EXTENDED REPORTS

Changes in bone mineral density in patients with Paget's disease treated with risedronate

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Abstract

Objectives—To study changes in bone mineral density (BMD) in patients with Paget's disease of bone treated with risedronate.

Methods—Whole body dual energy x ray absorptiometry (DXA) scans were carried out on 20 patients with Paget's disease treated with oral risedronate. DXA scanning was carried out at baseline and 11 months. Whole body bone mineral content (BMC) was measured. In addition, regions of interest were drawn around the skull, individual lumbar vertebrae, hemipelvis, femora, and tibiae to obtain BMD for these sites. An uncoupling index was also calculated as the area under the curve for serum alkaline phosphatase (ALP) divided by the area under the curve for hydroxyproline excretion (HYPRO) for the period of treatment.

Results—Median whole body BMC increased from 3057 g to 3156 g ($p < 0.001$) resulting from an increase in pagetic and non-pagetic BMD. From the analysis of regions of interest it was found that pagetic trabecular bone showed the largest increase in BMD. The pretreatment HYPRO and the uncoupling index were significantly related to the change in BMD for all pagetic sites for a patient ($r = 0.65$, $p < 0.01$ and $r = 0.57$, $p < 0.05$ respectively).

Conclusion—Bisphosphonate treatment of Paget's disease results in an increase in BMD of pagetic bone without redistribution of mineral from non-pagetic bone. The remodelling space and extent of uncoupling are significantly related to increases in BMD at pagetic sites.

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Bisphosphonates are now widely used in the treatment of a variety of bone diseases.¹⁻³ Current evidence suggests a dual mode of action, with a direct inhibitory effect on osteoclasts^{4,5} as well as an indirect inhibitory effect via osteoblasts.^{6,7} As a result of inhibition of osteoclastic activity, both the temporal relation between

bone resorption and formation, as well as the volume of the remodelling space, are transiently shifted in favour of formation. These effects would be expected to increase bone mineral density (BMD), the magnitude of the increase in BMD being related to the change in bone turnover. These mechanisms are the basis of the use of bisphosphonates in the treatment of osteoporosis.⁸⁻¹⁰

Paget's disease of bone is characterised by increased bone turnover, often at multiple skeletal sites. The primary abnormality is believed to be that of increased osteoclastic resorption with a secondary effect on bone formation.¹¹ Despite this increased rate of remodelling the normal coupling between bone resorption and formation remains intact,^{12,13} although the remodelling space is increased. It would be predicted that bisphosphonate treatment of Paget's disease would increase bone mass by decreasing bone resorption and the resorption space,¹³ although there is a surprising lack of data. In this paper we report our measurements of bone density using dual energy x ray absorptiometry (DXA), before and after treatment with risedronate, a new cyclic bisphosphonate.

Methods

PATIENTS AND STUDY DESIGN

Twenty patients with Paget's disease of bone (12 males and eight females, median age 75.6 years; range 62-89) were treated with oral risedronate 30 mg/day for three months, which was repeated after a four month period of observation if serum alkaline phosphatase (ALP) activity had not returned to normal values. The patients were followed up at monthly intervals and at each visit a clinical assessment was carried out and samples were taken for serum ALP measurement (normal range 80-280 IU/l), and urinary hydroxyproline (HYPRO: normal range <12-20 $\mu\text{mol}/\text{mmol}$ of creatinine).

Whole body bone mineral content (BMC) was measured at baseline and 11 months after the start of treatment, by DXA using a Lunar DPXL densitometer (Lunar Radiation Corporation, Madison, WI). The patients were placed supine on the examination couch with

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Figure 1 Whole body DXA image showing regions of interest apart from the skull. Regions were drawn and numbered as indicated. The pagetic area in the patient shown was the left hemipelvis (region 7), which was more dense than the contralateral normal hemipelvis (region 6).

their arms pronated. Their legs were strapped together at the knees and ankles as described in the operators manual. Whole body images were acquired using the automated method: using the manual analysis software, regions of interest were drawn around individual lumbar vertebrae, hemipelvis, femora, and tibiae to obtain BMD for these sites (fig 1). BMD for the skull was obtained from the automated analysis. Not only did this allow these various skeletal sites to be examined independently, but also enabled calculation of the sum of the change in BMD for each pagetic site (expressed in g/cm²) for an individual patient.

One patient withdrew from the study after the first course because of an inability to maintain follow up and one patient only received the first three month course of risedronate because of the need to undergo total hip replacement. Two patients did not have DXA at 11 months because of logistical reasons. Cross sectional baseline data are reported for all 20 patients and longitudinal data for the 16 who satisfactorily completed the study. We were unable to measure BMD of the lumbar vertebrae in one patient because of scoliosis, and the femora and hemipelvis in two patients because of hip prosthesis. Previous bone scintigrams and plain x rays were used to identify areas of pagetic involvement and the regions divided into affected and unaffected bones (table 1). Upper limb data were not acquired because this is a comparatively rare site for Paget's disease¹⁴ and the bones around the thoracic cage are not amenable to DXA.

A Hologic spine phantom (Hologic Corp, Waltham, MA) showed a 1.9 (0.4)% (mean (SD)) increase in BMD (n=10) at four months and 0.7 (1.4)% increase in BMD (n = 9) at 11 months. The long term coefficient of variation

from daily phantom measurements over three years was 0.42%. The reproducibility of analysis of BMD in each of the regions measured five times in one patient was 1.3–3% for individual vertebrae, 0.8% for the hemipelvis, 0.5% for femora, and 0.8% for tibiae.

ALP and HYPPO were used to explore the influence of remodelling space and uncoupling on BMD. We hypothesised that the pretreatment bone turnover would indirectly reflect remodelling space on the assumption that the higher the bone turnover the greater the number of bone remodelling units.¹⁵ In addition we assessed uncoupling by plotting ALP and HYPPO as a percentage of pretreatment values with time from 0 to 11 months as shown in figure 2 for one patient. The area under the curves (AUC) for ALP and HYPPO were calculated. The ratio ALP AUC/ HYPPO AUC was obtained for each patient and termed the uncoupling index.

A value greater than 1 would imply that bone formation was in excess of resorption and a value less than 1, the converse. The Fig P graphics program (Fig P Software Corp, Durham, NC) was used to plot ALP and HYPPO with time. In this program the AUCs are determined automatically using the trapezoidal rule and are part of the statistical output for a line graph.

Data were log transformed where appropriate and Pearson's correlation coefficient used to assess relations between variables. The Wilcoxon matched paired signed rank test was used to assess differences between variables. All tests were two tailed and a p value of < 0.05 was considered statistically significant. The SPSS for Windows program (SPSS Inc, Chicago, IL) was used for these statistical analyses.

Results

BASELINE BMD (N = 20)

The median whole body BMC at baseline was 2862 g (interquartile range 2351–3475); pagetic bone in the lumbar spine, hemipelvis, and femora had a greater BMD compared with unaffected bone before treatment (table 1). The tibiae were not analysed because of the small numbers of affected bones at this site.

CHANGE IN BMD WITH TREATMENT (N = 16)

Median whole body BMC increased from 3057 g (interquartile range 2510–3568) to 3156 g (interquartile range 2592–3793), which was statistically significant (p < 0.001). Table 2 shows the changes in BMD with treatment. Both pagetic and non-pagetic sites showed a

Table 1 Baseline BMD (g/cm²) for skeletal regions of interest for all patients (n=20). Values are median (interquartile range) with the exception of the three patients with Paget's disease of the tibiae. Significance testing for the pagetic tibiae were not performed given the small numbers

Region	Total	Pagetic	Non-pagetic	p Value
Skull	1.98 (1.75 to 2.16)	1.94 (1.74 to 2.11)	2.01 (1.79 to 2.13)	Not significant
Lumbar vertebrae	1.34 (1.05 to 1.62)	1.66 (1.36 to 1.89)	1.27 (1.03 to 1.47)	0.006
Hemipelvis	1.31 (1.13 to 1.53)	1.39 (1.23 to 1.57)	1.05 (0.92 to 1.15)	Not significant
Femora	1.37 (1.13 to 1.58)	1.48 (1.21 to 1.70)	1.23 (1.08 to 1.50)	0.035
Tibiae	1.12 (0.94 to 1.34)	1.45 (not calculated)	Not calculated

Figure 2 Changes in ALP and HYPRO with time. Shaded bars represent duration of risedronate treatment. The area under the curves for ALP and HYPRO were calculated and expressed as an uncoupling index (see text for details).

statistically significant increase in BMD, though the increases in pagetic sites were of a greater magnitude and achieved a higher degree of significance.

DIFFERENCES BETWEEN PAGETIC AND NON-PAGETIC BONE (N = 16)

Table 2 shows the change in BMD for pagetic and non-pagetic sites. The greatest change in BMD occurred in pagetic lumbar vertebrae with a median increase of 0.25 g/cm² (interquartile range 0.03–0.44), which was significantly greater than non-pagetic vertebrae (median increase 0.05 g/cm² interquartile range –0.06 to 0.20), $p < 0.05$. Pagetic bone in the skull and hemipelvis tended to show a greater increase compared with non-pagetic but this did not reach statistical significance at either site, possibly because of the small numbers, while changes in BMD at the femora were unaffected by pagetic involvement.

RELATION BETWEEN BONE TURNOVER AND CHANGE IN BMD

Median pretreatment ALP was 1387 IU/l (interquartile range 1145–1923), which

Figure 3 Relation between uncoupling index and sum of change in BMD for all pagetic sites within a patient ($n = 16$). Pearson's coefficient $r = 0.57$, $p < 0.05$.

decreased to 240 IU/l (interquartile range 180–387) after treatment. Median pretreatment HYPRO was 110 mmol/μmol of creatinine (interquartile range 57–145), which decreased to 13 mmol/μmol of creatinine (interquartile range 10–22). There was no relation between pretreatment markers of bone turnover or uncoupling index and changes in whole body BMC. The sum of the change in BMD, however, for each pagetic site within a patient was significantly related to the uncoupling index, $r = 0.57$, $p < 0.05$ (fig 3) and pretreatment HYPRO, $r = 0.65$, $p < 0.01$, but not to pretreatment ALP, $r = 0.12$, $p = 0.69$.

Discussion

DXA is now an accepted method for assessment and monitoring the treatment of diseases such as osteoporosis.^{16,17} DXA permits BMD measurement at sites in the skeleton vulnerable to fractures, such as the lumbar spine, femoral neck, and wrist as well as providing a whole body measurements. It also allows regions of interest to be defined, so that the BMD of focal areas within the skeleton can be assessed.¹⁸ We have used this capability to study patients with Paget's disease before and after treatment with the cyclic bisphosphonate, risedronate, to investigate changes in focal BMD.

Baseline pagetic areas of the skeleton tended to be more dense than non-pagetic (table 2). Whole body BMC and BMD for pagetic and non-pagetic sites increased significantly with

Table 2 Pretreatment, post-treatment, and change in BMD (g/cm²) ($n=16$). The values are median (interquartile range). The numbers in italics refer to the total number of pagetic and non-pagetic sites for these patients. Significance testing for the pagetic tibiae were not performed given the small numbers

Site	Pretreatment	Post-treatment	Change	p Value
<i>Skull</i>				
Pagetic (10)	1.94 (1.71 to 2.09)	2.09 (1.90 to 2.31)	0.15 (0.06 to 0.30)	0.005
Non-pagetic (6)	2.01 (1.74 to 2.12)	2.13 (1.95 to 2.24)	0.05 (0.04 to 0.31)	0.050
<i>Lumbar vertebrae</i>				
Pagetic (22)	1.73 (1.39 to 1.91)	1.98 (1.58 to 2.37)	0.25 (0.03 to 0.44)	< 0.001
Non-pagetic (53)	1.29 (1.09 to 1.47)	1.38 (1.14 to 1.57)	0.05 (–0.06 to 0.22)	0.036
<i>Hemipelvis</i>				
Pagetic (25)	1.47 (1.26 to 1.59)	1.48 (1.27 to 1.66)	0.07 (0.02 to 0.12)	0.002
Non-pagetic (5)	1.00 (0.99 to 2.25)	1.09 (1.01 to 1.22)	0.00 (–0.03 to 0.05)	0.500
<i>Femora</i>				
Pagetic (14)	1.57 (1.24 to 1.72)	1.55 (1.30 to 1.75)	0.05 (0.02 to 0.07)	0.005
Non-pagetic (16)	1.28 (1.10 to 1.49)	1.49 (1.18 to 1.62)	0.05 (0.02 to 0.10)	0.001
<i>Tibiae</i>				
Pagetic (3)	1.45	1.38		
Non-pagetic (29)	1.10 (0.94 to 1.29)	1.15 (1.00 to 1.33)		

risedronate treatment showing that reduction of bone turnover has a generalised effect on the skeleton. The greatest increases in BMD occurred at pagetic sites, however, particularly those with the largest proportion of trabecular bone (vertebrae), whereas areas of predominantly cortical bone (femora) tended to show the smallest increase with little difference between those with and without pagetic involvement. This difference probably reflects the larger volume of the remodelling space in trabecular compared with cortical bone¹⁵ and is consistent with the direct relation between biochemical markers of bone turnover and changes in BMD. It is intriguing that the increase in BMD at all pagetic sites for a patient shows a significant positive correlation with pre-treatment HYPRO (a marker of bone resorption) but not with ALP (a marker of bone formation). This possibly reflects the importance of bone resorption as the primary abnormality in the pagetic process while changes in bone formation are a secondary phenomenon. In addition it should be noted that the magnitude of the change in BMD may have been an underestimate in some patients who did not have normal bone turnover at the end of the study. Thus further bisphosphonate treatment could potentially lead to further increases in BMD in these patients. Lastly, although there was a drift in the phantom measurements over the study period, this alone would not be responsible for the difference in increase in BMD between pagetic and non-pagetic sites, because both would have been equally affected.

The other determinant of the gain in bone with bisphosphonate treatment is the degree of uncoupling between bone resorption and formation resulting from bisphosphonate treatment and shown by the positive relation between the uncoupling index and the increase in BMD. Whole body BMC increased, but the changes were not related to either pretreatment HYPRO or the uncoupling index, probably reflecting the focal nature of the pagetic process, which is 'diluted' by normal bone. Furthermore, the increase in whole body BMC suggests that the increase in pagetic BMD was not caused by redistribution from normal sites, although the lack of a coefficient of variation for this measurement should be considered in the interpretation of this observation.

There are few previous studies of BMD in Paget's disease. In a cross sectional study using dual photon absorptiometry in a group of 66 patients the BMD of pagetic areas was significantly greater than normal contralateral sites.¹⁹ Divergent effects have been found with bisphosphonate treatment on axial and appendicular bone density.^{20,21} Both these studies assessed BMD only at the lumbar spine and radius. Measurement of BMD at the lumbar spine using dual photon absorptiometry and the proximal radius using single photon absorptiometry, during etidronate and pamidronate treatment, showed a non-significant increase in BMD at the lumbar spine but a significant decrease at the proximal radius.²⁰ This study was limited both in patient numbers as

well as by the fact that no attempt was made to differentiate pagetic from non-pagetic bone. In a more detailed study of pamidronate treatment,²¹ BMD was measured at the lumbar spine using DXA and the forearm using single photon absorptiometry. As in this study, pagetic vertebrae showed the greatest increase in BMD but there was also a decrease at the midshaft and ultradistal radius of both pagetic and non-pagetic bone (confined to the highest dose group) confirming the findings of Guesens *et al.*²⁰ These authors also showed an inverse relation between change in ultradistal forearm BMD and increase in intact parathyroid hormone concentrations, suggesting that the mechanism of bone loss at the ultradistal radius was related to secondary hyperparathyroidism and raising the possibility of increased fracture risk.

In conclusion we have shown, using DXA, that pagetic bone is more dense than non-pagetic bone before treatment. With bisphosphonate treatment, whole body BMC increases because of increases at pagetic and non-pagetic sites. The greatest increases in BMD occur at trabecular sites affected with Paget's disease and reflect the pretreatment remodelling space and the extent of bisphosphonate induced uncoupling of remodelling. Whether these changes influence the risk of fractures, both in pagetic and non-pagetic bone is still unclear.

- 1 Campbell G, Compston J, Crisp A, eds. *The management of common metabolic bone disorders*. London: Cambridge University Press, 1993.
- 2 Nordin BEC, Need AG, Morris HA, eds. *Metabolic bone and stone disease*. London: Churchill Livingstone, 1993.
- 3 Patel S, Lyons A, Hosking DJ. Drugs used in the treatment of metabolic bone disease *Drugs* 1993;46:594-617.
- 4 Flanagan AM, Chambers TJ. Dichloromethylene bisphosphonate (Cl₂MBP) inhibits bone resorption through injury to osteoclasts that resorb Cl₂MBP-coated bone. *Bone and Mineral* 1989;6:33-43.
- 5 Carano A, Teitelbaum SL, Konsek JD, Schlesinger PH, Blair HC. Bisphosphonate directly inhibit the bone resorption activity of isolated avian osteoclasts in vitro. *J Clin Invest* 1990;85:456-61.
- 6 Khokher MA, Dandona P. Diphosphonates inhibit human osteoblasts secretion and proliferation. *Metabolism* 1989;38:184-7.
- 7 Sahini M, Guenther HL, Fleisch H, Collin P, Martin TJ. Bisphosphonate act on rat osteoclast bone resorption through the mediation of osteoblasts *J Clin Invest* 1993;91:2004-11.
- 8 Fleisch H. Prospective use of bisphosphonate compounds in osteoporosis. *J Clin Endocrinol Metab* 1993;76:1397-8.
- 9 Harris ST, Gertz BJ, Genant HK, Eyre DR, Survill TT, Ventura JN, *et al.* The effect of short term treatment with alendronate on vertebral density and biochemical markers of bone remodelling in early postmenopausal women. *J Clin Endocrinol Metab* 1993;76:1399-406.
- 10 Patel S. Current and potential future drug treatments for osteoporosis. *Ann Rheum Dis* 1996;55:700-14.
- 11 Roodman GD. Paget's disease and osteoclast biology. *Bone* 1996;19:209-12.
- 12 Harris WH, Heaney RD. Skeletal renewal and metabolic bone disease. *N Engl J Med* 1969;280:193-202.
- 13 Hamdy RC. Paget's disease of bone: assessment and management. In: Hamdy RC, ed. *Paget's disease of bone*. New York: Praeger, 1981.
- 14 Harinck HJ, Bijvoet OLM, Vellenga CJLR, Blanksma HJ, Frilink WB. Relationship between signs and symptoms in Paget's disease of bone. *Q J Med* 1986;226:134-51.
- 15 Kanis JA. Pathophysiology and histopathology. In: Kanis JA. *Pathophysiology and treatment of Paget's disease of bone*. London: Martin Donitz, 1991.
- 16 Kellie SE. Measurement of bone density with dual-energy x-ray absorptiometry (DEXA). *JAMA* 1992;267:286-94.
- 17 Jergas M, Genant HK. Current methods and recent advances in the diagnosis of osteoporosis. *Arthritis Rheum* 1993;36:1649-62.
- 18 Seto H, Kageyama M, Nomura K, Kakishita M, Tonami S. Precision of total-body and regional bone mineral measurement by dual-energy X-ray absorptiometry. *Radiat Med* 1991;9: 110-3.

- 19 Nuti R, Righi G, Turchetti V, Martini G, Lepore C. Total body and regional bone mineral analysis by dual - photon absorptiometry in Paget's disease of bone. *Bone and Mineral* 1988;3:359-67.
- 20 Guesens P, Wouters C, Nijs J, Dequeker J. Effect of the bisphosphonates EHDP and APD on bone mineral density in patients with Paget's disease In: Christiansen C, *et al*, eds. *Osteoporosis*. Copenhagen: Osteoporosis ApS, 1990: 1451-52.
- 21 Price RI, Gutteridge DH, Stuckey BGA, Kent GN, Rettalack RW, Prince RL, *et al*. Rapid, divergent changes in spinal and forearm bone density following short-term intravenous treatment of Paget's disease with pamidronate disodium. *J Bone Miner Res* 1993;8:209-17.

Figure 1 Morbus coxae senilis. (A) Marked enlargement of the acetabulum, (B) deformity of the femoral head and of the femoral neck, (C) joint capsule.

Comment

The term 'morbus coxae senilis' (synovium: deforming osteoarthritis) was frequently used in the past to define late stages of hip osteoarthritis).

Kirmission. Malattie degli arti. In: Duplay S, Reclus P, eds. *Trattato di chirurgia*. Turin: Unionne Tipografico Editrice, 1895.