

**Teriparatide Improves Bone Quality and Healing of Atypical Femoral Fractures  
Associated with Bisphosphonate Therapy**

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## Abstract

Bone remodelling suppressants like the bisphosphonates reduce bone loss and slow progression of structural decay. As remodelling removes damaged bone, when remodelling suppression is protracted, bone quality may be compromised predisposing to microdamage accumulation and atypical femoral fractures. The aim of this study was to determine whether teriparatide therapy assists in fracture healing and improves bone quality in patients with bisphosphonate associated atypical femoral fractures.

A prospective study was conducted involving 14 consecutive patients presenting during two years with atypical femoral fracture. All patients were offered teriparatide therapy unless contraindicated. Age and sex matched control subjects without fragility fractures or anti-resorptive treatment were recruited. High resolution peripheral micro-computed tomography (HRpQCT) scans of the distal radius and distal tibia were analysed for their cortical bone tissue mineralisation density using new software (StrAx1.0, StrAxCorp, Australia) at baseline and 6 months after teriparatide.

Administration of 20 micrograms of teriparatide subcutaneously daily for six months to five of the 14 patients was associated with 2-3 fold increase in bone remodelling markers ( $p = 0.01$ ) and fracture healing. At the distal radius, the proportion of less densely mineralised bone increased by 29.5 percent ( $p = 0.01$ ), and the proportion of older, more densely mineralised bone decreased by 16.2 percent ( $p = 0.03$ ). Similar observations were made at the distal tibia. Of the nine patients managed conservatively or surgically, seven had poor fracture healing with ongoing pain, one sustained a contralateral atypical fracture and one had fracture union after 1 year. Teriparatide may assist in healing of atypical fractures and restoration of bone quality.

Keywords: Atypical femur fractures, Bisphosphonates, High Resolution Computed Tomography, Osteoporosis, Teriparatide.

## Introduction

Bone remodelling is the cellular machinery responsible for the removal and replacement of damaged bone with an equal volume of new bone.<sup>1</sup> In adulthood, bone remodelling produces bone loss and structural decay because less bone is deposited than was removed during each remodelling event.<sup>2</sup> After menopause, bone loss and structural decay accelerate as oestrogen deficiency increases the intensity of bone remodelling.

Antiresorptive agents like the bisphosphonates reduce the intensity of bone remodelling slowing the progression of structural decay. Bone mineral density (BMD) does not only stabilise, it increases because refilling of resorptive cavities present at the onset of treatment proceeds with the concurrent appearance of fewer new remodelling cavities.<sup>3</sup> Bone matrix formed months prior to treatment undergoes more complete secondary mineralisation rather than being removed and replaced with younger less fully mineralised bone matrix.

When bone matrix becomes more densely and more completely mineralised, it becomes brittle; it cannot absorb energy by deforming when loaded so the energy imparted to the bone is dissipated by micro-cracking.<sup>4</sup> More homogeneously mineralised bone matrix offers less resistance to micro-crack propagation, so cracks lengthen.<sup>5</sup> Remodelling suppression reduces structural decay but may compromise bone material composition as reduced removal of microdamage, increased occurrence and propagation of microcracks increase net microdamage burden and compromises the material strength of bone.<sup>6</sup>

Atypical femoral fractures are transverse or oblique stress fractures without comminution occurring in the cortex of the subtrochanteric region sometimes associated with prolonged remodelling suppression induced by bisphosphonates.<sup>7-9</sup> Management of complete fractures is surgical fixation using an intramedullary rod. Management of incomplete fractures is uncertain with some investigators proposing prophylactic surgery.<sup>7</sup> Given the benefits of teriparatide in fracture healing,<sup>10-12</sup> several case reports of healing of atypical fractures and osteonecrosis of the jaw,<sup>13-15</sup> we studied 14 patients with atypical femoral fractures associated with bisphosphonate therapy to test the hypothesis that teriparatide treatment will stimulate bone remodelling leading to replacement of more fully mineralised bone matrix with younger more heterogeneously mineralised bone matrix and fracture healing.

## Material and Methods

Fourteen patients (13F, 1M, age  $76 \pm 1.9$ ) presented with thigh pain occurring spontaneously or with minimal trauma to Austin Health between June 1, 2009 and September 31, 2011. All reported four to ten years exposure to bisphosphonates (alendronate = 11, risedronate = 1, sequential pamidronate/ zoledronate = 2). Complete atypical femoral fractures (n = 6) were defined as transverse or short oblique fractures without comminution. Incomplete fractures (n = 8) were defined as an incomplete fracture line on the lateral cortex, or abnormalities on technetium bone scan/ MRI suggestive of stress fractures in the lateral cortical region.<sup>7</sup> All fractures were adjudicated by a second independent radiologist. Fracture union was regarded to have occurred if a fracture line was no longer visible. Bisphosphonates were ceased after confirmation of atypical fracture. All patients were treated with cholecalciferol and calcium supplements and offered teriparatide unless contraindicated. Patients treated with teriparatide were monitored for worsening of pain in case of fracture line extension.

C-telopeptide (CTX) and procollagen Type 1 N-terminal propeptide (P1NP) were measured in fasting morning serum at baseline and repeated after six months (Roche Diagnostics, Mannheim, Germany, coefficient of variation for CTX and P1NP were ~4%). Reference range for pre-menopausal women was <570 ng/L for CTX and <59 µg/L for P1NP. Visual Analog Scale (VAS) pain score was used to assess pain at the time of fracture and on subsequent clinic review.

Bone micro-architecture of the distal tibia and radius were quantified at baseline using high resolution peripheral micro- computed tomography (HRpQCT) (Xtreme CT, Scanco Medical AG, Brüttisellen, Switzerland).<sup>16</sup> Cortical thickness (Ct.Th) and density (Ct.vBMD) were measured and the results were expressed as a standardised deviation (Z score) derived from age- and sex- matched controls (284 female, 98 male). Of the 14 patients, three did not have baseline scans post surgical fixation. Scans with movement artefacts were excluded from analysis (tibial image from one teriparatide treated patient and radial images from five control subjects).

HRpQCT scans were repeated after 6 months of treatment in the teriparatide group (age 77.5 ± 1.6 years), and after 6 months of observation in 5 age and sex matched healthy controls (age 77.3 ± 1.3 years). The bone matrix mineralisation density and its distribution were quantified using StrAx1.0 (StraxCorp, Melbourne, Australia), a new software used to process images obtained using HRpQCT.<sup>17</sup> The software uses an algorithm to separate bone from background and then separate bone into its cortical, transitional zone and trabecular compartments without thresholding. Voxels within cortical bone with an attenuation value produced by fully mineralized bone (~1200 mg hydroxyapatite) are identified and assigned a value of 100%. The remaining voxels are classified relative to this maximum mineralization value as follows: (i) zero; exclusively occupied by void (having a similar attenuation as the background), (ii) 1-50% of the maximum, (iii) 51-70% of the maximum, (iv) 71-95% of the maximum, (v) greater than 95% of the maximum. We did not attempt to distinguish the relative contributions of submaximally mineralized bone matrix volume versus void volume to the net voxel attenuation value. However, a decrease in attenuation relative to the maximum value indicates the voxel now contains new bone, void or both.

Teriparatide is approved for use in Australia to treat patients with severe osteoporosis who re-fracture despite anti-resorptive therapy and is the standard of care for the five treated patients. The use of µCT in these patients is approved by the Austin Health Ethics Committee (H2006/02704). Control subjects were recruited via a separate Nutritional and Fall Study (H2004/02075).

Descriptive parameters were expressed in mean and standard error of the mean (SEM). Paired t-test was used to analyse HRpQCT parameters at baseline and six months in the teriparatide and control group. Measurements of Ct.Th. and Ct.vBMD were expressed as age- and sex specific standardised Z-scores, one sample t-test was used to calculate difference to a hypothetical mean of zero. A significant level of  $p < 0.05$  was used in all analyses.

## Results

Of the 14 patients, six had unilateral and eight had bilateral atypical femoral fractures. Five patients agreed to treatment with teriparatide, one following completion of the stress fracture and four patients because of persisting fracture non-union and ongoing pain during 8-12 months post incomplete fracture. The remaining nine patients (5 with complete, 4 with

incomplete fractures) were not treated due to contraindications [Paget's disease (n = 2), primary hyperparathyroidism (n = 1), multiple myeloma (n = 1), breast cancer (n = 2)] and refusal to self-inject (n = 3). The mean duration of bisphosphonates exposure was similar in the teriparatide group and the group managed conservatively (eight and six years respectively).

In the five patients treated with teriparatide for 6 months, bone remodelling markers increased (baseline mean CTX = 191 ng/L, increased 196 percent,  $p = 0.057$ ; baseline mean P1NP = 21 mcg/L, increased 343 percent,  $p = 0.01$ ). The distal radius cortical void-mineralised matrix distribution curve shifted left and the mean cortical bone tissue mineralisation density decreased (Fig. 1a-c) as the proportion of voxels with lower density increased by 29.5 percent ( $p = 0.01$ ), and the proportion of voxels with higher density decreased by 16.2 percent ( $p = 0.03$ ) (Table 1). Similar observations were made at the distal tibia (voxels with lower density increased by 2.4 percent (N.S.), voxels with higher density decreased by 7.8 percent ( $p = 0.07$ ) (Fig. 1d-f). There was no shift in the void-mineralised matrix distribution curve in controls. Technetium uptake at the fracture sites decreased following teriparatide treatment (Fig. 2). Fracture union occurred in 2 patients with the fracture line no longer visible. Two patients became pain-free and the remaining three patients had improvement in pain scores (mean follow-up VAS = 2.4/10).

Tibial cortical thickness and radial vBMD were elevated prior to treatment in the 10 cases with available HRpQCT scans (Fig. 3). In the five patients treated with teriparatide, tibial cortical thickness decreased by 2.8 percent, cortical vBMD decreased by 0.3 percent (neither change being statistical significance). Radial cortical thickness decreased by 4.1 percent ( $p = 0.02$ ) and cortical vBMD decreased by 2.1 percent ( $p = 0.008$ ). Cortical parameters were unchanged in the control group at 6 months.

During follow up of the nine patients who did not receive teriparatide, three had prophylactic surgery to stabilize the incomplete atypical fractures, one of these patients suffered a contralateral atypical femoral fracture, one had fracture union and became pain-free 12 months post surgery and the third had ongoing pain and poor healing. Of the remaining six patients (4 with complete fractures and 2 with incomplete fractures) all had non-union and persistent pain one year post fracture (mean follow-up VAS = 4.9/10).

## Discussion

We report that treatment of five patients with teriparatide for six months was associated with increased bone remodelling and partial or complete healing of atypical fractures and pain relief. Treatment replaced older more fully mineralised bone matrix with younger, less densely mineralised bone matrix restoring the heterogeneity in tissue mineralisation density distribution, a property of bone matrix which limits micro-crack propagation.<sup>2</sup>

Atypical femoral fractures are stress fractures associated with suppression of bone remodelling induced by bisphosphonates.<sup>18</sup> Subtrochanteric fractures account for 0.5% of all femoral fractures but appear to be becoming more common.<sup>19</sup> The fractures are bilateral in 38% of cases and are associated with pain and limited mobility, extension of the fracture line results in complete fractures, subsequent displacement, increased morbidity and mortality.<sup>20</sup>

Bone is a hierarchical structure.<sup>2</sup> Differences in material composition at the pico-, nano- and micro-structural levels prevent cracking, or limit crack propagation when it occurs.<sup>21</sup> For

example, differences in the mineral density and mineralised fibre direction in adjacent lamellae within an osteon and the cement line delimitating an osteon from the surrounding interstitial space reduce the likelihood of cracking within osteons. Crack occurs most commonly within the interstitial bone between osteons as these are least remodelled and have the highest tissue mineral density and highest pentosidine cross linking of collagen.<sup>2</sup>

Treatment with bisphosphonates reduces the intensity of bone remodelling, reduces bone loss and partly reverses and then slows the progression of structural decay.<sup>3</sup> When protracted, remodelling suppression may compromise bone's material composition by allowing more complete secondary mineralisation of bone matrix. Higher doses of bisphosphonates are also associated with increased pentosidine crosslinking.<sup>22</sup> Both effects increase matrix stiffness and so reduce peak tolerated strain; the degree to which matrix can deform during loading without cracking. The stiffening by increased matrix mineralization and pentosidine cross linking reduces ductility; the structure becomes more brittle.<sup>23-25</sup>

As the energy imposed during loading can no longer be dissipated in bending, the energy is dissipated by the occurrence of micro-cracks. Provided that these micro-cracks may remain small, complete fracture does not occur. However, with continued secondary mineralisation of more and more of the bone matrix volume, adjacent regions of bone become more fully and more similarly mineralised. This homogeneity in tissue mineralisation reduces the resistance to crack propagation; a crack tip can propagate through a homogeneously mineralised bone more easily than a heterogeneously mineralised bone. Thus, remodelling suppression appears to increase micro-fracture burden by increasing its production, allowing cracks to lengthen and reducing crack removal.<sup>26-28</sup>

Intermittent teriparatide administration has been reported to accelerate pelvic fracture and distal radial fracture healing by enhancing callus formation.<sup>11,12,29</sup> This treatment increases bone remodelling resulting in the removal of more completely mineralised bone and replacement with newly synthesized and less densely mineralised bone;<sup>30</sup> the opposite sequence of events produced by remodelling suppressants.<sup>8</sup> While remodelling intensity is increased, there is net deposition of bone within each of the greater numbers of remodelling units as teriparatide promotes the differentiation, work and lifespan of osteoblasts in existing and newly created bone remodelling units.<sup>31</sup> Teriparatide also increases bone formation on quiescent bone surfaces.<sup>32</sup>

In this study, teriparatide was associated with decreased pain and fracture healing after six months of treatment. Teriparatide was contraindicated or refused in 9 patients. Pain did not resolve in eight of nine subjects with persistence of poor fracture healing. In addition, one patient suffered a further femoral fracture. These observations, while anecdotal, and not based on the results of a randomized double blind controlled study, support the findings of other case reports.<sup>13,14</sup>

Cortical thickening in the femoral shaft has been reported in these patients.<sup>20</sup> However rigorously controlled evaluation of the existence cortical thickness has not been undertaken. Unnanuntana et al did not confirm increased thickness in patients after 5 years of bisphosphonate treatment.<sup>33</sup> While there may be focal tenting consistent with a periosteal reaction to the stress fracture, bisphosphonates are not anabolic; they do not deposit new bone matrix on the periosteal or endocortical surface. Therefore, cortical thickening reported here and elsewhere is likely to be artefactual. Refilling of intracortical pores and trenches upon the endocortical surface with mineralised bone and secondary mineralisation of existing bone

matrix during bisphosphonate therapy alters edge detection creating the illusion of cortical thickening. For similar reasons, the reduction in the *seemingly* thicker radial cortex by 4.1 percent is also likely to be artefactual. Teriparatide increased remodelling upon the intracortical surfaces replacing more fully mineralised bone matrix with less completely mineralised bone matrix that attenuated photons less producing an apparent reduction in cortical thickness. Similarly the reduction in volumetric density is due to replacement of older more mineralized bone with younger less densely mineralized bone. This has been demonstrated in iliac biopsy samples with widening of the bone mineral density distribution curve post teriparatide treatment.<sup>34</sup>

The small sample size and lack of randomisation is a limitation in this study. Several controls had illnesses that were not present in the cases given teriparatide so that matching was not ideal. The metabolic diseases which prevented the use of teriparatide were mostly mild (2 patients with inactive Paget's disease, 1 patient with primary hyperparathyroidism and normocalcemic while on bisphosphonate, 1 patient with a distant history of cured localised breast cancer). Although the mean duration of bisphosphonate use was similar between the two groups, the mean accumulated dose was higher in the control group due to intravenous bisphosphonate use. However, atypical femoral fractures are rare so prospective randomized placebo controlled double blind trials to determine whether intermittent teriparatide treatment promotes fracture healing are unlikely to be feasible in the near future.

### **Conclusions**

Teriparatide increased remodelling, removed old, more fully mineralised bone matrix and replaced it with new, less fully mineralised bone matrix and improved fracture healing. Surgical fixation did not protect the contralateral femur from fracture. While these findings lack the rigor of a randomized double blind placebo controlled trial, and so should be regarded as hypothesis generating rather than hypothesis testing, they do support the notion that teriparatide may be a reasonable therapeutic option before resorting to surgery for incomplete atypical femoral fractures.

### **Disclosure:**

All authors state that they have no conflicts of interest.

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## Figure Legends

### Figure 1: Increased tissue heterogeneity post teriparatide treatment

Cross sections of distal radius (a-c) and tibia (d-f) in a patient with atypical fracture. The voxels of the cortex are categorized into 5 groups (see Methods). The attenuation value produced by fully mineralized bone (~1200 mg hydroxyapatite) is assigned a value of 100%. The remaining voxels are classified relative to this maximum mineralization value as follows: (i) white: zero, exclusively occupied by void (having a similar attenuation as the background) (ii) blue: 1-50% of the maximum (iii) green: 51-70% of the maximum (iv) yellow: 71-95% of the maximum (v) red: greater than 95% of the maximum. The changes in the distribution of voxels within each of the 5 categories are captured by the left shift in the void bone matrix distribution curve. After 6 months teriparatide treatment, of the total number of voxels, more contain bone of lower density and less contain bone of higher density; voxels of higher density (yellow in circle a and d) became less dense (green in circle b and e). The reduction in density of a given voxel may be due to replacement of mineralized bone matrix by new less densely mineralized bone matrix, and/or void.

### Figure 2: Reduction in bone scan uptake post teriparatide treatment

Bone scintigraphy scans pre- and post- teriparatide treatment showing reduction in the intensity of isotope uptake (n=4). (One teriparatide treated patient refused a repeat scan as she had fracture union and was pain free.)

### Figure 3: Baseline cortical parameters

Baseline standardised Z scores (adjusted for age and sex) for cortical thickness (Ct.Th.) and cortical volumetric bone mineral density (Ct.vBMD) assessed by  $\mu$ CT in 10 patients with atypical fractures. \* P = 0.04<sup>#</sup> P = 0.06.

Table 1: Proportional changes in the five categories of voxels mineralization density values pre and post teriparatide treatment.

Radius	(i) Void			(ii) 1-50% of the maximum mineralization			(iii) 51-70% of the maximum mineralization			(iv) 71-95% of the maximum mineralization			(v) >95% of the maximum mineralization		
	Pre	Post	% Δ	Pre	Post	% Δ	Pre	Post	% Δ	Pre	Post	% Δ	Pre	Post	% Δ
A	0.32	0.57	77.82	36.37	42.96	18.13	46.52	39.59	-14.90	16.76	16.49	-1.60	0.03	0.39	1202.13
B	0.10	0.10	-0.54	6.97	10.58	51.67	45.52	52.95	16.32	47.18	36.21	-23.24	0.23	0.16	-28.84
C	0.35	0.34	-1.36	16.86	18.96	12.50	46.05	48.86	6.12	36.59	31.70	-13.39	0.16	0.13	-15.02
D	0.37	0.29	-20.32	27.46	33.06	20.42	43.00	43.24	0.58	29.07	23.21	-20.14	0.12	0.19	64.51
E	0.09	0.22	155.66	19.64	28.39	44.57	55.11	51.80	-6.00	25.15	19.40	-22.87	0.02	0.19	991.27
Mean	0.25	0.30	42.25	21.46	26.79	29.46	47.24	47.29	0.42	30.95	25.40	-16.25	0.11	0.21	442.81
SEM	0.06	0.08	33.00	4.96	5.60	7.81	2.06	2.55	5.30	5.17	3.72	4.07	0.04	0.05	269.49

Tibia	(i) Void			(ii) 1-50% of the maximum mineralization			(iii) 51-70% of the maximum mineralization			(iv) 71-95% of the maximum mineralization			(v) >95% of the maximum mineralization		
	Pre	Post	% Δ	Pre	Post	% Δ	Pre	Post	% Δ	Pre	Post	% Δ	Pre	Post	% Δ
A	1.38	1.29	-6.0	53.35	52.23	-2.1	35.72	36.98	3.54	9.49	9.48	-0.1	0.07	0.02	-69.0

			4			1						2			4
B	0.1 8	0.0 8	- 55. 67	31. 29	32. 71	4.5 3	53. 83	53. 83	- 0.0 1	14. 69	13. 37	- 9.0 1	0.0 1	0.0 2	113. 10
C	0.6 7	1.1 8	76. 41	55. 11	59. 57	8.0 9	38. 91	34. 68	- 10. 87	5.3 1	4.5 7	- 14. 00	0.0 0	0.0 0	0.00
D	3.0 3	2.5 0	- 17. 37	52. 30	51. 92	- 0.7 4	34. 18	35. 95	5.1 7	10. 46	9.6 1	- 8.0 7	0.0 3	0.0 2	- 41.0 2
Mea n	1.3 2	1.2 6	- 0.6 7	48. 01	49. 11	2.4 4	40. 66	40. 36	0.5 4	9.9 9	9.2 6	7.8 0	0.0 3	0.0 2	0.76
SEM	0.6 2	0.4 9	27. 80	5.6 0	5.7 4	2.3 6	4.5 0	4.5 1	3.6 1	1.9 2	1.8 0	2.8 7	0.0 2	0.0 1	40.0 4

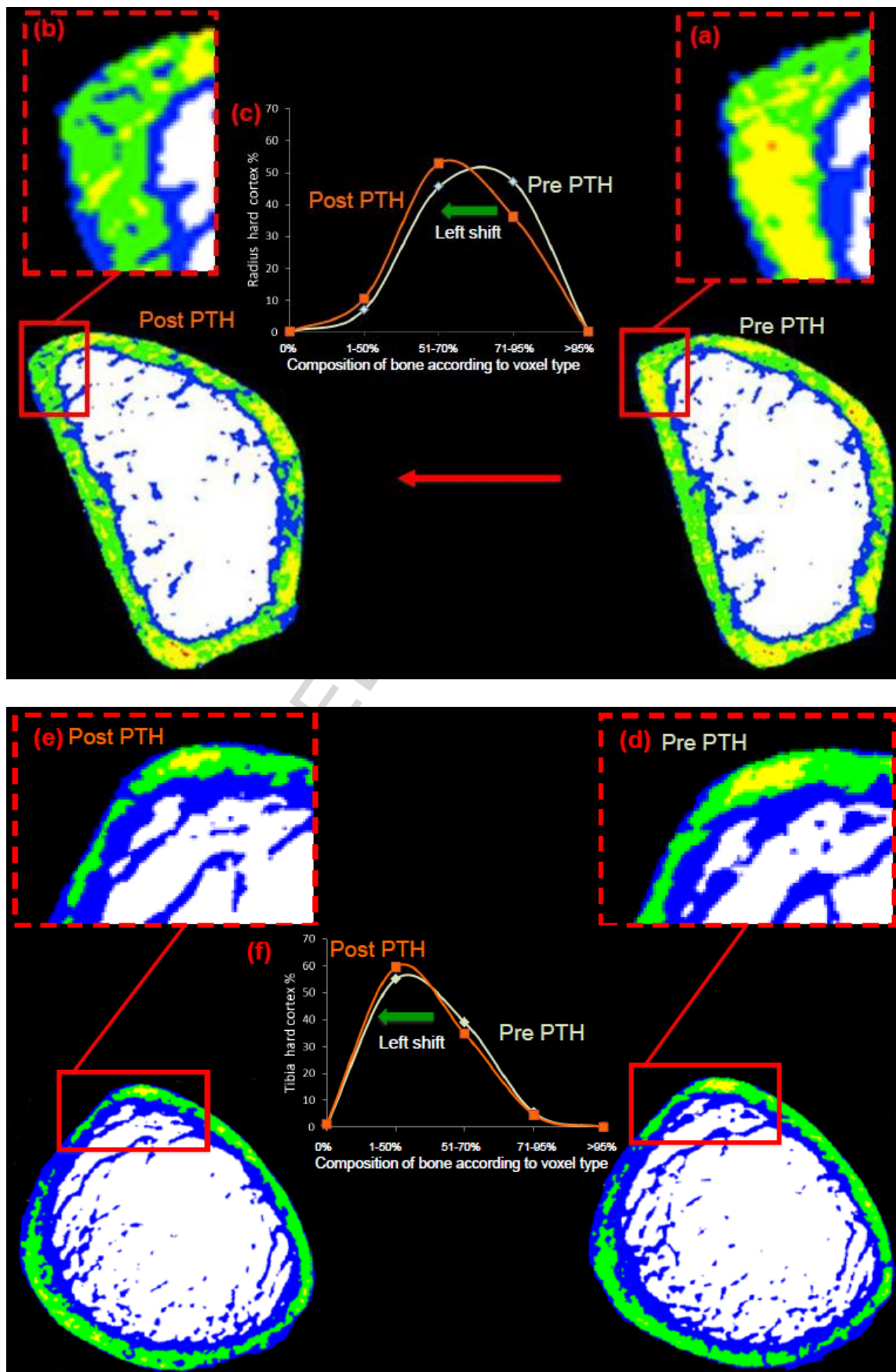
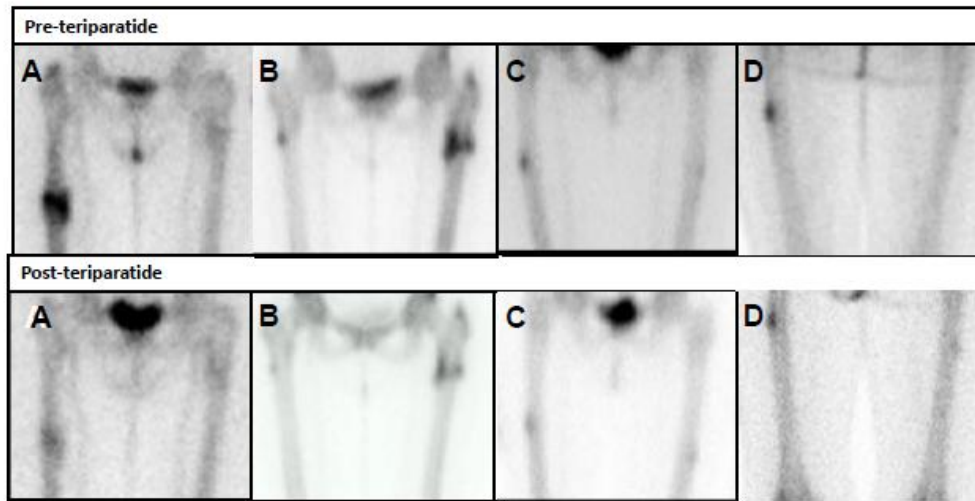


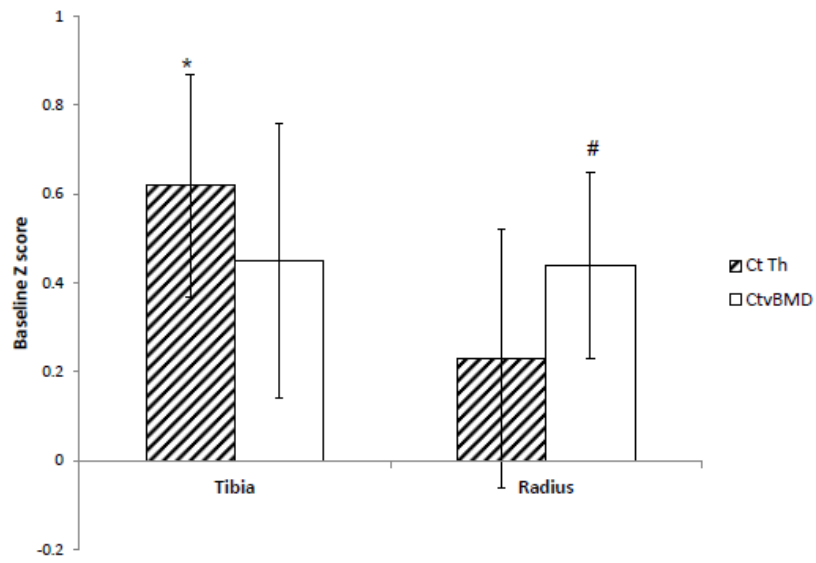
Figure 1

Figure2



ACCEPTED

Figure3



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## Highlights

- Bisphosphonates suppress bone remodelling, which can lead to microdamage accumulation and atypical femoral fractures.
- Teriparatide given to five patients with atypical fractures was associated with an increase in bone remodelling markers and fracture healing.
- The volume of less densely and homogeneously mineralised bone increased and the proportion of older, more densely mineralised bone decreased.
- Teriparatide may assist in healing of atypical fractures and restoration of bone quality.



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