ELSEVIER

Bone 40 (2007) 1447–1452

BONE

www.elsevier.com/locate/bone

Review

Skeletal actions of intermittent parathyroid hormone: Effects on bone remodelling and structure

Juliet E. Compston

School of Clinical Medicine, University of Cambridge, Cambridge CB2 2QQ, UK

Received 31 July 2006; revised 26 August 2006; accepted 1 September 2006
Available online 12 October 2006

Abstract

Intermittent administration of parathyroid hormone peptides has anabolic skeletal effects and reduces fracture risk in postmenopausal women with osteoporosis but the cellular and structural mechanisms by which these effects are mediated have not been fully established. In cancellous and endocortical bone, there is evidence that both modelling and remodelling-based formation contribute to the increase in bone mass although the contribution of these at different time points in the response to PTH has not been established. Despite the large increase in spine bone mineral density, however, significant increases in iliac crest cancellous bone volume and trabecular thickness have not been consistently demonstrated, possibly reflecting site-specific differences in PTH-induced skeletal effects and/or the large sampling and measurement variance associated with assessment of iliac crest cancellous bone volume and structure. In iliac crest cortical bone, increased cortical thickness has been demonstrated, due at least in part to increased endosteal bone formation; there is also some evidence for increased formation on periosteal surfaces. At some sites an increase in cortical porosity may also occur and the overall effects on cortical bone strength, particularly at the hip, remain to be established. Studies in iliac crest bone indicate a trend towards a lower mineralisation density of bone matrix and increased heterogeneity of mineralisation, consistent with new bone formation. In addition, there is a reduction in mineral crystallinity and a shift towards more divalent collagen cross-links, indicating a change towards a younger bone profile.

The potential clinical implications of these effects on bone are currently unknown. The stimulatory effect of PTH peptides on bone formation may favour their use in low turnover bone disease and in states of advanced bone loss. Furthermore, if beneficial effects on cortical bone strength are confirmed, efficacy at non-vertebral sites might be superior to those observed with antiresorptive drugs. Better definition of the effects of intermittent PTH administration on cancellous and cortical bone remodelling and structure at different skeletal sites may inform these speculations and is an important area for future research.

Keywords: Parathyroid hormone; Anabolic; Bone modelling; Bone remodelling; Microarchitecture

Contents

E-mail address: jec1001@cam.ac.uk.

8756-3282/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.bone.2006.09.008

Introduction

The recent development of bone forming agents has provided an exciting new option for the prevention of osteoporotic fractures. Daily administration of parathyroid hormone (PTH) peptide 1-34 [1] and PTH 1-84 peptide [2] reduces vertebral fracture risk in postmenopausal women with osteoporosis and, for the former, a reduction in non-vertebral fractures has also been demonstrated. Given the predominantly catabolic skeletal effects of continuous PTH administration, the mechanisms by which intermittent administration produce anabolic effects are of considerable interest and have implications for the development of other bone forming agents.

Cellular and structural basis of anabolic skeletal effect of intermittent PTH: cancellous bone

In the spine, intermittent administration of PTH induces large increases in areal bone mineral density; for example, subcutaneous administration of 20 or 40 μg daily of recombinant human PTH peptide 1-34 to postmenopausal women with osteoporosis was associated with a 10–15% increase after a median treatment period of 19 months [1]. The magnitude of these changes suggests that there is a substantial increase in bone formation but the mechanisms by which this is achieved remain incompletely defined.

In cancellous bone, increases in the amount of bone may occur by remodelling-based or modelling-based bone formation. In the case of the former, the largest increases in bone mass are achieved where an increase in remodelling rate is combined with a positive remodelling balance, as shown in Fig. 1. It is generally assumed that the positive remodelling balance is attributable to an increase in the amount of bone within individual bone remodelling units although a reduction in erosion depth would have a similar effect, provided that the amount of bone formed did not change. Modelling-based bone formation occurs when bone is formed in the absence of prior resorption (Fig. 1) and is generally not observed in normal adult human bone [3,4].

Distinguishing between remodelling-based and modelling-based bone formation is not straightforward because modelling-based bone formation may occur on surfaces that are undergoing remodelling. Furthermore, if there is overspill of bone formation beyond the margins of bone remodelling units, the appearance on histological sections may suggest modelling-based rather than remodelling-based bone formation [4]. Notwithstanding these potential difficulties, two approaches have been adopted to identifying these different mechanisms of bone formation. The first relies upon the time course of the increase in bone formation rate following PTH administration and is based on the assumption that if evidence of increased formation is seen earlier than the duration of the resorptive phase of remodelling (i.e., approximately 6 weeks) then it can reasonably be inferred that modelling-based formation has occurred [4,5]. The second approach is based on the appearance of the bone surface underneath the newly formed bone. In the case of remodelling-based bone formation, this is irregular as a result of the previous bone resorption; furthermore, interruption of the collagen fibres, viewed under polarised light, indicates that prior resorption has occurred [6]. Conversely, a smooth surface is seen beneath bone formed by modelling and the collagen fibres have a similar orientation to the adjacent bone tissue [3,7]. Neither of these methods is without its problems; in the case of the first, it could be argued that the process of bone remodelling is accelerated by PTH and thus the duration of the resorptive phase may be shorter than normal. Secondly, while the presence of a crenated surface at the base of bone remodelling units is a reliable sign of the remodelling process it may be more difficult to identify surfaces on which modelling has occurred and hence the contribution of the latter may be underestimated. Finally, interruption of collagen fibres may be a cutting artefact and requires confirmation in longitudinally cut sections [8].

Evidence for the presence of modelling-based bone formation associated with intermittent PTH administration was first reported by Hodsman et al. in postmenopausal women with osteoporosis treated with cyclic hPTH (1-34), 50 μg daily, for 28 days every 3 months with or without sequential calcitonin therapy. In bone biopsies obtained 28 days after the start of treatment, double tetracycline-labelled surfaces and the surface-based bone formation rate were significantly increased when compared to controls, suggesting that bone formation had occurred during this early phase on quiescent bone surfaces [5,9]. Subsequently, Dempster et al. [10] reported the presence of modelling-based bone formation, using the criterion of a smooth cement line, on cancellous and endocortical bone surfaces 28 days after initiation of teriparatide in postmenopausal women with osteoporosis. Using the technique of quadruple tetracycline labelling to study short-term (4 weeks) treatment-induced changes in a single bone biopsy, Lindsay et al. observed a combination of modelling and remodelling-based bone formation, the latter predominating and accounting for 70% and 78% of bone formed in cancellous and endocortical bone, respectively. Because the eroded perimeter was not higher in PTH-treated women than in a control population, suggesting that new remodelling sites were not being created, they concluded that most of the new bone formation in the early treatment period occurred at sites that were already undergoing bone remodelling when treatment was started. In addition, they hypothesised that overspill of bone formation beyond the limits

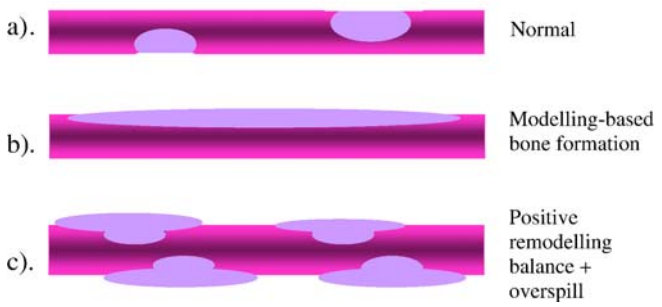

Fig. 1.

of the resorbed cavity accounted for a substantial proportion of the modelling-based bone formation that was observed.

This possibility of "overspill" adds further complexity to the distinction between modelling and remodelling-based formation because it might occur either as a consequence of reduced apoptosis of osteoblasts already participating in the remodelling process or as a result of activation of lining cells in the vicinity of the remodelling unit, the latter perhaps being preferentially located to sites adjacent to remodelling units as a result of the local cytokine/growth factor environment. Modelling-based formation may occur as a result of direct activation by PTH of the lining cells to form active osteoblasts [11]; the observation that chronic but not single pre-dosing with alendronate blunts the anabolic response to intermittent PTH is consistent with this hypothesis because chronic bisphosphonate exposure may be required to reduce protein prenylation in osteoblasts and hence impair their function [12].

These data indicate that at least in the early stages of intermittent PTH therapy, modelling-based formation occurs in cancellous and endocortical bone, probably often although not exclusively occurring as an extension of remodelling-based bone formation beyond the original margins of the resorption cavity. In the first month or so of treatment, modelling contributes up to one third of bone formation, but with longer treatment periods it may become less prominent. Thus, in a comparison of biopsies from postmenopausal women treated for a median period of 19 months with either 20 or 40 μg daily of teriparatide, Ma et al. [8] reported that modelling accounted for only approximately 2.8% and 7.7% respectively of bone formation in cancellous bone.

Whether the remodelling rate is increased as a result of PTH administration is unclear. Because measurements of activation frequency are formation based and rely on the assumption that formation follows resorption, they are unreliable in the presence of modelling-based bone formation. The lack of any increase in eroded perimeter after one months treatment in the study of Lindsay et al. [4] and after 6 and 18 months treatment when compared to ALN in the study of Arlot et al. [13] would suggest that the rate of remodelling is not increased. Conversely Hodsman et al. [9] reported a significant increase in eroded surfaces at both 28 days and 2 years after the start of treatment, while Dempster et al. [14] demonstrated a significant reduction on the endocortical surface after 18–36 months of treatment. However, measurements of eroded surface are subject to large measurement variance and, additionally, will be influenced if there are changes in the duration of the reversal period. Nevertheless, the increase in biochemical markers of bone resorption following teriparatide therapy would support an increase in remodelling rate. This occurs after the increase in bone formation and reaches a peak between 6 and 12 months [15], consistent with other evidence that modelling-based formation is maximal early after treatment is started and that the relative contribution of remodelling-based bone formation increases thereafter.

From the available evidence therefore, three mechanisms by which PTH increases bone mass can be proposed, although their relative contribution at different time points during treatment remains to be established. Firstly, true modelling, in which new bone is formed on quiescent bone surfaces independent of current remodelling activity, secondly mixed remodelling/modelling in which there is overfilling of remodelling units with extension of bone formation beyond the margins of the resorption cavity and thirdly, an increase in remodelling rate associated with a positive remodelling balance. Interestingly, although an increase in mean wall width has been reported in some studies, particularly in endocortical bone [8,9,14,16], this finding has not been universal [13,17] and, where present, the increase has generally been small. This may reflect the predominance of bone structural units that had already been completed before the onset of treatment and the extension of bone formation laterally beyond the margins of the original resorption cavity.

Effects of intermittent PTH on cancellous bone microarchitecture

While antiresorptive agents maintain existing architecture [18,19], anabolic agents have the potential to reverse structural disruption. Investigation of the effects of intermittent PTH therapy provides some evidence that may indeed occur, based on measurements on connectivity and trabecular shape. Thus, connectivity density in men and women with osteoporosis treated with PTH (1-34) increased after 3 years treatment [14], and in women with osteoporosis treated for a median of 19 months [17] connectivity density was significantly higher in PTH-treated women than in those receiving placebo. Although increased connectivity density may reflect trabecular plate perforation or intra-trabecular tunnelling rather than restoration of structure, the finding that there was also a significant improvement in the structure model index, an indicator of the proportion of rods and plates, is consistent with a trend towards reversal of age-related changes in bone [17]. Interestingly, increases in trabecular thickness have often been small and have generally failed to attain statistical significance [4,8,9,13,14,17]; whether this reflects an increase in trabecular number or perhaps topologically strategic thickening of some trabeculae and thinning of others is uncertain. Finally, although some studies have demonstrated an increase in cancellous bone area and volume [17,20,21], this finding has not been universal [4,9,14]. The reason for the apparent discrepancy between these findings and the large increases observed in spinal bone mineral density remains unclear but possible considerations include site-specific differences in PTH response and the large variability in the measurement of iliac crest bone volume, due to both sampling and measurement variance [22].

Effects of intermittent PTH on cortical bone

The small or even negative changes in bone mineral density at sites containing large proportions of cortical bone contrast sharply with the large increases observed at predominantly cancellous sites such as the spine [1,23,24]. This initially led to concerns that increases in cancellous bone mass might occur at

the expense of cortical bone [20,25], but subsequent studies indicate that at least at some skeletal sites, beneficial changes occur in cortical bone architecture and the fracture reduction at non-vertebral sites demonstrated in postmenopausal women with osteoporosis would be consistent with this view [1,26]. Nevertheless, the effects of intermittent PTH on cortical bone mass and architecture remain poorly defined.

Interpretation of the changes in bone mineral density at cortical sites is complex because they are affected not only by alterations in volumetric bone density but also in cortical width, cortical porosity and bone size, which have independent and differing effects on bone strength. In iliac crest bone an increase in cortical width has been a consistent finding [9,14,17] but a significant increase in cortical porosity was not demonstrated [14,9,17]. At least some of the increase in cortical thickness at this site can be accounted for by increased endosteal bone formation and there is also some evidence for new bone formation on the periosteal surface [10].

In a cross-sectional study, indices of cortical structure and strength in the distal radius were assessed by peripheral quantitative computed tomography (pQCT) in postmenopausal women with osteoporosis who had been randomly assigned to treatment with placebo or teriparatide, 20 or 40 μg/day [30]. In the treatment groups total and cortical bone areas, total bone mineral content and periosteal circumference were all significantly higher than in the placebo group with greater polar cross-sectional moments of inertia. While these data would be consistent with beneficial effects of intermittent PTH at this site, the cross-sectional design of the study limits the conclusions that can be drawn.

In the femoral neck, measurements of volumetric bone mineral density indicate an increase in cortical volume in the femoral neck although areal bone mineral density was unchanged and volumetric bone mineral density slightly decreased after one years treatment with intermittent parathyroid hormone (1-84) [31]. Collectively, these data would be consistent with an increase in cortical thickness associated with increased cortical porosity; although increased cortical porosity adversely affects bone strength, the beneficial effects of an associated increase in cortical thickness may override this effect [27], particularly if the increase in porosity occurs predominantly in endocortical rather than periosteal bone [28,29]. In addition, the finding in a longer study in men [32] that areal bone mineral density in the proximal femur increased during the second year of treatment with parathyroid hormone may indicate that increased intracortical remodelling is an early and transient phenomenon. Using hip structure analysis, increases of femoral neck cross-sectional area were reported in women treated with teriparatide with beneficial effects on biomechanical parameters [33]. It should be noted that the cross-sectional area is a measure of the surface area of bone in the cross-section, not bone size; indeed, in this study significant reductions in periosteal diameter were found in teriparatide-treated women when compared to the placebo group. Furthermore, the assumptions inherent in this methodology again limit the strength of the conclusions that can be drawn [34].

Overall, therefore, the current evidence indicates that increases in cortical width occur in response to intermittent PTH administration, at least at some skeletal sites. This change may initially be accompanied by increased cortical porosity. Increased endocortical bone formation contributes to the increase in cortical thickness but whether similar changes occur at the periosteum remains uncertain. Changes in cortical bone are site specific and, in particular, may be influenced by variations in load bearing at different sites. Thus, the predominantly negative changes in bone mineral density in the distal radius as opposed to positive changes in the proximal femur would be consistent with the synergistic effects of mechanical loading and intermittent PTH reported in animal models [35,36].

Effects of intermittent parathyroid hormone on the bone matrix/mineral composite

Aspects of bone composition and structure other than bone mass and architecture that may affect bone strength include matrix mineralisation and collagen cross-linking. The degree of mineralisation and its distribution is closely related to bone turnover, with an increase in both homogeneity and degree of mineralisation in bone from individuals treated with bisphosphonates [37–39]. Using quantitative back-scattered electron imaging and small angle X-ray scattering in paired iliac crest biopsies from women before and after treatment with intermittent PTH (1-34), Misof et al. [16] demonstrated a trend towards lower mineralisation density and increased heterogeneity, consistent with new bone formation, although no significant changes in collagen/mineral structure were seen.

In a cross-sectional study in 38 postmenopausal women with osteoporosis randomised to placebo or teriparatide, Fourier transform infrared imaging was used to determine matrix mineralisation, mineral crystal maturity and the ratio of pyridinoline to dehydro-dihydroxy-lysinonorleucine collagen cross-links in iliac crest bone [40]. Significant treatment effects were seen in cancellous, endosteal and periosteal bone, with lower matrix mineralisation and crystal maturity and a shift towards more divalent collagen cross-links in women who had been treated with teriparatide. While the biomechanical consequences of these changes are currently unclear, they indicate a change towards a younger bone profile and may therefore contribute to the increase in bone strength and reduced fracture risk associated with PTH therapy.

Potential clinical implications of mechanisms underlying anabolic skeletal effect of intermittent PTH

The marked differences in mode of action between antiresorptive drugs and intermittent PTH have potential, although as yet unproven, therapeutic implications. The ability of PTH to stimulate bone remodelling and modelling suggests that it might be the treatment of choice in low turnover disease, for example in bone disease associated with long-term glucocorticoid therapy [41] and in some forms of renal osteodystrophy [42]. Delmas et al. [43] recently reported that

teriparatide-induced fracture reduction was independent of pre-treatment bone turnover, thus supporting its efficacy in low turnover osteoporosis, but further studies are required to establish whether it is superior to antiresorptive agents in such patients. Secondly, evidence for improvement [14,17], as opposed to maintenance [18,19], of bone microarchitecture following PTH administration indicates that it may be more effective than antiresorptive drugs in individuals with severe osteoporosis in whom substantial structural disruption has already occurred. The very large increases in spine bone mineral density might be expected to translate into greater anti-fracture efficacy at this site although in the absence of head-to-head studies with fracture outcomes this remains unproven and in fact the magnitude of vertebral fracture reduction after 18 months teriparatide therapy is similar to that observed after one year in women treated with risedronate [44]. Finally, beneficial effects on cortical bone may result in greater efficacy at non-vertebral sites; however, these effects may be site specific and the effects of PTH on bone structure in the proximal femur and on hip fracture risk are currently undefined.

References

[1] Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster J-Y, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001;344:1434–41.

[2] European 2006 Preotact. Summary of Product Characteristics.

[3] Takahashi H, Hattner R, Epker BN, Frost HM. Evidence that bone resorption precedes formation at the cellular level. Henry Ford Hosp Med Bull 1964;12:359–64.

[4] Lindsay R, Cosman F, Zhou H, Bostrom MP, Shen VW, Cruz JD, et al. A novel tetracycline labeling schedule for longitudinal evaluation of the short-term effects of anabolic therapy with a single iliac crest biopsy: early actions of teriparatide. J Bone Miner Res 2006;21:366–73.

[5] Hodsman AB, Steer B. Early histomorphometric changes in response to parathyroid hormone in osteoporosis: evidence for de novo bone formation on quiescent surfaces. Bone 1993;14:523–7.

[6] Vedi S, Webb A, Tighe JR, Compston JE. Measurement of total resorption surface in human iliac crest biopsies. Metab Bone Dis Relat Res 1984;5: 275–80.

[7] Erben RG. Trabecular and endocortical bone surfaces in the rat: modeling or remodeling? Anat Rec 1996;246:39–46.

[8] Ma YL, Zeng Q, Donley DW, Ste-Marie L-G, Gallagher JC, Dalsky G, et al. Teriparatide increases bone formation in modeling and remodeling osteons and enhances IGF-II immunoreactivity in postmenopausal women with osteoporosis. J Bone Miner Res 2006;21:855–64.

[9] Hodsman AB, Kisiel M, Adachi JD, Fraher LJ, Watson PH. Histomorphometric evidence for increased bone turnover without change in cortical thickness or porosity after 2 years of cyclical hPTH(1-34) therapy in women with severe osteoporosis. Bone 2000;27:311–8.

[10] Dempster DW, Zhou H, Cosman F, Nieves J, Adachi JD, Fraher LJ, et al. PTH treatment directly stimulates bone formation in cancellous and cortical bone in humans. J Bone Miner Res 2001;16:S179.

[11] Dobnig H, Turner RT. Evidence that intermittent treatment with parathyroid hormone increases bone formation in adult rats by activation of bone lining cells. Endocrinology 1995;136:3632–8.

[12] Gasser JA, Ingold P, Rebmann A, Susa M. The blunting of the bone anabolic response to PTH observed after frequently dosed bisphosphonates in rats may be explained by inhibition of farnesyl diphosphate synthase in osteoblasts. J Bone Miner Res 2005;20(Suppl 1):S78–9.

[13] Arlot M, Meunier PJ, Boivin G, Haddock L, Tamayo J, Correa-Rotter R, et al. Differential effects of teriparatide and alendronate on bone remodelling in postmenopausal women assessed by histomorphometric parameters. J Bone Miner Res 2005;20:1244–53.

[14] Dempster DW, Cosman F, Kurland ES, Zhou H, Nieves J, Woelfert L, et al. Effects of daily treatment with parathyroid hormone on bone microarchitecture and turnover in patients with osteoporosis: a paired biopsy study. J Bone Miner Res 2001;16:1846–53.

[15] Dobnig H, Sipos A, Jiang Y, Fahrleitner-Pammer A, Ste-Marie L-G, Gallagher JC, et al. Early changes in biochemical markers of bone formation correlate with improvements in bone structure during teriparatide therapy. J Clin Endocrinol Metab 2005;90:3970–7.

[16] Misof BM, Roschger P, Cosman F, Kurland ES, Tesch W, Messmer P, et al. Effects of intermittent parathyroid hormone administration on bone mineralisation density in iliac crest biopsies from patients with osteoporosis: a paired study before and after treatment. J Clin Endocrinol Metab 2003;88:1150–6.

[17] Jiang Y, Zhao JJ, Mitlak BH, Wang O, Genant HK, Eriksen EF. Recombinant human parathyroid hormone (1-34) [teriparatide] improves both cortical and cancellous bone structure. J Bone Miner Res 2003;18: 1932–41.

[18] Chavassieux PM, Arlot ME, Reda C, Wei L, Yates AJ, Meunier PJ. Histomorphometric assessment of the long-term effects of alendronate on bone quality and remodelling in patients with osteoporosis. J Clin Invest 1997;100:1475–80.

[19] Borah B, Dufresne TE, Chmielewski PA, Johnson TD, Chines A, Manhart MD. Risedronate preserves bone architecture in postmenopausal women with osteoporosis as measured by three-dimensional microcomputed tomography. Bone 2004;34:736–46.

[20] Reeve J, Meunier PJ, Parsons JA, Bernat M, Bijvoet OLM, Courpron P, et al. Anabolic effect of human parathyroid hormone fragment on trabecular bone in involutional osteoporosis: a multicentre trial. Brit Med J 1980; 280:1340–4.

[21] Bradbeer JN, Arlot ME, Meunier PJ, Reeve J. Treatment of osteoporosis with parathyroid peptide (h-PTH 1-34) and oestrogen: increase in volumetric density of iliac cancellous bone may depend on trabecular spacing as well as increased thickness of packets of newly formed bone. Clin Endocrinol 1992;37:282–9.

[22] Wright CDP, Vedi S, Garrahan NJ, Stanton M, Duffy SW, Compston JE. Combined inter-observer and inter-method variation in bone histomorphometry. Bone 1992;13:205–8.

[23] Rubin MR, Cosman F, Lindsay R, Bilezekian JP. The anabolic effect of parathyroid hormone. Osteoporos Int 2002;13:267–77.

[24] Orwoll ES, Scheele WH, Paul S, Adami S, Syversen U, Diez-Perez A, et al. The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. J Bone Miner Res 2003;18:9–17.

[25] Horwitz M, Stewart A, Greenspan SL. Sequential parathyroid hormone/alendronate therapy for osteoporosis—robbing Peter to pay Paul? J Clin Endocrinol Metab 2000;85:2127–8.

[26] Prince R, Sipos A, Hossain A, Syversen U, Ish-Shalom S, Marcinowska E, et al. Sustained nonvertebral fragility fracture risk reduction after discontinuation of teriparatide treatment. J Bone Miner Res 2005;20: 1507–13.

[27] Hirano T, Burr DB, Turner CH, Sato M, Cain RL, Hock JM. Anabolic effects of human biosynthetic parathyroid hormone fragment (1-34), LY333334, on remodeling and mechanical properties of cortical bone in rabbits. J Bone Miner Res 1999;14:536–45.

[28] Mashiba T, Burr DB, Turner CH, Sato M, Cain RL, Hock JM. Effects of human parathyroid hormone (1-34), LY333334, on bone mass, remodeling, and mechanical properties of cortical bone during the first remodeling cycle in rabbits. Bone 2001;28:538–47.

[29] Burr DB, Hirano T, Turner CH, Hotchkiss C, Brommage R, Hock JM. Intermittently administered human parathyroid hormone (1-34) treatment increases intracortical bone turnover and porosity without reducing bone strength in the humerus of ovariectomised cynomolgus monkeys. J Bone Miner Res 2001;16:157–65.

[30] Zanchetta JR, Bogado CE, Ferretti JL, Wang O, Wilson MG, Sato M, et al. Effects of teriparatide [recombinant human parathyroid hormone (1-34)] on cortical bone in postmenopausal women with osteoporosis. J Bone Miner Res 2003;18:539–43.

[31] Black DM, Greenspan SL, Ensrud KE, Palermo L, McGowan JA, Lang TF, et al. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. N Engl J Med 2003;349: 1207–15.
[32] Finkelstein JS, Hayes A, Hunzelman JL, Wyland JJ, Lee H, Neer RM. The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. N Engl J Med 2003;349:1216–26.
[33] Uusi-Rasi K, Sievanen H, Vuori I, Pasanen M, Heinonen A, Oja P. Associations of physical activity and calcium intake with bone mass and size in healthy women at different ages. J Bone Miner Res 1998;13: 133–42.
[34] Beck TJ, Looker AC, Ruff CB, Sievanen H, Wahner HW. Structural trends in the aging femoral neck and proximal shaft: analysis of the third national health and nutrition examination survey dual energy X-ray absorptiometry data. J Bone Miner Res 2000;15:2297–304.
[35] Kim CH, Takai E, Zhou H, von Stechow D, Muller R, Dempster DW, et al. Trabecular bone response to mechanical and parathyroid hormone stimulation: the role of mechanical microenvironment. J Bone Miner Res 2003;18:2116–25.
[36] Turner RT, Lotinun S, Hefferan TE, Morey Holton E. Disuse in adult male rats attenuates the bone anabolic response to a therapeutic dose of parathyroid hormone. J Appl Physiol 2006;101:881–6.
[37] Boivin G, Chavassieux PM, Santora AC, Yates AJ, Meunier PJ. Alendronate increases bone strength by increasing the mean degree of mineralisation of bone tissue in osteoporotic women. Bone 2000;27: 687–94.
[38] Boivin G, Vedi S, Purdie DW, Compston JE, Meunier PJ. Influence of estrogen therapy at conventional and high doses on the degree of mineralisation of iliac bone tissue: a quantitative microradiographic analysis in postmenopausal women. Bone 2005;36:562–7.
[39] Roschger P, Rinnerthaler SJY, Rodan GA, Fratzl P, Klaushofer K. Alendronate increases degree and uniformity of mineralisation in cancellous bone and decreases the porosity in cortical bone of osteoporotic women. Bone 2001;29:185–91.
[40] Paschalis EP, Glass EV, Donley DW, Eriksen EF. Bone mineral and collagen quality in iliac crest biopsies of patients given teriparatide: new results from the fracture prevention trial. J Clin Endocrinol Metab 2005; 90:4644–9.
[41] Dempster DW. Bone histomorphometry in glucocorticoid-induced osteoporosis. J Bone Miner Res 1989;4:137–47.
[42] Salusky IB, Goodman WG. Adynamic renal osteodystrophy: is there a problem? J Am Soc Nephrol 2001;12:1978–85.
[43] Delmas PD, Licata AA, Reginster JY, Crans GG, Chen P, Misurski DA, et al. Fracture risk reduction during treatment with teriparatide is independent of pretreatment bone turnover. Bone 2006;39:237–43.
[44] Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis. A randomized controlled trial. JAMA 1999;282:1344–52.