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Skeletal Manifestations of Hypoparathyroidism

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ABSTRACT

Chronic PTH deficiency has a marked effect on the skeleton, leading to characteristic decreases in bone remodeling and increases in bone mass. An effect on fracture risk has not been demonstrated, although biochemical, imaging, and histomorphometric data indicate abnormalities in skeletal properties[1,21,21,21,2]. Replacement with PTH leads to a new skeletal state that is maintained with long-term treatment.

1. Introduction

Chronic PTH deficiency has a marked effect on the skeleton. In healthy adults, bone mass is tightly regulated by a balance between bone resorption and formation in the process of bone remodeling. As PTH is a key regulator of the rate of bone remodeling, a reduction or absence of circulating PTH levels leads to characteristic decreases in bone remodeling [2–6] and increases in bone mass [1,7–11]. Numerous lines of evidence employing biochemical, imaging, and histomorphometric methodologies have revealed that the skeleton is abnormal when PTH is absent [1,2], and that these deficits might be reversed with PTH treatment [3,4,12].

2. Skeletal manifestations of hypoparathyroidism

2.1. Biochemical markers of bone turnover in hypoparathyroidism

Low biochemical markers of bone turnover are a common feature of hypoparathyroidism [13,14]. This was demonstrated in a report in which biochemical markers of bone turnover were measured in 64 hypoparathyroid subjects (48 women and 16 men) who were treated with vitamin D [3]. The etiologies of the hypoparathyroid state were post–thyroid surgery ($n = 32$), autoimmune ($n = 30$) and DiGeorge syndrome ($n = 2$), and the mean disease duration was 15 ± 13 (SD) years. Vitamin D intake varied from 50 to 75,000 IU/d and calcium supplementation ranged between 0 and 9 g/d. Circulating markers of bone formation (P1NP, BAP and osteocalcin) and of bone resorption (TRAP-5b and serum CTx) were in the lower half of the normal reference range [3]. Other studies have demonstrated similarly low biochemical markers of bone turnover [4–6]. Preliminary data suggest that these low levels might be associated with decreased circulating osteogenic precursor cells [15] and increased circulating sclerostin levels [16].

2.2. Bone mineral density in hypoparathyroidism

Chronically low bone turnover in hypoparathyroidism leads to bone mass that is relatively higher than age-and sex-matched controls [7–10]. Bone mass, for example, was 21–28% higher in 13 women, 10–13 years after thyroidectomies complicated by hypoparathyroidism, as compared to 13 women whose thyroidectomies were not complicated by hypoparathyroidism [7]. Typically, the T- and *Z*-score increases in hypoparathyroidism exceed “1” at most sites that include trabecular and cortical bone, with the lumbar spine having the highest scores [1]. Bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA) in postmenopausal women with post-thyroidectomy hypoparathyroidism was increased when compared with the age-predicted mean at the lumbar spine and proximal femur, although not at the distal one-third radius [17]. Hypoparathyroidism was also found to slow the expected rate of postmenopausal bone loss as measured by DXA [8]. When a small group of hypoparathyroid subjects was compared to those with primary hyperparathyroidism (PHPT), the hypoparathyroid subjects did not show the catabolic effects of PTH to decrease bone density at the femoral neck [17].

Greater insight into the architectural basis of the increase in bone mass has been obtained by peripheral quantitative computed tomography (pQCT). Using this technique, volumetric bone mineral density (vBMD) and geometry of the distal radius and midradius was compared among postmenopausal women with postsurgical or idiopathic hypoparathyroidism, PHPT, and normal controls [11]. At the cancellous-enriched 4% distal radius site, trabecular vBMD was higher in the rank order hypoparathyroidism > control > PHPT. At the 20% midradius

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site, cortical vBMD was similarly greater in the same rank order. These BMD differences among the three groups could be explained by differences in bone geometry. At both radial sites, total bone area and both periosteal and endosteal surfaces were greater in PHPT than in hypoparathyroidism patients and controls, and cortical thickness and area were higher in the rank order hypoparathyroidism > control > PHPT. High resolution pQCT of the radius and tibia has recently corroborated an increase in cortical vBMD in both men ($n = 12$) and women ($n = 48$) with hypoparathyroidism as compared to normative controls [18]. In that report, decreased cortical porosity was also present at the radius and tibia in women and at the tibia in men. However, finite element analysis did not differ between hypoparathyroid and control subjects, suggesting that estimated bone strength was not altered [18].

2.3. Histomorphometry in hypoparathyroidism

Detailed information on the effects of hypoparathyroidism on the skeleton is available from histomorphometric analysis of iliac crest bone biopsies. The first histomorphometric study of bone in hypoparathyroidism, involving 12 hypoparathyroid patients, suggested that PTH deficiency is associated with distinctly abnormal bone turnover [2]. The study subjects, who had either postoperative or idiopathic hypoparathyroidism, were all treated with varying doses of vitamin D. As compared to euparathyroid age- and sex-matched controls, hypoparathyroid subjects had a markedly extended quiescent period (7.6 vs. 1.7 yrs, $p < 0.001$), along with a decreased resorption rate (0.9 vs. 3.8 μm/day, $p < 0.001$), formation rate (0.016 vs 0.081, $p < 0.001$) and activation frequency (0.13 vs. 0.6 year^{-1}, p < 0.001) [2]. Despite the notable reduction in bone remodeling activity, variables measuring the amount and microarchitecture of cancellous bone, such as cancellous bone volume, trabecular thickness, and marrow space star volume, were normal. A similarly profound suppression of bone turnover was reported in an earlier study on hypoparathyroid dogs, in which treatment with vitamin D was not able to restore normal bone turnover [19].

A larger histomorphometric report involved 64 subjects with hypoparathyroidism treated with vitamin D and 45 age- and gender-matched control subjects [1,3]. In contrast to the earlier smaller study [2], cancellous bone volume was increased in the hypoparathyroid subjects (Figs. 1 and 2). The structural basis for the increased cancellous bone volume in hypoparathyroidism was an increase in trabecular width; trabecular number and trabecular spacing did not differ from those in control subjects. Cortical width also tended to be greater in the hypoparathyroid subjects, and cortical porosity was lower than in control subjects, but this difference was not statistically significant. Remodeling activity was measured separately in cancellous, endocortical, and intracortical skeletal envelopes. Osteoid width and surface were reduced in the hypoparathyroid subjects in all three envelopes. The tetracycline-based bone formation rate (BFR) was significantly lower in all three envelopes in the hypoparathyroid subjects, with the greatest reduction observed on the cancellous envelope (Fig. 3). The reduction in BFR was a result of significant decreases in both mineral apposition rate and mineralized surface in all three envelopes. The eroded surface did not differ between the hypoparathyroid and control subjects, but the bone-resorption rate was significantly lower in the hypoparathyroid subjects in all three envelopes. As in the earlier study [2], these findings were indicative of a profound reduction in the bone turnover rate in hypoparathyroidism, with an attendant increase in bone mass in both cancellous and cortical compartments.

The effects of PTH deficiency on cancellous and cortical bone mass, which were observed initially by noninvasive imaging and by 2D histomorphometry, were corroborated by the 3D analytical capability of micro–computed tomography (μCT) [20]. Results from this study confirmed the increase in cancellous bone volume and trabecular thickness in hypoparathyroid subjects and demonstrated increased trabecular number and trabecular connectivity in comparison with matched control subjects. In addition, the structural model index, an estimation of the plate-rod characteristic, was lower in hypoparathyroidism, indicating that the trabecular structure was more plate-like than rod-like (Fig. 4) [20].

The material composition of the bone matrix in hypoparathyroidism has also been investigated. Using backscatter electron imaging, it was found that the mean mineralization density in iliac bone from subjects with hypoparathyroidism did not differ from that of control subjects, although there was greater inter-individual variation in mineralization parameters in the hypoparathyroidism subjects than in the control subjects [21]. This result is unexpected because one might have anticipated that mineralization density would be greater in hypoparathyroidism owing to the low turnover and accompanying increase in mineralization as the bone "ages." It suggests that mineralization density is controlled by other parameters, in addition to the degree of secondary mineralization, and suggests that the higher BMD by densitometry in hypoparathyroidism is due largely to the increase in bone tissue volume rather than an increase in the amount of mineral within the tissue.

2.4. Fracture risk in hypoparathyroidism

Prospective data on fracture risk in hypoparathyroidism do not exist. Case-controls studies, however, show no differences in overall fracture rate as compared with the general population [22,23]. Analyses of specific fracture types showed that patients with non-surgical hypoparathyroidism have a higher hazard ratio for upper extremity fractures (1.94; 95% CI: 1.31–2.85) compared with controls and that patients with post-surgical hypoparathyroidism have a lower hazard ratio for the same fracture (0.69; CI: 0.49–0.97) [24]. In a retrospective cohort, 21/120 patients (18%) sustained fractures over 7 years of follow up [25]. A cohort of nonsurgical hypoparathyroid subjects had an

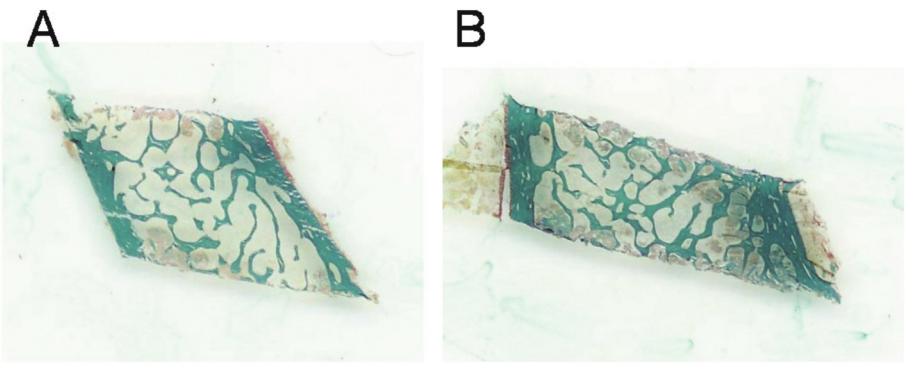

Fig. 1. Low-power view of iliac crest bone biopsies from a control subject (A) and a subject with hypoparathyroidism (B). Goldner trichrome stain. Note the increase in cancellous bone volume and cortical thickness in the hypoparathyroid subject. Reproduced with permission from Ref. [1].

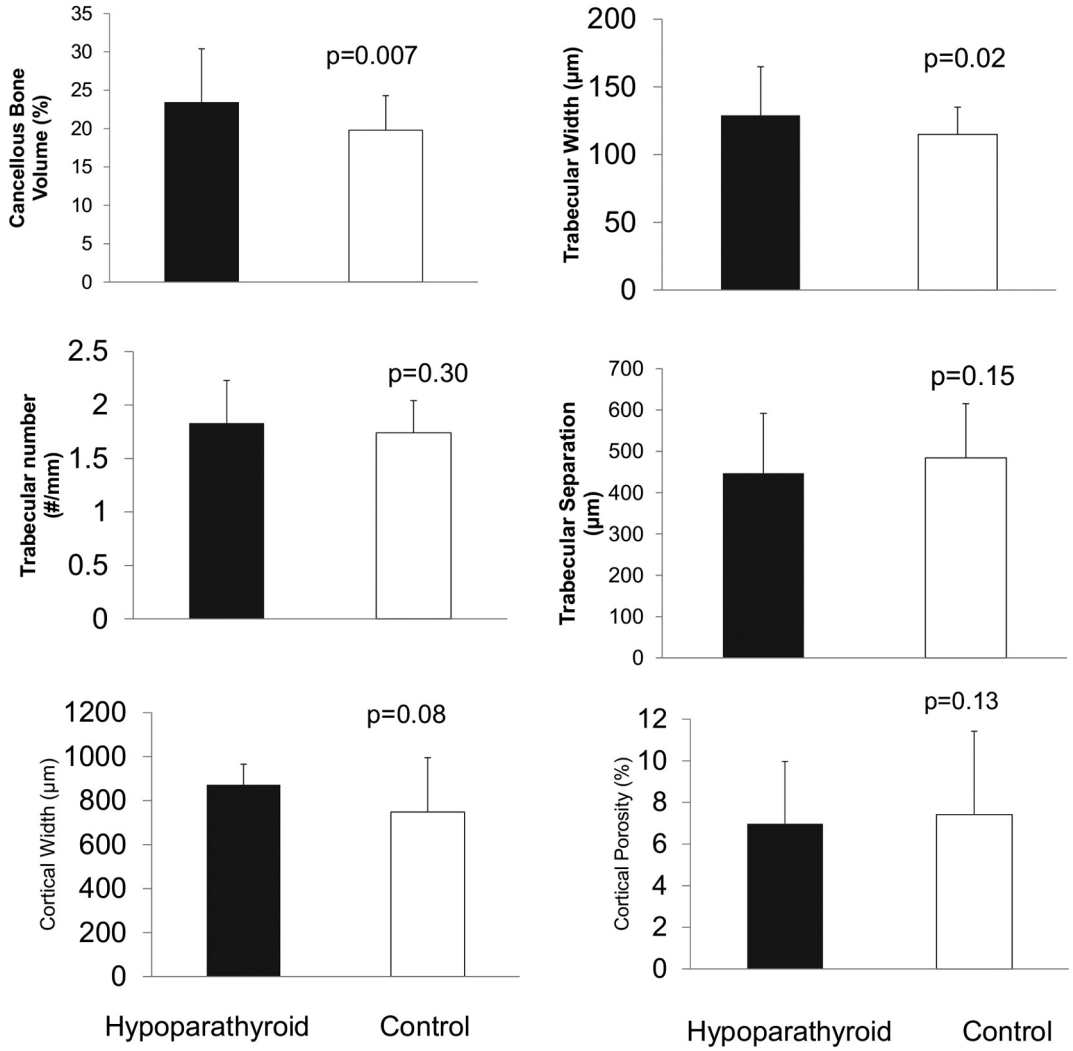

Fig. 2. Cancellous and cortical bone parameters obtained by histomorphmetry in subjects with hypoparathyroidism (black bars) and controls (white bars). Reproduced with permission from Ref. [15].

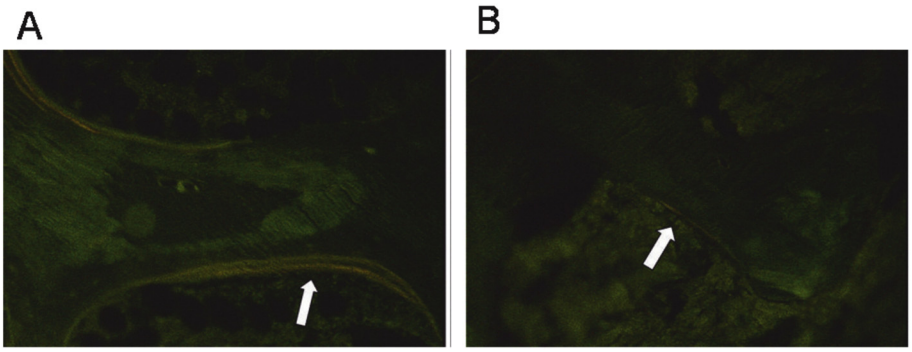

Fig. 3. Tetracycline labels in a control (A) and hypoparathyroid (B) subject. Tetracycline uptake was markedly reduced in the hypoparathyroid subject, reflecting the low bone turnover rate. Reproduced with permission from Ref. [1].

increase in morphometric vertebral fractures, but a high rate of anticonvulsant use was a possible confounder [26]. A simulated strength study with stress loading of images by finite element analysis suggested intact mechanical strength in hypoparathyroidism (Fig. 5) [27]. Overall, there is reason to be concerned about the fragility of bone in hypoparathyroidism because of the skeletal abnormalities that have been described [1], but further data are necessary to address this point.

3. Skeletal effects of PTH treatment in hypoparathyroidism

Until recently, hypoparathyroidism was the only classic hormone deficiency state for which there was not an approved hormone replacement treatment. The skeletal effects of PTH treatment in hypoparathyroidism have been investigated, both with the use of the foreshortened PTH [1–34] molecule [3,5,26–29] as well as with the full rhPTH(1–84) formulation [2,4,12,30,31]. While conventional therapy

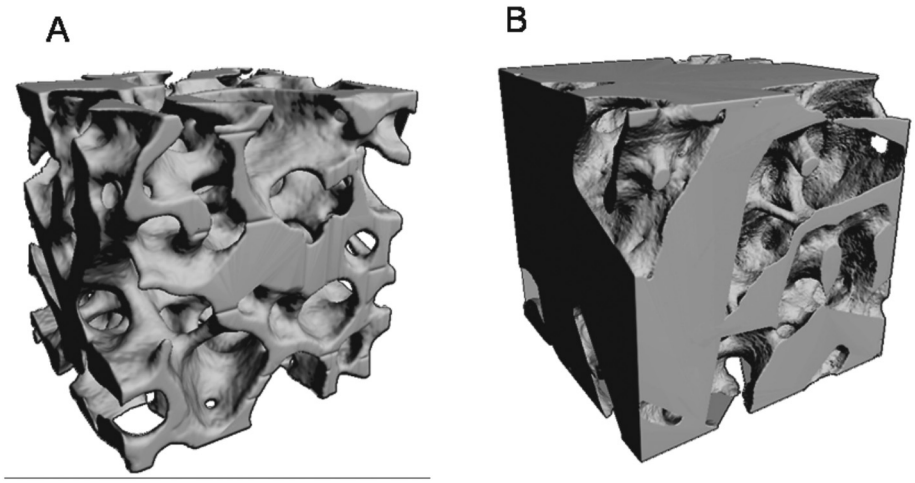

Fig. 4. Reconstructed μCT images of cancellous bone from a control (A) and hypoparathyroid (B) subject. Note the dense trabecular structure in hypoparathyroidism. Reproduced with permission from [20].

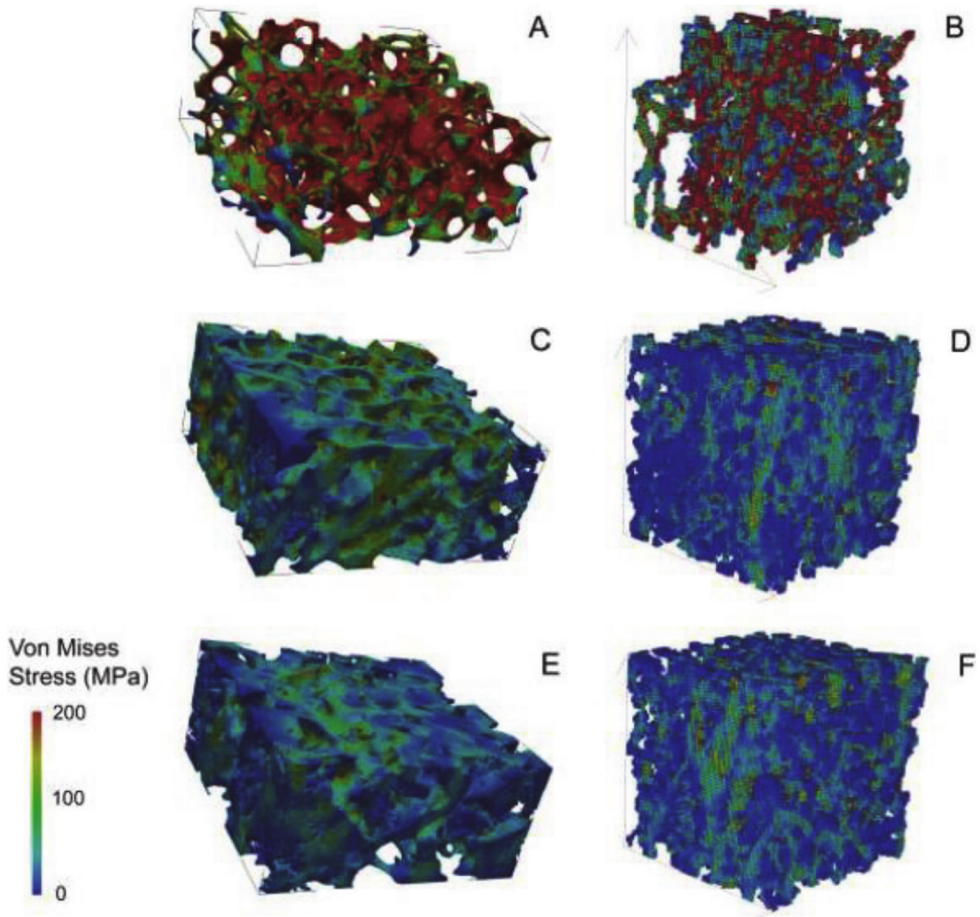

Fig. 5. Images showing tissue stress levels under axial loading generated by micro–finite element analysis based on micro–computed tomography of the iliac crest bone biopsies (A, C, E) and high-resolution peripheral quantitative computed tomography (B, D, F) of the radius in a premenopausal woman with idiopathic osteoporosis (A, B), a normal premenopausal control (C, D), and a patient with hypoparathyroidism (E, F). Dark blue indicates the regions with lowest stress, and dark red indicates the regions with highest stress. The lowest stress levels are seen in the subject with hypoparathyroidism. Reproduced with permission from Ref. [27]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

for hypoparathyroidism is not able to alter the skeletal abnormalities in hyopaparathyroidism [1], use of PTH has shown reversal of many of these abnormalities. In 2015, the FDA approved rhPTH(1–84) as an adjunct to calcium and vitamin D for the treatment of adults with hypoparathyroidism; in 2017, it was approved by the EMA as well.

3.1. Effects of PTH treatment on bone turnover

Biochemical markers of bone turnover initially increase dramatically with PTH treatment [4–6,28]. In a cohort study by Gafni et al. of 5 hypoparathyroid subjects treated with PTH [1–34] for 1.5 years, bone turnover markers increased from 2 to 7-fold from baseline [6]. In a longer and larger randomized parallel group study, 27 hypoparathyroid patients (postsurgical $n = 11$, idiopathic $n = 8$, calcium receptor sensing mutation $n = 6$, polyglandular failure $n = 2$) were treated by Winer et al. for 3 years with either PTH [1–34] or calcitriol titrated to serum calcium levels [4]. Markers of bone turnover, including alkaline phosphatase, osteocalcin, urinary pyridinoline and deoxypyroidinoline, rose markedly above the normal range, although a slight downward trend was evident beginning at 2.5 years [4]. More recently, Sikjaer

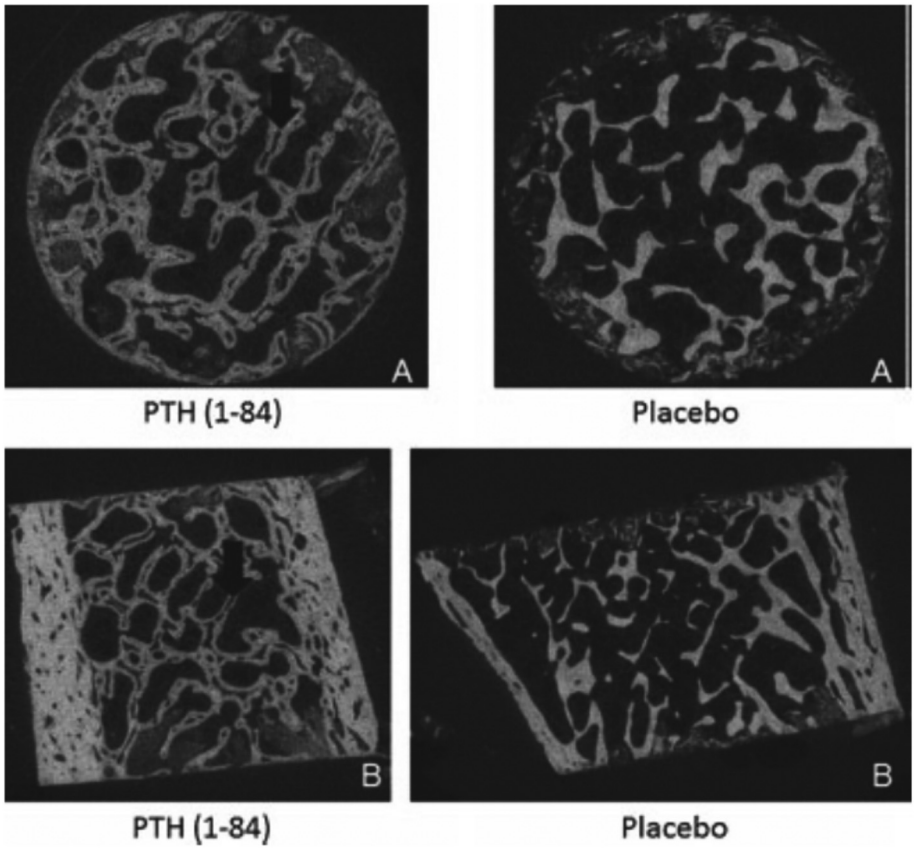

Fig. 6. Iliac crest biopsies, one with intratrabecular tunneling from a patient treated with PTH(1–84) 100 mg/day for 24 weeks and one without tunneling from a placebo-treated patient. (A) Cross-sectional view; (B) longitudinal sectional view. Reproduced with permission from Ref. [12].

et al. found in a 6 month randomized double-blind placebo-controlled study of rhPTH(1–84) administered to 62 hypoparathyroid patients (postsurgical $n = 58$, idiopathic $n = 4$) at a dose of 100 μg/d that biochemical markers of bone turnover rose dramatically (P1NP by 1315% and s-CTx increased by 1209%), although the levels of osteocalcin and s-CTx appeared to plateau between 20 and 24 weeks [5]. Similarly, in 33 subjects (postsurgical $n = 20$, idiopathic $n = 12$, DiGeorge n = 1) treated by Rubin et al. with rhPTH (1–84) for 6 years, bone turnover markers increased significantly, reaching a 3-fold peak from baseline values at 6–12 months and subsequently declining but remaining higher than pretreatment values [29]. In the largest clinical trial of rhPTH (1–84), known as REPLACE, hypoparathyroid patients ($n = 134$) were randomized to rhPTH(1–84) or placebo for 24 weeks [30]. The primary end point, defined as > 50% reductions of activated vitamin D and calcium supplements, while maintaining serum calcium concentrations within the target range, was achieved in significantly more of the patients treated with rhPTH(1–84) than with placebo (53% versus 2%) [30]. Biochemical markers of bone turnover increased significantly with rhPTH(1–84) at 24 weeks [31]. Recent results from the 5 year open-label extension trial, known as RACE ($n = 40$), showed maintenance of reductions in activated vitamin D and calcium supplements [32]. Bone turnover markers over the 5 years increased from baseline, peaking early in treatment, and then stabilizing to new steady-state levels [33]. Taken together, these data suggest that PTH has an initial exuberant effect to increase biochemical markers of bone turnover, with subsequent tempering over time to a new, steady-state, more euparathyroid level. Notably, the skeletal effects of PTH injections appear to depend on the frequency of administration. Once-daily or twice-daily hPTH [1–34] injections [34] [35] and alternate-day or once-daily rhPTH(1–84) injections produce persistently increased levels of bone turnover markers [4,29]. In contrast, continuous infusion of hPTH [1–34] by pump normalized the levels of bone turnover markers in a 12-week study [34], but further studies of pump delivery of hPTH [1–34] are required to determine its long-term effects on bone [35].

3.2. Effects of PTH treatment on bone mineral density

Treatment with PTH [1–34] as titrated to serum calcium levels, when compared to calcitriol by Winer et al., did not lead to a change in BMD over 3 years in adult hypoparathyroid patients, although there was a tendency for non-significant decreases at the lumbar spine and radius [4]. In children, there was a significant decrease at radial BMD after 3 years of PTH [1–34,36]. When rhPTH(1–84) was given by Sikjaer et al. to adults at 100 μg/d for 6 months, BMD decreased at the whole body, spine, hip and femoral neck, but not at the forearm; the BMD decreases correlated with the increases in biochemical markers of bone turnover [5]. Quantitative computed tomography (QCT) analysis of this cohort showed that vBMD in cancellous bone increased, despite the decrease in aBMD at the lumbar spine, while cortical vBMD decreased [5]. In the 6 year treatment study of rhPTH(1–84), lumbar spine BMD increased ($3.8 \pm 1\%$, $P = 0.004$) as did total hip BMD ($2.4 \pm 1\%$, $P = 0.02$), whereas femoral neck BMD remained stable and the distal one third radius decreased ($-4.4 \pm 1\%$, $P < 0.0001$). In the randomized REPALCE trial, at 24 weeks bone density decreased toward normal levels [31]. In the RACE extension, BMD was stable or slightly reduced, with the greatest decline at the distal one third radius [33]. These data suggest that the relative distribution of trabecular and cortical bone might vary with PTH treatment at specific skeletal sites.

3.3. Effects of PTH treatment on histomorphometric indices

Iliac crest bone biopsies were obtained by Sikjaer et al. in 51

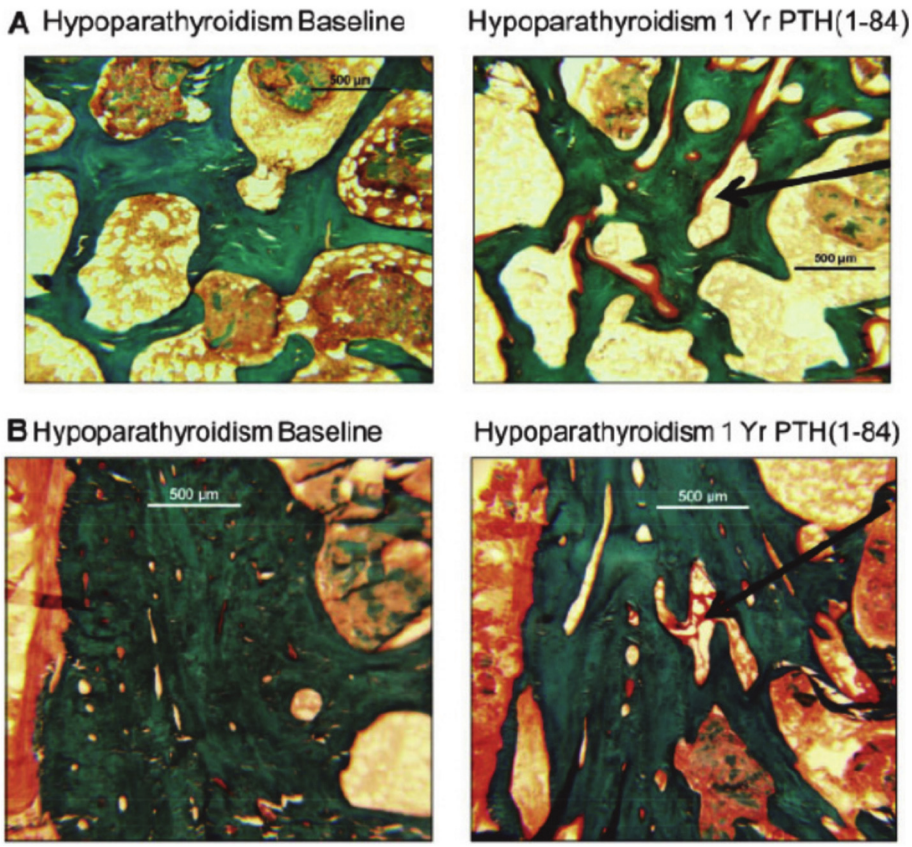

Fig. 7. Iliac crest biopsy illustrating changes in the trabecular (A) and cortical (B) structure before and after 1 year of PTH(1–84) treatment in a hypoparathyroid subject. Note the increases in trabecular tunneling and cortical porosity (arrows) in the post-treatment biopsy. Reproduced with permission from [3].

patients in the 6 month RCT of rhPTH(1–84) treatment (PTH group $n = 26$; placebo group $n = 25$) [12]. MicroCT analysis demonstrated lower trabecular thickness with PTH treatment, with an increase in the bone surface and the presence of a more complex trabecular network, suggesting the development of thinner and better connected trabeculae [12]. Intratrabecular tunneling, or the longitudinal splitting of a single trabeculae into two thinner new trabeculae (Fig. 6) was detected in the rhPTH(1–84) group. The presence of intratrabecular tunneling was associated with greater calcium mobilization, as demonstrated by higher bone turnover and a tendency toward a greater decrease in calcium and active vitamin D supplementation [5,12]. With regard to cortical bone, at 6 months more Haversian canals per unit area were observed, with a trend toward increased cortical porosity, although cortical bone tissue density did not differ [12]. A comparable pattern was observed in the open-label 1.5 year study of Gafni et al., with an increase in cancellous bone volume, trabecular number and cortical porosity and a decrease in trabecular separation [6].

In a two year study of open-label rhPTH(1–84) treatment for two years, paired iliac crest bone biopsies were performed before and after rhPTH(1–84) treatment at 1 year ($n = 14$) and at 2 years ($n = 16$); a separate group had an early "quadruple-label" biopsy [37] at 3 months (n = 16) [3]. An early anabolic effect was apparent, with an early increase in the mineralizing surface (MS), osteoid surface and bone formation rate at 3 months (MS at baseline: 0.39 ± 0.6% vs MS at 3 months: 5.47 ± 6.0%; $p = 0.004$), which peaked at 12 months (MS at baseline: 0.7 ± 0.6% vs MS at 1 year: 7.1 ± 6.0%, $p = 0.001$) and was similar to euparathyroid levels at 2 years (MS at baseline: 1.18 ± 2.2% vs MS at 2 years: 3.34 ± 0.8%; $p = 0.04$; MS in healthy controls: 4.33 ± 3.2%). The remodeling changes were most prominent in the cancellous envelope at 1 year; within 2 years, with the exception of osteoid surface, the differences were no longer significant at the endocortical and intracortical envelopes [3]. Structural changes after rhPTH(1–84) treatment included reduced trabecular width (144 ± 34 microm to 128 ± 34 microm, $p = 0.03$) and increases in trabecular number (1.74 ± 0.34/mm to 2.07 ± 0.50/mm, $p = 0.02$) at 2 years. As in the studies of Sikjaer et al. and Gafni et al., intratrabecular tunneling was apparent (Fig. 7). Cortical porosity increased at 2 years (7.4% ± 3.2% to 9.2% ± 2.4%, p = 0.03; Fig. 7), although cortical width did not change.

Longitudinal 3-D analysis of the biopsies by microCT confirmed that the microstructural changes, including decreased trabecular thickness and increased connectivity density, occurred relatively early with PTH treatment and were detectable to a greater extent at one than at two years [38]. Backscattered electron imaging of the biopsies showed that with rhPTH(1–84) treatment over 1 year there was a decrease in the degree of mineralization and an increase in the heterogeneity of mineralization [39]. After 2 years of rhPTH(1–84), the degree of mineralization was similar to baseline, although the greater heterogeneity in matrix mineralization persisted. These data suggest that the greatest effects on microstructural changes and bone mineralization density distribution occur within the first year of PTH exposure to the hypoparathyroid skeleton.

Extended data on the histomorphometric effects of rhPTH(1–84) suggest that significant skeletal changes are sustained with long-term treatment (Fig. 8) [40]. In 13 hypoparathyroid patients treated for an average of 8.3 ± 1 years with rhPTH(1–84), persistent increases in bone remodeling were evident. In comparison to pre-treatment values, mineralizing surface increased by 26-fold (0.3 ± 1 to 7.9 ± 7%, $p = 0.003$); bone formation rate increased by 15-fold (0.003 ± 0.01 to 0.047 ± 0.05 $\mu m^2/\mu m/d$, $p = 0.007$); osteoid width doubled (1.9 ± 1 to 4.3 ± 1 lamellae, $p = 0.017$) and osteoid surface tripled (3.3 ± 3 to 10.8 ± 6%, $p = 0.011$). Bone resorption as measured by eroded surface increased (4.6 ± 2 to 7.5 ± 3%, $p = 0.021$). Certain parameters, including the osteoid surface, mineralizing surface and eroded surface,

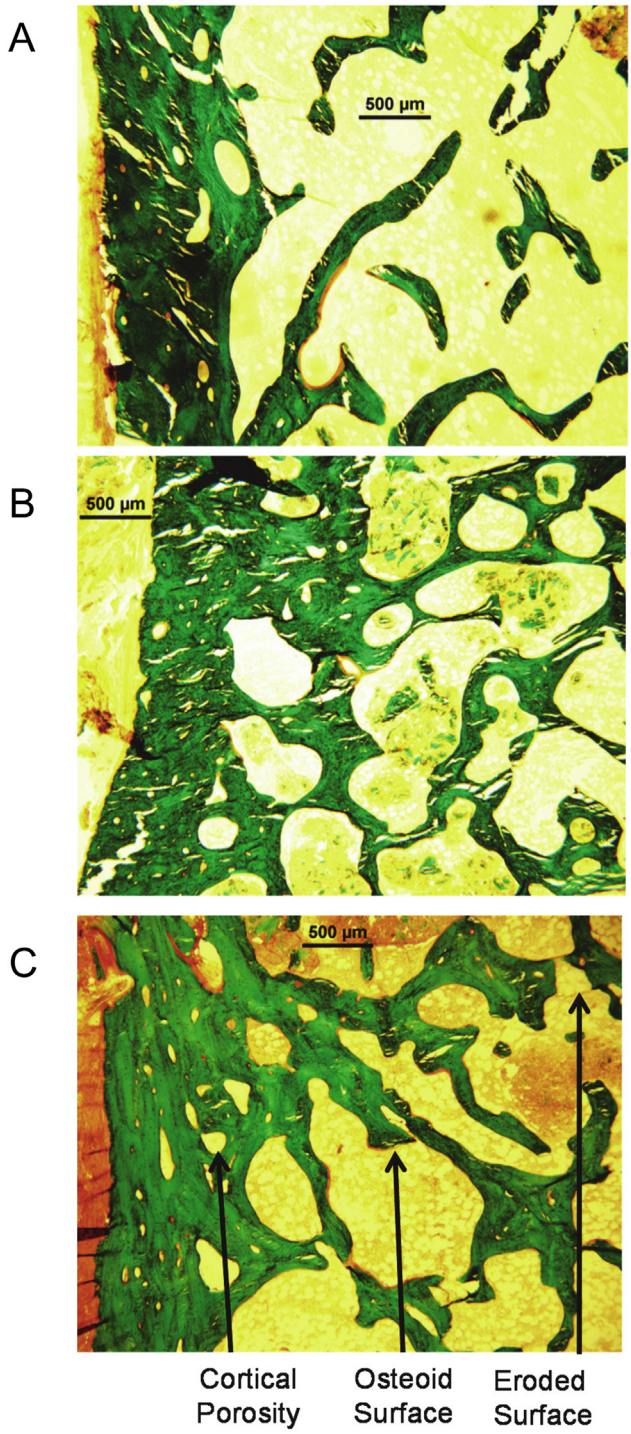

Fig. 8. Representative histomorphometric images in a control subject and in a hypoparathyroid subject before and after 8 years of rhPTH(1–84) treatment. In comparison to the control image (A) the baseline untreated hypoparathyroid image (B) demonstrates increased cortical width. The long- term image (C) shows an increase in cortical porosity and trabecular tunneling as well as in unmineralized osteoid (osteoid surface, in red) and eroded surface (arrow) as compared to the baseline hypoparathyroid image. Reproduced with permission from [40]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

significantly exceeded normal values [40].

As in the 2 year histomorphometric report [3], long-term structural changes demonstrated intra-trabecular tunneling, with increases in cancellous bone volume (19.6 ± 5 to 29.1 ± 11%, p = 0.017) and trabecular number (1.8 ± 1 to 2.5 ± 1 #/mm, $p = 0.025$) [40]. The cancellous bone volume and trabecular number surpassed control levels, indicating that after nearly a decade of rhPTH(1–84), a prolonged and continuous anabolic effect at cancellous sites is evident. Cortical porosity tended to increase (6.3 ± 5 to 9.5 ± 3%, $p = 0.07$) with long-term rhPTH(1–84), exceeding control levels [40]. While the persistent nature of the cortical porosity might raise a concern vis a vis cortical bone strength, the cortices still reassuringly remained thicker than normal. Notably, in hypoparathyroidism a different paradigm exists than in that of postmenopausal osteoporosis where an increase in cortical remodeling accompanied by a decrease in cortical thickness could be problematic. In the setting of hypoparathyroidism, though, it is theoretically possible that increased remodeling might result in the replacement of older, overly mature bone with younger and more resilient bone. A contrary view is that given that fracture risk is not increased in hypoparathyroidism, the increases in cortical porosity and eroded surface might indicate that bone turnover is over-stimulated with long-term daily injections of rhPTH(1–84). Other rhPTH(1–84) dosing regimens, such as twice daily administration or a continuous infusion via a pump, might mitigate over-stimulation of turnover, if it is present.

3.4. Effects of PTH treatment on fractures

Data are not available on the effects of PTH treatment in hypoparathyroidism on fracture risk. It is thus unknown whether the radiologic and histomorphometric skeletal changes observed with PTH treatment have clinical consequences. Notably, fracture incidence might be difficult to determine because of the rarity of this disease and the need for a large number of subjects that are typically required to ascertain fracture incidence in a tested population.

3.5. Osteosarcoma risk with PTH treatment

PTH [1–34] and rhPTH(1–84) were found to increase osteosarcoma risk in rats [41]. However, the risk is dose-related and the non-carcinogenic doses for both PTH [1–34] (4.5 µg/kg/d) and rhPTH(1–84) (10 µg/kg/d) are significantly above those used to treat hypoparathyroidism [42]. Although this issue could be of particular concern in children with unfused epiphyses, the 3 year data of Winer et al. in children [36] and a 13 year case report [43] are reassuring in this regard. Moreover, longstanding hyperparathyroidism is not associated with the development of osteosarcomas despite chronically elevated PTH levels [44]. Furthermore, no increased rate of osteosarcoma has emerged despite extensive use of hPTH [1–34] in patients with hypoparathyroidism or osteoporosis since Forteo was approved in 2002, although most of the latter were treated for only 2 years [45].

4. Summary

Hypoparathyroidism is associated with marked abnormalities in bone parameters. With PTH replacement, a new skeletal state becomes established and sustained. The skeletal findings in hypoparathyroidism and the effects of PTH treatment speak to the fundamental importance of PTH in the maintenance of bone structure and function. Future work is needed to determine whether fractures rates in hypoparathyroidism are altered with PTH treatment.

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References

[1] M.R. Rubin, D.W. Dempster, H. Zhou, et al., Dynamic and structural properties of the skeleton in hypoparathyroidism, J. Bone Miner. Res. 23 (2008) 2018–2024.
[2] B.L. Langdahl, L. Mortensen, A. Vesterby, E.F. Eriksen, P. Charles, Bone histomorphometry in hypoparathyroid patients treated with vitamin D, Bone 18 (1996) 103–108.
[3] M.R. Rubin, D.W. Dempster, J. Sliney Jr.et al., PTH(1-84) administration reverses abnormal bone-remodeling dynamics and structure in hypoparathyroidism, J. Bone Miner. Res. 26 (2011) 2727–2736.
[4] K.K. Winer, C.W. Ko, J.C. Reynolds, et al., Long-term treatment of hypoparathyroidism: a randomized controlled study comparing parathyroid hormone-(1-34) versus calcitriol and calcium, J. Clin. Endocrinol. Metab. 88 (2003) 4214–4220.
[5] T. Sikjaer, L. Rejnmark, L. Rolighed, L. Heickendorff, L. Mosekilde, The effect of adding PTH(1-84) to conventional treatment of hypoparathyroidism: a randomized, placebo-controlled study, J. Bone Miner. Res. 26 (2011) 2358–2370.
[6] R.I. Gafni, J.S. Brahim, P. Andreopoulou, et al., Daily parathyroid hormone 1-34 replacement therapy for hypoparathyroidism induces marked changes in bone turnover and structure, J. Bone Miner. Res. 27 (2012) 1811–1820.
[7] S. Abugassa, J. Nordenstrom, S. Eriksson, G. Sjoden, Bone mineral density in patients with chronic hypoparathyroidism, J. Clin. Endocrinol. Metab. 76 (1993) 1617–1621.
[8] K. Fujiyama, T. Kiriyama, M. Ito, et al., Attenuation of postmenopausal high turnover bone loss in patients with hypoparathyroidism, J. Clin. Endocrinol. Metab. 80 (1995) 2135–2138.
[9] E. Seeman, H.W. Wahner, K.P. Offord, R. Kumar, W.J. Johnson, B.L. Riggs, Differential effects of endocrine dysfunction on the axial and the appendicular skeleton, J. Clin. Invest. 69 (1982) 1302–1309.
[10] J.S. Touliatos, J.I. Sebes, A. Hinton, D. McCommon, J.G. Karas, G.M. Palmieri, Hypoparathyroidism counteracts risk factors for osteoporosis, Am J Med Sci 310 (1995) 56–60.
[11] Q. Chen, H. Kaji, M.F. Iu, et al., Effects of an excess and a deficiency of endogenous parathyroid hormone on volumetric bone mineral density and bone geometry determined by peripheral quantitative computed tomography in female subjects, J. Clin. Endocrinol. Metab. 88 (2003) 4655–4658.
[12] T. Sikjaer, L. Rejnmark, J.S. Thomsen, et al., Changes in 3-dimensional bone structure indices in hypoparathyroid patients treated with PTH(1-84): a randomized controlled study, J. Bone Miner. Res. 27 (2012) 781–788.
[13] K. Kruse, U. Kracht, K. Wohlfart, U. Kruse, Biochemical markers of bone turnover, intact serum parathyroid horn and renal calcium excretion in patients with pseudohypoparathyroidism and hypoparathyroidism before and during vitamin D treatment, Eur. J. Pediatr. 148 (1989) 535–539.
[14] K. Mizunashi, Y. Furukawa, R. Miura, S. Yumita, H.E. Sohn, K. Yoshinaga, Effects of active vitamin D3 and parathyroid hormone on the serum osteocalcin in idiopathic hypoparathyroidism and pseudohypoparathyroidism, J. Clin. Invest. 82 (1988) 861–865.
[15] M.R. Rubin, J.S. Manavalan, D.W. Dempster, et al., Parathyroid hormone stimulates circulating osteogenic cells in hypoparathyroidism, J. Clin. Endocrinol. Metab. 96 (2011) 176–186.
[16] A.G. Costa, S. Cremers, M.R. Rubin, et al., Circulating sclerostin in disorders of parathyroid gland function, J. Clin. Endocrinol. Metab. 96 (2011) 3804–3810.
[17] Y. Duan, V. De Luca, E. Seeman, Parathyroid hormone deficiency and excess: similar effects on trabecular bone but differing effects on cortical bone, J. Clin. Endocrinol. Metab. 84 (1999) 718–722.
[18] N.E. Cusano, K.K. Nishiyama, C. Zhang, et al., Noninvasive assessment of skeletal microstructure and estimated bone strength in hypoparathyroidism, J. Bone Miner. Res. 31 (2016) 308–316.
[19] H.H. Malluche, C. Matthews, M.C. Faugere, P. Fanti, D.B. Endres, R.M. Friedler, 1,25-Dihydroxyvitamin D maintains bone cell activity, and parathyroid hormone modulates bone cell number in dogs, Endocrinology 119 (1986) 1298–1304.
[20] M.R. Rubin, D.W. Dempster, T. Kohler, et al., Three dimensional cancellous bone structure in hypoparathyroidism, Bone 46 (2010) 190–195.
[21] E.P. Paschalis, P. Roschger, M.R. Rubin, et al., Bone mineralization density and collagen cross-link ratios in hypoparathyroidism, J. Bone Miner. Res. 2006 (2009).
[22] L. Underbjerg, T. Sikjaer, L. Mosekilde, L. Rejnmark, The epidemiology of nonsurgical hypoparathyroidism in Denmark: a nationwide case finding study, J. Bone Miner. Res. 30 (2015) 1738–1744.
[23] L. Underbjerg, T. Sikjaer, L. Mosekilde, L. Rejnmark, Cardiovascular and renal complications to postsurgical hypoparathyroidism: a Danish nationwide controlled historic follow-up study, J. Bone Miner. Res. 28 (2013) 2277–2285.
[24] L. Underbjerg, T. Sikjaer, L. Mosekilde, L. Rejnmark, Post-surgical hypoparathyroidism - risk of fractures, psychiatric diseases, cancer, cataract, and infections, J. Bone Miner. Res. 29 (11) (2014) 2504–2510.
[25] D.M. Mitchell, S. Regan, M.R. Cooley, et al., Long-term follow-up of patients with hypoparathyroidism, J. Clin. Endocrinol. Metab. 97 (2012) 4507–4514.
[26] H. Chawla, S. Saha, D. Kandasamy, R. Sharma, V. Sreenivas, R. Goswami, Vertebral fractures and bone mineral density in patients with idiopathic hypoparathyroidism on long-term follow-up, J. Clin. Endocrinol. Metab. 102 (2017) 251–258.
[27] A. Cohen, D.W. Dempster, R. Muller, et al., Assessment of trabecular and cortical architecture and mechanical competence of bone by high-resolution peripheral computed tomography: comparison with transiliac bone biopsy, Osteoporos. Int. 21 (2010) 263–273.
[28] N.E. Cusano, M.R. Rubin, D.J. McMahon, et al., Therapy of hypoparathyroidism with PTH(1-84): a prospective four-year investigation of efficacy and safety, J. Clin. Endocrinol. Metab. 98 (2013) 137–144.
[29] M.R. Rubin, N.E. Cusano, W.W. Fan, et al., Therapy of hypoparathyroidism with PTH(1-84): a prospective six year investigation of efficacy and safety, J. Clin. Endocrinol. Metab. 101 (2016) 2742–2750.
[30] M. Mannstadt, B.L. Clarke, T. Vokes, et al., Efficacy and safety of recombinant human parathyroid hormone (1-84) in hypoparathyroidism (REPLACE): a double-blind, placebo-controlled, randomised, phase 3 study, Lancet Diabetes Endocrinol. 1 (2013) 275–283.
[31] Changes in Bone Turnover Markers and Bone Mineral Density with Recombinant Human Parathyroid Hormone, rhPTH(1–84), in Hypoparathyroidism: Potential Utility as Surrogate Endpoints for Monitoring - the REPLACE Study, Accessed Suppl 1, 28, at, 2013. http://www.asbmr.org/education/AbstractDetail?aid=f7964cf6-851e-4ce3-a8f4-5120b7e275ca.
[32] D. Shoback, J. Bilezikian, H.G. Bone, et al., Five-year efficacy and safety of recombinant human parathyroid hormone 1-84 (rhPTH[1-84]) for the treatment of adults with chronic hypoparathyroidism: analysis from the open-label race study, Endocr. Rev. 39 (2018).
[33] M. Mannstadt, J. Bilezikian, H.G. Bone, et al., Bone turnover in patients with hypoparathyroidism treated for 5 years with recombinant human parathyroid hormone, rhPTH(1–84), in the open-label RACE study, J. Bone Miner. Res. 33 (Suppl. 1) (2018).
[34] K.K. Winer, B. Zhang, J.A. Shrader, et al., Synthetic human parathyroid hormone 1-34 replacement therapy: a randomized crossover trial comparing pump versus injections in the treatment of chronic hypoparathyroidism, J. Clin. Endocrinol. Metab. 97 (2012) 391–399.
[35] K.K. Winer, K.A. Fulton, P.S. Albert, G.B. Cutler Jr., Effects of pump versus twice-daily injection delivery of synthetic parathyroid hormone 1-34 in children with severe congenital hypoparathyroidism, J. Pediatr. 165 (2014) 556–563 (e1).
[36] K.K. Winer, N. Sinaii, J. Reynolds, D. Peterson, K. Dowdy, G.B. Cutler Jr., Long-term treatment of 12 children with chronic hypoparathyroidism: a randomized trial comparing synthetic human parathyroid hormone 1-34 versus calcitriol and calcium, J. Clin. Endocrinol. Metab. 95 (2010) 2680–2688.
[37] R. Lindsay, F. Cosman, H. Zhou, et al., A novel tetracycline labeling schedule for longitudinal evaluation of the short-term effects of anabolic therapy with a single iliac crest bone biopsy: early actions of teriparatide, J. Bone Miner. Res. 21 (2006) 366–373.
[38] M.R. Rubin, A. Zwahlen, D.W. Dempster, et al., Effects of parathyroid hormone administration on bone strength in hypoparathyroidism, J. Bone Miner. Res. 31 (2016) 1082–1088.
[39] B.M. Misof, P. Roschger, D.W. Dempster, et al., PTH(1-84) administration in hypoparathyroidism transiently reduces bone matrix mineralization, J. Bone Miner. Res. 31 (2016) 180–189.
[40] M.R. Rubin, H. Zhou, N.E. Cusano, et al., The effects of long-term administration of rhPTH(1-84) in hypoparathyroidism by bone histomorphometry, J. Bone Miner. Res. 33 (11) (2018) 1931–1939.
[41] A. Watanabe, S. Yoneyama, M. Nakajima, et al., Osteosarcoma in Sprague-Dawley rats after long-term treatment with teriparatide (human parathyroid hormone (1-34)), J. Toxicol. Sci. 37 (2012) 617–629.
[42] J. Jolette, C.E. Wilker, S.Y. Smith, et al., Defining a noncarcinogenic dose of recombinant human parathyroid hormone 1-84 in a 2-year study in Fischer 344 rats, Toxicol. Pathol. 34 (2006) 929–940.
[43] T.A. Theman, M.T. Collins, D.W. Dempster, et al., PTH(1-34) replacement therapy in a child with hypoparathyroidism caused by a sporadic calcium receptor mutation, J. Bone Miner. Res. 24 (2009) 964–973.
[44] S.J. Silverberg, E. Shane, T.P. Jacobs, E. Siris, J.P. Bilezikian, A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery, N. Engl. J. Med. 341 (1999) 1249–1255.
[45] E.B. Andrews, A.W. Gilsenan, K. Midkiff, et al., The US postmarketing surveillance study of adult osteosarcoma and teriparatide: study design and findings from the first 7 years, J. Bone Miner. Res. 27 (2012) 2429–2437.