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Original Article

Hylonome

Treatment of postmenopausal osteoporotic women with parathyroid hormone 1-84 for 18 months increases cancellous bone formation and improves cancellous architecture: A study of iliac crest biopsies using histomorphometry and micro computed tomography

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Histomorphometry studies in rhesus monkeys have shown that daily treatment with full-length parathyroid hormone 1-84 (PTH) increases bone formation and bone volume. However, there is no published information on the effects of PTH treatment on bone microarchitecture in humans. We obtained iliac crest biopsies from postmenopausal osteoporotic women given daily injections of placebo or 100 μg PTH for 18 months to assess the effects of treatment on cancellous and cortical bone formation and structure. All subjects received background treatment with Ca (700 mg) and vitamin D (400 IU). At baseline there were no significant differences between groups in age, weight, bone turnover markers, and spine and hip bone mineral density.

Intact biopsies were collected from 8 placebo- and 8 PTH-treated women at month 18. Prior to sectioning for histomorphometry, the biopsies were subjected to micro-computed tomography (μCT) to quantify the 3-D and 2-D structure of trabecular and cortical bone, respectively. The results of the histomorphometric and μCT analyses are summarized in Table 1.

Cancellous bone formation rate (BFR) was significantly higher in PTH-treated subjects and was primarily the result of an increased mineralizing surface (MS/BS); mineral appositional rate (MAR) was not increased significantly. Osteoblast and osteoid surfaces were 58% and 35%, respectively, higher in the PTH-treated group, but the increases were not significant. No index of bone resorption was significantly affected by PTH treatment, although a trend towards increased activation frequency (Ac.F) was noted. Maintenance of elevated BFR at month 18 was confirmed by measurement of serum levels of the bone formation marker, bone-specific alkaline phosphatase, which were 38% higher in PTH-treated subjects than in the placebo group at month 18.

Values for cancellous bone structure and the differences between groups were very similar whether obtained by histomorphometry or by μCT. Trabecular bone volume (BV/TV) measured by histomorphometry was 48% higher in subjects treated with PTH; this increase was the combined effect of 24 and 17% higher trabecular number (Tb.N) and thickness (Tb.Th), respectively, and resulted in a 21% lower trabecular separation (Tb.Sp). The increase in Tb.N appeared to result from the splitting of thickened trabeculae by tunneling osteoclasts. Trabecular connectivity (Conn.D) measured by μCT was 22% higher and the structure model index (SMI) was 55% lower in PTH-treated subjects. A reduction in SMI indicates a change in trabecular architecture from a rod-like to a more plate-like structure.

No significant effects of PTH treatment were observed on periosteal or endocortical BFR, or on cortical thickness (Ct.Th) or porosity (Ct.Po). There was a >60% mean difference in Ct.Th between the 2 cortices of the iliac crest; the

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	Histomorphometry			Micro-CT		
Parameter	**Placebo**	**PTH**	**P-value***	**Placebo**	**PTH**	**P-value***
MS/BS (%)	5.9 ± 1.3	12.1 ± 3.4	0.046			
MAR (μm/day)	0.48 ± 0.04	0.53 ± 0.02	0.208			
BFR/TV ($mm^3/mm^3/yr$)	0.027± 0.007	0.079± 0.031	0.021			
Ac.F (/yr)	0.39 ± 0.10	0.69 ± 0.18	0.074			
ES/BS (%)	1.67 ± 0.48	1.75 ± 0.35	0.674			
BV/TV (%)	15.5 ± 1.6	22.8 ± 2.5	0.036	16.1 ± 1.4	23.3 ± 2.0	0.036
Tb.N (/mm)	1.19 ± 0.09	1.47 ± 0.09	0.046	1.25 ± 0.04	1.40± 0.06	0.093
Tb.Th (μm)	130 ± 10	152 ± 9	0.172	159 ± 11	186 ± 12	0.128
Tb.Sp (μm)	858 ± 59	678 ± 39	0.046	771 ± 23	696 ± 27	0.036
Conn.D ($/mm^3$)				3.93 ± 0.52	4.81± 0.34	0.074
SMI				1.09 ± 0.16	0.49± 0.25	0.046
Ct.Th (μm)	804 ± 101	712 ± 68	0.916	731 ± 56	712 ± 86	0.834
Ct.Po (%)	4.2 ± 0.8	5.6 ± 0.8	0.294			

Values are mean ± SE, n=8/group. *Mann-Whitney U-test

Table 1. Results of the histomorphometric and μCT analyses.

Ct.Th results shown are the averages of the 2 cortices.

The new bone produced by PTH treatment had normal lamellar structure and mineralization; there were no abnormal histological findings, including marrow fibrosis or osteomalacia.

In conclusion, treatment of osteoporotic women for 18 months with PTH resulted in marked increases in cancellous bone formation and bone volume in the iliac crest without significantly affecting bone resorption. PTH treatment improved trabecular connectivity, and restored trabecular architecture from a rod-like to a plate-like structure. We propose that these changes are accomplished, at least in part, by a novel mechanism in which trabeculae are first thickened and then split by tunneling. The improved trabecular architecture is consistent with the marked decrease in vertebral fracture incidence in postmenopausal osteoporotic women treated with PTH for 18 months.

Structural values obtained for trabecular and cortical bone were remarkably similar between histomorphometry and μCT. Thus, histomorphometry and μCT imaging are complementary techniques that provide information on the effects of treatment on bone structure and the underlying mechanisms responsible for the observed changes, in this case, in response to PTH treatment.