Combination Anabolic and Antiresorptive Therapy for Osteoporosis: Opening the Anabolic Window

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Antiresorptive agents for osteoporosis are a cornerstone of therapy, but anabolic drugs have recently increased our options. By stimulating bone formation, anabolic agents reduce fracture incidence by improving bone qualities in addition to increasing bone mass. The only anabolic agent currently approved for osteoporosis by the US Food and Drug Administration, teriparatide (recombinant human parathyroid hormone [1-34]), has emerged as a major approach to selected patients with osteoporosis. Recombinant human parathyroid hormone (1-84) is also available in Europe. Teriparatide increases bone density and bone turnover, improves microarchitecture, and changes bone size. The incidence of vertebral and nonvertebral fractures is reduced. A current concept in the mechanism of teriparatide action is related to its effect to stimulate processes associated with bone formation before it stimulates processes associated with bone resorption. This sequence of events has led to the concept of the anabolic window, the period of time when teriparatide is maximally anabolic. Newer approaches to the use of teriparatide alone and in combination with antiresorptive agents have led to ways in which the anabolic window can be expanded.

Introduction

Antiresorptive agents are a mainstay of osteoporosis therapy. With the introduction of teriparatide, recombinant human parathyroid hormone (PTH) (1-34), and more recently, PTH(1-84), as treatments for osteoporosis, we now have an alternative, namely anabolic skeletal therapy. By stimulating bone formation to a greater extent and earlier than bone resorption, PTH(1-34) and the full-length molecule, PTH(1-84), create a window during which its anabolic properties are maximal. PTH affects a number of skeletal properties besides bone density. These include bone size and microarchitecture. PTH has the potential to reconstruct the skeleton, an endpoint not shared by any of the antiresorptives [1]. Advances have recently been made in further understanding the mechanisms by which PTH is anabolic to the skeleton [2••]. On the clinical level, we have recently gained new insights into how antiresorptive agents and PTH can be used in sequence or in combination for maximal skeletal benefits.

PTH As an Anabolic Agent

In primary hyperparathyroidism, a disorder of chronic, continuous secretion of excess PTH, catabolic effects primarily at cortical sites such as the distal 1/3 radius are common. Nevertheless, even in this disorder of chronic PTH secretion, salutary effects can be seen at the cancellous skeleton, such as the lumbar spine [3]. The clinical clue to the utility of PTH as an anabolic skeletal agent came with the recognition that its anabolic potential is seen much more clearly when used in low doses and with intermittent administration. PTH is currently available in many countries as the recombinant human PTH(1-34) fragment teriparatide. The full-length molecule, human recombinant PTH(1-84), has been approved for use in some European countries and is now under investigation in the United States. Teriparatide leads to a rapid increase in bone formation markers followed sometime thereafter by increases in bone resorption markers. If these markers reflect physiologic events, PTH likely initially stimulates processes associated with bone formation (bone modeling) and only later promotes those associated with bone remodeling. This sequence of events has led to the concept of the "anabolic window," a period of time when the actions of PTH are maximally anabolic, as shown in Figure 1 [4].

The beneficial effects of teriparatide on bone qualities such as bone density, microarchitecture, and bone geom-

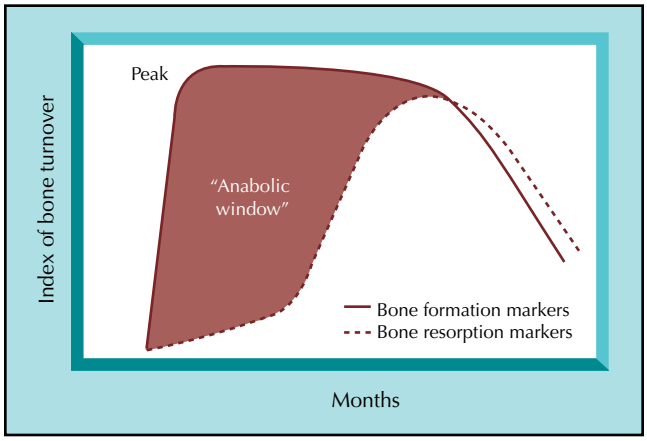

Figure 1. The anabolic window. Based on the difference in kinetics of changes between bone formation and bone resorption markers, an "anabolic window" is formed during which the actions of parathyroid hormone are thought to be maximally anabolic. (From Rubin and Bilezikian [50]; with permission.)

etry are seen in the cancellous skeleton [5]. At a cortical skeletal site, such as the distal 1/3 radius, PTH typically does not increase bone density. In fact, there may be a small decrease in bone mineral density (BMD) in association with an increase in cortical porosity. There may also be a transient decrease in BMD at the hip. An interesting feature of PTH therapy is the heterogeneity of responsivity that is greater than that observed with the use of bisphosphonates [6]. Rather than a narrow distribution of densitometric effects with the bisphosphonates, PTH is associated with a greater variability in densitometric responsiveness. Referencing individuals who experience a transient reduction in BMD, bone strength is not diminished because the increased porosity occurs only in the inner one third of bone, where the mechanical effect is minimal. Even more importantly, other positive effects of teriparatide at cortical bone, such as changes in bone geometry and microarchitecture, adequately compensate for any increase in cortical porosity [7–9]. PTH stimulates periosteal apposition, which leads to increases in cortical area, cortical thickness, and an overall increase in cross-sectional area [7,10]. Moreover, microarchitectural changes due to teriparatide are evident at cortical sites such as the distal 1/3 radius as well. These geometrical and microarchitectural changes strengthen cortical bone despite the small reduction in bone density [11].

Indications for Teriparatide

Teriparatide is indicated in men and in postmenopausal women with osteoporosis who are at high risk for fracture. In Europe, teriparatide and PTH(1-84) are approved for use only in postmenopausal women. Useful guidelines have been published to help select patients for teriparatide [1]. These guidelines help to address the general matter of who is at high risk for fracture. Patients who have already sustained an osteoporotic fracture are among the highest risk group because the likelihood of sustaining another fracture is very high [12]. In many countries, in fact, a previous osteoporotic fracture is a requirement for coverage with teriparatide. However, the T-score itself, even without an osteoporotic fracture, can confer high risk, especially if the T-score is very low (ie, < -3). Patient age is also important because it confers greater risk for any given T-score. A 75-year-old woman with a T-score of -2.5 is at greater risk for a fracture than is a 55-year-old woman with the same T-score. Other potential candidates for teriparatide are patients who cannot tolerate bisphosphonates. In addition, patients who fracture while on antiresorptive therapy could be considered, even though one could argue that bisphosphonate therapy prevented a more severe fracture or even multiple fractures. However, a fracture on antiresorptive therapy is an operational criterion for unsuccessful therapy, and thus, consideration for teriparatide therapy. In most countries, teriparatide is approved for a limited period of time (18–24 months).

Teriparatide as single therapy in postmenopausal osteoporosis

In the randomized, double-blind, pivotal clinical trial by Neer et al. [13], women with severe osteoporosis were treated with daily subcutaneous injections of placebo, or 20 or 40 μg of teriparatide. The average number of fragility fractures per patient was more than two, clearly defining this group as high risk. Over a follow-up period of 21 months, BMD increased by an average of 10% to 14%. Total hip BMD also improved, but more slowly and to a smaller extent (approximately 3%) in comparison with the lumbar spine. In the patients who received 20 μg of teriparatide, BMD did not change at the distal radius. The most important findings of this trial were significant reductions in new vertebral and nonvertebral fractures. This drug also is associated with dramatic improvements in microarchitectural features of bone. By post-hoc analysis, the reduction in fracture incidence due to teriparatide was not related to the number, severity, or site of previous fractures [14]. Further post-hoc analysis of this cohort demonstrated that the fracture risk reduction was largely independent of age and initial BMD [15]. In an observational cohort from this trial, fracture reduction was sustained for up to 30 months after teriparatide discontinuation, although many individuals in the original and treatment groups received bisphosphonate therapy during this follow-up period [16].

PTH(1-84) in postmenopausal osteoporosis

PTH(1-84), registered in Europe, has been studied less intensively than teriparatide. In a preliminary clinical trial, preparatory to the definitive clinical trial, patients were administered placebo or one of three doses of PTH(1-84): 50, 75, or 100 μg for 12 months [17]. There were time- and dose-related increases in lumbar spine BMD. Similar to the teriparatide studies, bone turnover markers

rose quickly. Histomorphometric analysis of bone biopsy specimens confirmed an anabolic response to PTH(1-84), with an increase in bone formation and improvements in cancellous architecture [18]. In contrast with the study by Neer et al. [13], in which the average number of fragility fractures per study subject was more than two, the incidence of baseline fragility fractures in the phase III PTH(1-84) study was only 19%. Nevertheless, a reduction in new vertebral fracture incidence was seen with PTH(1-84) in women both with and without prior vertebral fractures in the phase III trial that followed the dosing study [19••]. A reduction in nonvertebral fractures was not demonstrated. More hypercalcemia was seen in the PTH(1-84) trial than in the teriparatide trial, but inclusion criteria, which allowed enrollment of patients with hypercalcemia and hypercalciuria in the PTH(1-84) trial, might have led, at least in part, to the greater incidence of hypercalcemia [19••,20].

Teriparatide in men with osteoporosis

In the first randomized, double-blinded controlled trial of teriparatide in men, Kurland et al. [21] studied 23 men administered 400 U/day of teriparatide (equivalent to 25 μg/day) or placebo for 18 months. The men who received teriparatide demonstrated a 13.5% increase in lumbar spine bone density. Hip BMD increased significantly but more slowly and to a smaller extent in comparison with the lumbar spine. Cortical bone density at the distal radius did not change as compared with placebo. Bone turnover markers rose quickly and substantially in the men treated with teriparatide, with bone formation markers increasing and peaking earlier than bone resorption markers. The initial increase in bone formation was related, in part, to the baseline level of bone turnover and predicted by the short-term increase in osteocalcin, a bone formation marker. Orwoll et al. [22] performed a larger trial of 437 men that was the counterpart of the pivotal trial by Neer et al. [13] in postmenopausal women and followed an essentially identical protocol. BMD increased significantly in the 20-μg treatment group by 5.9% at the lumbar spine and by 1.5% at the femoral neck. These increases were independent of gonadal status, and thus the drug was also effective in hypogonadal men. Although fractures could not be assessed during the short 11-month trial, they were assessed in a follow-up observational period of 30 months. A total of 279 men from the original cohort had lateral thoracic and lumbar spine radiography 18 months after treatment was stopped. In the combined teriparatide treatment groups (20 and 40 μg), the risk of vertebral fracture was reduced by 51% ($P = 0.07$). Significant reductions were seen in the combined group compared with placebo when only moderate or severe fractures were considered (6.8% vs 1.1%; $P < 0.02$) [23]. As in the observational follow-up period in postmenopausal women, a substantial number of male study subjects in all groups (25% to 30%) reported use of antiresorptive therapy during the follow-up period. Men treated with placebo used antiresorptive therapy to a greater extent than those who were treated with either dose of teriparatide (36% vs 25%).

Sequential and Combination Therapy with Teriparatide and an Antiresorptive Agent

Previous use of an antiresorptive

About 50% of patients who receive teriparatide have previously been treated with bisphosphonates or other antiresorptives. In Europe, this figure approaches 100%. Cosman et al. [24] used teriparatide to treat postmenopausal women who were previously administered estrogen for at least 1 year. Increases in vertebral BMD began with no delay and continued in a linear fashion during the entire 3-year study. Ettinger et al. [25] studied the influence of raloxifene or alendronate before treatment with teriparatide. Fifty-nine postmenopausal women with T-scores of -2 or less had been treated for an average of 28 months with raloxifene or alendronate. In most respects, patients were well matched in terms of age, body mass index, and T-scores. Raloxifene did not impede the ability of teriparatide to increase BMD rapidly and linearly. In contrast, alendronate was associated with a 6-month delay before BMD in the lumbar spine began to increase. After 18 months, lumbar spine BMD increased by 10.2% in the prior raloxifene–treated group as compared with only 4.1% in the prior alendronate–treated patients ($P < 0.05$). The alendronate-treated group showed an initial decrease in hip BMD at 6 months, but at 18 months, mean total hip BMD was not different from baseline. During teriparatide treatment, bone markers in prior alendronate–treated patients increased later and peaked at levels about 1/3 lower than in prior raloxifene–treated patients.

These results imply that the potency of the antiresorptive to control bone turnover can determine the early response to teriparatide. Cosman et al. [26••] have helped to refine this point in a study of teriparatide in postmenopausal women who also had previously received alendronate for the same period of time. In contrast with the study by Ettinger et al. [25], their patients responded to teriparatide with rapid increases in BMD. However, baseline bone turnover markers were markedly different between the two studies before the initiation of teriparatide therapy, which may account for these differences. In the study by Ettinger et al. [25], bone turnover markers were markedly suppressed. In comparison, in the study by Cosman et al. [26••], bone turnover markers were less suppressed and closer to the range found in patients after alendronate therapy. Therefore, it is distinctly possible that it is not so much the specific antiresorptive used before teriparatide that dictates the subsequent densitometric response to teriparatide but rather the extent to which bone turnover is reduced. To support this idea, the response to teriparatide has been shown to be a function of the level of baseline bone turnover in patients not previ-

ously treated with any therapy for osteoporosis: the higher the level of turnover, the more robust the densitometric response to teriparatide [21].

The data of Cosman et al. [26••] and Ettinger et al. [25] have led to the hypothesis that bisphosphonates will have effects on subsequent PTH responsiveness as a function of the extent to which bone turnover is reduced by them. The hypothesis led to a clinical trial in which previous use of risedronate was compared with previous use of alendronate with regard to subsequent responsiveness to teriparatide. Approximately 150 patients who had received 2, 3, or more years of either bisphosphonate were switched to teriparatide (20 μg daily) for 1 year. The primary endpoint was change in P1NP, a sensitive, circulating bone formation marker, after 3 months. Other bone markers, such as bone-specific alkaline phosphatase, osteocalcin, serum CTX, and urinary NTX, were measured. Densitometric endpoints included lumbar and hip bone density by dual-energy x-ray absorptiometry (DXA) and by quantitative CT (QCT). The data have been presented in preliminary form and are summarized here [27,28]. Independent of years of prior bisphosphonate therapy, patients who received alendronate had significantly lower bone turnover markers than did those who received risedronate before teriparatide use, as expected. The change in P1NP after 3 months of teriparatide was greater in patients previously treated with risedronate, an observation that was also made for all other bone turnover markers. The change in BMD measured by DXA or by QCT at 12 months was significantly greater in previous risedronate users than in previous alendronate users. Although the results of this study suggest that baseline bone turnover markers might help to explain the major differences between these two bisphosphonates, vis-à-vis on subsequent teriparatide responsiveness, other explanations are possible. It also remains to be seen whether the previous use of risedronate permitted a greater anabolic window with teriparatide than with alendronate.

Concurrent use of anabolic and antiresorptive therapy

It is attractive to consider simultaneous combination therapy with an antiresorptive and PTH as potentially more beneficial than monotherapy with either class of therapeutic, given that their mechanisms of action are quite different from each other. If bone resorption is being inhibited (antiresorptive) while bone formation is being stimulated (anabolic), combination therapy might give better results than with either agent alone. Despite the intuitive appeal of this reasoning, important data to the contrary have been provided by Black et al. [29] and by Finkelstein et al. [30]. These two groups independently completed trials using a form of PTH alone, alendronate alone, or the combination of a PTH form and alendronate. Black et al. [29] studied postmenopausal women administered 100 μg of PTH(1-84). The study by Finkelstein et al. [30] involved men treated with 40 μg of teriparatide. In both studies, DXA and QCT were used to measure areal or volumetric BMD, respectively. With either measurement, monotherapy with PTH exceeded densitometric gains with combination therapy or alendronate alone at the lumbar spine. In fact, measurement of trabecular bone by QCT showed that combination therapy was associated with substantially smaller increases in BMD than monotherapy with PTH. Bone turnover markers followed the expected course for anabolic (increases) or antiresorptive (decreases) therapy alone. However, for combination therapy, bone markers followed the course of alendronate, not PTH therapy, with reductions in bone formation and bone resorption markers. This suggests that the impaired response to combination therapy, in comparison with PTH alone, might be due to the dominating effects of the antiresorptive agent on bone dynamics when both drugs are used together.

The results of these studies led to the concept that an antiresorptive agent that did not impair the anabolic actions of teriparatide while mitigating its effects on bone resorption might in fact be beneficial. Deal et al. [31••] addressed this point by studying the effects of raloxifene as the antiresorptive agent in combination with teriparatide. As hypothesized, in a 6-month proof-of-concept clinical trial, they showed that the combination of teriparatide and raloxifene may have more beneficial effects than monotherapy with teriparatide in postmenopausal osteoporosis. Raloxifene did not impair the actions of teriparatide to stimulate bone formation (in contrast with the study by Black et al. [29], in which alendronate impaired teriparatide's anabolic actions). Bone formation markers increased to the same extent in the teriparatide-only group and in the teriparatide and raloxifene groups. In contrast, when raloxifene was present with teriparatide, bone resorption markers were significantly lower than in the teriparatide-only group. The change in total hip BMD was significantly greater in patients treated with both teriparatide and raloxifene. Raloxifene, a less potent antiresorptive than alendronate, appears to allow teriparatide to stimulate bone formation, unimpeded, but impairs the ability of teriparatide to stimulate bone resorption. Thus, these actions may expand the anabolic window over that which is seen with teriparatide alone.

Yet another approach has been taken to enhance the anabolic window. Cosman et al. [26••] treated a group of women who had previously been treated with alendronate with teriparatide administered as daily therapy or cyclically every 3 months. Alendronate was continued throughout the entire study. The use of teriparatide daily or cyclically was associated with linear increases in BMD, as noted earlier, without any delay and to the same extent. However, the changes in bone turnover markers in the cyclical group were noteworthy. With every 3-month "pulse" of teriparatide, the bone formation marker, osteocalcin, was stimulated to the same extent. However, the bone resorption marker, N-telopeptide, was not able to

match the progressive increases in bone resorption seen in the arm that received teriparatide on a daily basis. With continued and similar stimulation of the anabolic arm of the anabolic window and progressive dampening of the resorptive arm of the anabolic window, with cyclical teriparatide exposure, one can see how in this paradigm of half-dose teriparatide the same increase in BMD was seen as with full dosing. Thus, the anabolic window could be regarded as having been expanded in this model as well.

Consequences of discontinuing anabolic therapy with PTH

Teriparatide is approved in most countries for a treatment period of 18 to 24 months. There are obvious concerns regarding the consequences of discontinuing therapy after this relatively short period of time. Some a priori concerns relate to the fact that new bone matrix is not fully mineralized after PTH therapy. Therefore, this new bone matrix could be at risk for resorption if a period of consolidation with an antiresorptive is not used [32].

Published data addressing this concern were initially based on observational trials. These studies, using either bisphosphonate [16,33,34] or estrogen [35,36] therapy after PTH, suggested that antiresorptive treatment may be necessary to maintain densitometric gains achieved during PTH administration. With a stronger experimental design, additional work by Black et al. [37••] has provided prospective data in a rigorously controlled, blinded fashion to address this issue. Postmenopausal women who had received PTH(1-84) for 12 months were randomly assigned to an additional 12 months of therapy with 10 mg of alendronate daily or placebo. There was a further 4.9% gain in lumbar spine BMD in patients who received alendronate, whereas those who received placebo experienced a substantial decline. By QCT analysis, the net increase in lumbar spine BMD over 24 months among those treated with alendronate after PTH(1-84) was 30%. In those who received placebo after PTH(1-84), the net change in bone density was only 13%. There were similar dramatic differences in hip BMD when those who followed PTH with alendronate were compared with those who were treated with placebo (13% vs 5%). The results of this study establish the importance of following PTH or teriparatide therapy with an antiresorptive.

Fracture efficacy was reported in the 30-month observational cohort [16] following the trial by Neer et al. [13]. Patients were given the option of switching to a bisphosphonate or not taking any further medications following teriparatide. Most patients (60%) were treated with antiresorptive therapy after PTH discontinuation. Gains in bone density were maintained in those who chose to begin antiresorptive therapy immediately after teriparatide. Reductions in BMD were progressive throughout the 30-month observational period in patients who elected not to follow teriparatide with any therapy. In a group that did not begin antiresorptive therapy until 6 months after teriparatide discontinuation, major reductions in BMD were seen during these first 6 months, but no further reductions were observed after antiresorptive initiation [33]. Despite these densitometric data, the effect of previous therapy with teriparatide and/or subsequent therapy with a bisphosphonate on fracture prevention persisted for as long as 31 months after teriparatide discontinuation. Nonvertebral fragility fractures were reported by proportionately fewer women previously treated with PTH (with or without a bisphosphonate), compared with those treated with placebo (with or without a bisphosphonate; $P < 0.03$). In a logistic regression model, it was concluded that bisphosphonate use for 12 months or longer added little to overall risk reduction for new vertebral fractures in this post-treatment period. However, the data were not separately analyzed into those who did or did not follow teriparatide treatment with an antiresorptive. Also, these findings come from an observational study in which participants self-selected for the use of antiresorptive therapy after PTH treatment, making the results even more difficult to interpret. One might anticipate a residual but transient protection against fracture after PTH treatment without follow-up antiresorptive therapy, which could wane over time. Additional studies are needed to address fracture outcomes specifically. However, the importance of following PTH or teriparatide therapy with an antiresorptive to maintain increases in bone mass is now clear.

Safety of PTH

Overall, PTH is well tolerated. In the teriparatide trials, hypercalcemia occurred in a very small percentage of patients. The recent postmarketing experience suggests that the incidence of verified hypercalcemia is even lower than initially reported [38]. Hypercalcemia occurred to a substantially greater extent with use of PTH(1-84) [19••]. The greater incidence of hypercalcemia may partly relate to the inclusion criteria in which patients in the PTH(1-84) group could be enrolled, even if their serum calcium was as much as 0.5 mg/dL above the upper limit of normal [19••]. Hypercalcemia is generally corrected by reducing the amount of supplemental calcium and vitamin D.

Osteosarcoma has been seen in rats that have been given very high doses of teriparatide or PTH(1-84) for prolonged periods of time [39]. It is unlikely that this animal toxicity is related to human skeletal physiology [40,41••], but in the United States, a "black box" warning is included in the labeling instructions. Recently, it was reported that a woman developed an unclear soft tissue malignancy that was later reported pathologically as an osteosarcoma [42]. If this was indeed an osteosarcoma, it is the only known case among more than 400,000 patients who have been treated with teriparatide. This incidence is consistent with the epidemiologic expectation of osteosarcoma in the general adult population, which is one per 250,000. Therefore, the report of a single case after so

many exposures should not change one's thinking relative to the risk of this rat toxicity occurring in humans.

Future Perspectives

In the future, PTH may be modified for easier and more targeted delivery. For example, a dermal preparation of PTH is under investigation [43]. PTH-related protein (PTHrP) has also been studied as an anabolic skeletal agent. In a small cohort of postmenopausal women, subcutaneous administration of PTHrP resulted in a 4.7% increase in lumbar spine density after only 3 months of treatment [44]. Less frequent administration of PTH, such as once weekly, might also be an effective treatment option, although the results thus far are disappointing [45]. However, a fusion protein linked to an Fc fragment was shown to have prolonged actions as an anabolic agent in rats when administered twice weekly [46]. Cyclic use of teriparatide against a backdrop of alendronate has already been covered [26••]. Cosman et al. [47] have shown that during long-term alendronate therapy, a rechallenge with PTH after 12 months off PTH increases bone formation, bone resorption, and BMD to a similar extent as during the first course of PTH administration. These data suggest that a future paradigm might be a second course of PTH administered 12 months after a first course of therapy in patients who remain at high fracture risk. Apart from forms and ways to administer exogenous PTH, Gowen et al. [48] described an oral calcilytic molecule that antagonizes the parathyroid cell calcium receptor, thus stimulating the endogenous release of PTH. This approach could represent a novel endogenous delivery system for intermittent PTH administration [49].

Conclusions

Although antiresorptives remain the mainstay of osteoporosis treatment, the advent of anabolic skeletal agents is changing our approach to therapy. PTH has clearly emerged as the most promising current anabolic treatment. For the first time, a drug is available that improves bone density and features of bone turnover, reduces fracture incidence, and also significantly improves microarchitectural and geometric properties of bone. These changes in bone quality induced by teriparatide are attractive considering the goal of therapy for osteoporosis, namely to improve the basic underlying abnormalities that give rise to skeletal fragility. Recent studies have given insight on the optimal use of this agent, including ways in which simultaneous or sequential therapy with antiresorptives can be used to maximal advantage.

Disclosure

Dr. Bilezikian has been a consultant for Eli Lilly, NPS Pharmaceuticals, Merck, Novartis, and the Alliance for Better Bone Health.

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