NOVEL EFFECTS OF HIGH DOSES OF OLPADRONATE ON CORTICAL BONE AND MECHANISM OF FRACTURE IN YOUNG-RAT FEMURS

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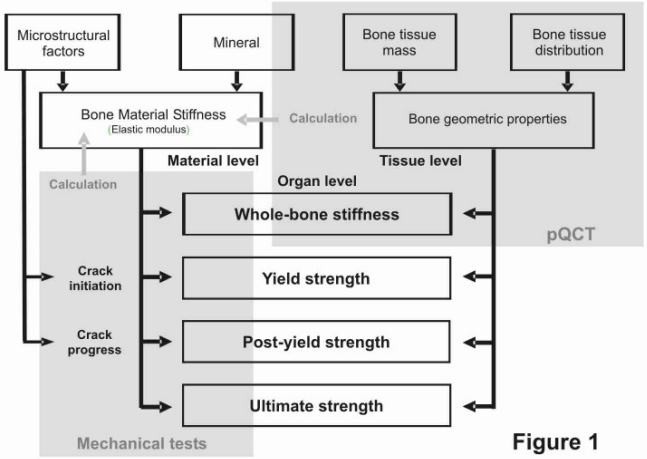

Figure 1

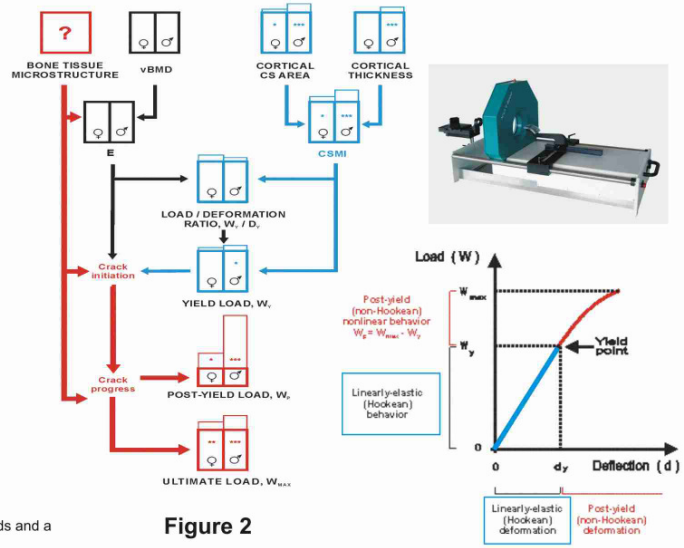

Figure 2

GENERAL BACKGROUND AND AIM OF THE STUDY

Bisphosphonate (BP) effects on the skeleton are not fully understood. There are large difference between compounds and a wide spectrum of pleiotropic actions on different aspects of bone strength has been reported *(Ferretti, 1995)*.

Some of these effects may impact on bone material's properties and affect post-yield strength (**Fig 1**). The effects of BPs on bone material's properties and post-yield strength may be blunted by their strong effects on bone remodeling.

Olpadronate (dimethyl-pamidronate, OPD) had been shown to improve significantly bone stregth in young rats, especially so in male animals *(Ferretti et al, Bone 1995)* and in ovariectomized rats *(Cointry et al, Bone, 1995)*, with some positive impact on the post-yield strength of the bones. These findings contrast with some reports of negative BP effects on bone material's properties and post-yield strength which would have increased bone brittleness.

This study aimed to determine whether the administration of high doses of OPD affects the mass, diaphyseal design and mineralization of femurs in young rats (an almost pure-modeling model), concomitantly impairing, maintaining or improving the intrinsic stiffness of cortical tissue and the pre- and post-yield strength of the bones.

MATERIAL & METHODS

Twenty male and 22 female 4-5-week-old rats received orally 45 or 90 mg/kg/d OPD for 3 months (8/9 male/female controls).

Periosteal perimeter, cortical vBMD (vCtD), cross-sectional area (CSA), bending moment of inertia (xCSMI), cortical bone elastic modulus (E), stiffness and yield and post-yield strength of femur diaphyses were determined by pQCT and bending tests.

A Bone Strength Index (BSI = vCtD * CSMI), previously validated as a bone strength predictor for rat femur diaphyses in bending *(Ferretti et al, Bone, 1996)* was calculated taking into account the intrinsic stiffness of bone mineralized tissue (as expressed by vCtD) and the architectural efficiency of its distribution concerning bending stress (as assessed by the xCSMI). This index does not capture any of the microstructural factors (not assessed in this study) which may affect bone material stiffness, especially concerning post-yield strength.

RESULTS

No dose-effect relationships were detected, hence the data were pooled into male and female groups of control or treated rats. Effects of OPD on the biomechanically relevant variables studied are shown in absolute terms in **Table I** and as percentages of control values in **Figure 2.**

Treatment enhanced periosteal perimeter, CSA and xCSMI proportionally (**Fig 3**) with no change in vCtD and E.

While yielding stiffness and strength were mildly improved, post-yield strength was strikingly increased (males +385%; females +80%; **Table I** and **Fig 2**). Despite the close correlation observed between effects on CSMIs and ultimate strenght of the bones (**Fig 4**), ultimate strength was enhanced mainly as a consequence of the increase in post-yield properties (**Fig 5**) rather than in pre-yield or geometric properties.

The calculated BSI underestimated significantly the actually measured bone strength in all treated rats (**Fig 6**).

INTERPRETATION

The expected improvement in bone geometry and pre-yield properties suggests a mild anabolic effect of OPD. The large effects on post-yield properties (bone toughness) and the unability of the BSI for predicting the measured bone strength suggest a role for microstructural factors unrelated to mineralization.

Sex-related differences in treated animals are attributable to a better bioavailability of the drug and a much larger body weight in male than in female rats, perhaps in connection with differences in the mechanical stimulation of bone structure.

No deterioration of any material, geometric or mechanical property was observed in treated rats, despite the high doses employed.

Results reveal novel effects of OPD on bone strength and mechanism of fracture unrelated to tissue mineralization and stiffness, possibly associated with a positive interaction on the bone *mechanostat*, with little or no involvement of bone remodeling.

References
Cointry GR et al. Bone 17(4S):S373-S378, 1995.
Ferretti JL, In:Bisphosphonates on Bones. Bijvoet O et al (Eds) Elsevier, Amsterdam, 1995; pp211-229.
Ferretti JL et al. Bone 16(4S):S285-S293, 1995.
Ferretti JL et al. Bone 18:97-102, 1996.

Table. MEANS AND (SD'S) OF EVERY STUDIED VARIABLE IN THE DIFFERENT GROUPS OF ANIMALS.

?	Female rats Control	Female rats Treated	Male rats Control	
Treated				
Allometric variables				
Body weight, g	295 (26)	285 (23)	517 (39)$_{s3}$	
490 (49)$_{s3}$				
Periosteal perimeter, mm	10.7 (0.55)	11.3 (0.40)^{t3}	12.6 (0.35)$_{s3}$	13.5
(0.78)$_{s3}^{t3}$				
Endosteal perimeter, mm	5.75 (0.55)	6.56 (0.46)^{t3}	7.32 (0.51)$_{s3}$	7.70
(0.78)$_{s3}$				
Average cortical thickness, mm	0.734 (0.021)	0.739 (0.044)	0.811 (0.051)$_{s3}$	0.920
(0.036)$_{s3}^{t3}$				
Cortical bone area (CSA), mm^2	6.37 (0.38)	6.84 (0.49)^{t1}	8.39 (0.49)$_{s3}$	10.13
(0.53)$_{s3}^{t3}$				
bw-Adjusted CSA, mm^2	5.56 (0.38)	6.21 (0.43)^{t2}	5.67 (0.45)	7.45
(0.43)$_{s3}^{t3}$				
Moment of inertia (xCSMI), mm^4	5.33 (0.81)	6.14 (0.88)^{t1}	9.28 (0.97)$_{s3}$	12.19
(1.35)$_{s3}^{t3}$				
bw-Adjusted xCSMI, mm^4	4.51 (0.76)	5.52 (0.80)^{t1}	4.47 (1.38)	7.86
(1.50)$_{s3}^{t3}$				
Bone material properties				
BMC of cortical bone, mg	8.23 (0.42)	8.82 (0.67)^{t1}	11.17 (0.73)$_{s3}$	
13.48 (0.73)$_{s3}^{t3}$				
vBMD of cortical bone, mg/cm^3	1302 (27)	1299 (30)	1326 (17)	
1325 (23)				
Elastic modulus, MPa	1437 (345)	1419 (348)	943 (155)$_{s3}$	825
(148)$_{s3}$				
Pre-yield behavior of bones				
Diaphyseal stiffness, N/mm	162.7 (25.7)	188.8 (40.7)	189.7 (28.2)	
202.1 (40.2)				
Yield load, N	104.2 (7.6)	116.3 (22.0)^{t3}	146.5 (35.7)	
158.6 (27.0)^{t3}				
Post-yield behavior of bones				
Ultimate load (W_{max}), N	122.4 (10.2)	149.0 (23.5)^{t3}	158.6 (22.1)	205.2
(36.2)$_{s3}^{t3}$				
bw-Adjusted ultimate load, N	117.9 (10.4)	145.6 (22.6)^{t2}	131.8 (23.1)	
181.2 (34.7)$_{s3}^{t3}$				
Post-yield load fraction, N	16.5 (5.1)	33.1 (11.5)^{t1}	12.1 (4.2)	46.6
(14.5)$_{s1}^{t3}$				

Numeral sub- or super-indices (1,2,3) indicate p<0.05, p<0.01, and p<0.001 significance levels of inter-sex differences between control or treated animals ($_s$) and treatment-induced changes compared to sex-matched controls (^{t}), respectively.

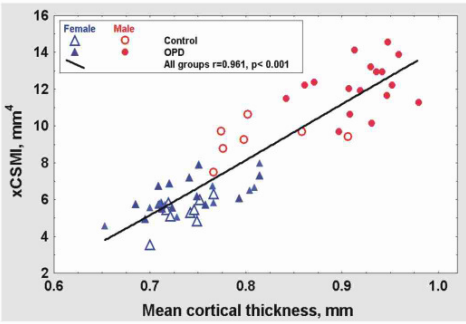

Figure 3

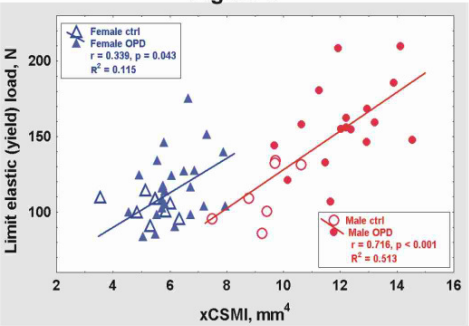

Figure 4

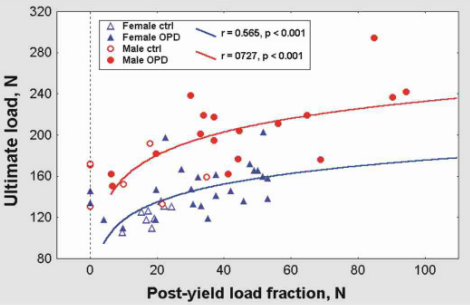

Figure 5

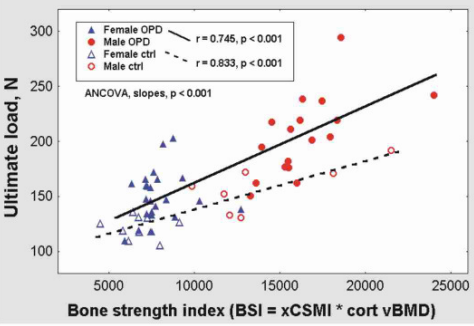

Figure 6