowing of left tibia and mild bowing of right tibia in an 80-year-old woman

are transverse in nature. These may be preceded by incomplete fractures at the convex surfaces of the bones, termed fissure fractures. Nonunion of fractures is not uncommon particularly in the femur.

## Quantitative Ultrasound and Dual X-ray Densitometry

To explore the explanation for the predisposition of tibial pagetic bones to fracture, one group has utilized quantitative ultrasound analyses and dual X-ray densitometry [5]. In ten patients with a single tibia affected by Paget's disease, the pagetic tibia was compared with the normal tibia. As expected, the mean bone area and the estimated bone volume of the pagetic tibiae were greater than those of the normal tibiae. Also, as expected, the bone mineral content and areal bone mineral density of the pagetic tibiae were greater. However, there was no significant difference in the volumetric bone densities. In studies of osteoporosis patients, measurement of speed of sound across bone correlates with bone mineral density [6]. This was not the case in the comparison of pagetic and normal tibiae. The speed of sound across the pagetic tibiae was significantly slower. This was thought to reflect a difference in bone quality but not in bone calcium content. The investigators hypothesized that in Paget's disease, there is a loss of the normal longitudinal osteonal orientation and that if sound is transmitted perpendicular to the osteons, the sound is transmitted at a slower speed.

## Analysis of Bone Biopsies

In another attempt to investigate the abnormal mechanical integrity of pagetic bone, 49 pagetic iliac crest bone biopsies and 49 control biopsies in the Hamburg Bone Registry in Germany were studied [7••]. None of the pagetic patients had been treated with drugs to suppress bone turnover.

The undecalcified specimens were imbedded in methylmethacrylate and were studied by a variety of techniques including histomorphometry, quantitative backscattered electron imaging (QBEI), Fourier transform infrared spectroscopy (FTIS), polarized light microscopy, nanoindentation, reference point indentation (RPI), in situ fracture toughness tests, and 3D synchrotron microCT. This allowed the investigators to characterize mineral and collagen quality, trabecular and cortical morphology, and mechanical properties of the pagetic and control bone.

## Characterization of Mineral and Collagen Quality

The pagetic bone revealed a greater degree of heterogeneity of bone mineralization with an overall lower bone mineral content using QBEI. Bone quality was assessed by FTIR. Mineral-to-matrix ratio and carbonate-to-phosphate ratio were lower in the pagetic bone. The latter ratio corresponds to carbonate substitution for phosphate in the mineral lattice. This suggests that the osteons have a younger age than those of normal bone. A higher collagen crosslink ratio was found in the pagetic bone, which indicates that there are changes in the secondary structure of the collagen and/or increased amounts of noncollagenous proteins such as osteonectin, osteocalcin, and osteopontin. Taken together, it appears that there are changes in the composition and quality of the bone in Paget's disease which produce a lower, heterogeneous degree of bone mineralization and a younger tissue age.

## Characterization of Trabecular and Cortical Morphology

Evaluation of the trabecular bone in the iliac crests of the pagetic bone by histomorphometry demonstrated an increase in bone volume and increased bone turnover. There was a 2.5-fold increase in trabecular bone volume, a threefold increase in trabecular number, and almost a 4.5-fold decrease in trabecular spacing while the trabecular thickness was no different from the control bone. There was also increased osteoid and increased numbers of osteoblasts as well as osteoclasts.

In the cortices of the control bones, the 3D synchrotron X-ray imaging revealed a predominantly parallel orientation of the osteons whereas the pagetic bones did not. Polarized light microscopy of the control bones revealed that the osteons had alternating light and dark lamellae reflecting normal collagen fiber orientation while the pagetic bone cortical bone consisted of a mosaic of immature woven bone and lamellar bone.

## Mechanical Properties

Nanoindentation is a technique developed to measure the hardness of small volumes of material. The deformation resistance of the specimens was assessed by calculating Young's modulus, which is the ratio of stress to strain, and hardness. The pagetic specimens had a 14 % lower Young's modulus and a 19 % lower hardness than the control specimens. RPI parameters revealed significantly higher indentation depths in the pagetic bone without a change in the average energy dissipated. Taken together, these techniques demonstrated that pagetic bone has a lower modulus and less resistance to plastic deformation.

To investigate the pathogenesis of fractures, tests of fracture mechanics were done on the hydrated cortices of the pagetic and control bones. Fracture toughness was measured as a function of crack extension. Unexpectedly, the fracture toughness of the transversely oriented control and pagetic samples was not significantly different. The image of the crack as determined by electron microscopy and synchrotron X-ray microCT did reveal differences between control and pagetic bone. In the control bone, the crack took a deflected path whereas in the pagetic bone, the crack was straighter. This was likely explained by the differences in microstructure between control and pagetic bone.

## Conclusions

The disease process which is responsible for the development of Paget's disease accounts for the deformity and propensity for fractures. It is likely that early treatment of the osteolytic phase would prevent these complications but this requires further study.

## Compliance with Ethical Standards

**Conflict of Interest** Frederick R. Singer declares no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
  - Of major importance
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