The Waning of Teriparatide Effect on Bone Formation Markers in Postmenopausal Osteoporosis Is Associated with Increasing Serum Levels of DKK1

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Context: The effect of teriparatide (TPD) on bone turnover is initially exuberant but then diminishes. TPD is thought to stimulate bone formation by down-regulating the expression of specific Wnt antagonists, such as of sclerostin and Dickkopf-1 (DKK1).

Objective: Our objective was to determine whether long-term treatment with TPD is associated with increasing serum levels of either sclerostin or DKK1.

Design and Setting: Ancillary observation was made of patients participating in a randomized clinical trial.

Patients, Intervention, and Outcomes: Fifty-five women with postmenopausal osteoporosis were randomly allocated to treatment for 18 months with either TPD 20 μg daily or placebo.

Results: In the TPD group, both N-propeptide of type I collagen and C-terminal telopeptide of type I collagen rose significantly by 108 and 175% within the first 6 months. At month 18, the mean values decreased significantly compared with month 12 (-10 and -12%, respectively), but they were still significantly higher than baseline ($+84$ and 152%, respectively). Sclerostin remained stable over the entire study period in both groups. DKK1 did not change during the first 6 month of treatment, but only in the active group, it rose significantly at month 12 (median change $+26.9$%) and remained elevated at month 18 ($+29.7$%), at the time when the pharmacological effect of treatment with TPD appeared to be declining.

Conclusion: Long-term (>12 months) treatment with TPD is associated with an increase in serum levels of DKK1 that might be associated with the appearance of declining effect on bone formation markers. **(*J Clin Endocrinol Metab* 96: 1555–1559, 2011)**

The canonical Wnt signaling pathway regulates osteoblast differentiation and bone formation (1) by activating β-catenin. Activating mutations of Wnt coreceptors results in increased bone mass, whereas inhibition of this pathway leads to reduced bone mass (2–5).

Specific Wnt antagonists such as sclerostin and Dickkopf-1 (DKK1) can block Wnt signaling and actions by binding to Wnt, thus preventing interactions with its receptors and coreceptors (6–11).

Sclerostin is expressed exclusively by osteocytes. DKK1 expression is widespread in embryonic mice, whereas in adults, it is almost exclusively confined to osteoblasts and maturing osteocytes (12). Whereas reduced expression of DKK1 in mice results in a high bone mass phenotype, increased expression in transgenic mice leads to osteopenia (12, 13).

In some pathological conditions, DKK1 is also expressed by other cells. In patients with multiple myeloma, DKK1 is expressed in plasma cells, and its serum level is positively correlated with the presence of bone lesions (14, 15). In addition, in myeloma patients responding to treatment, DKK1 levels decrease (16).

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2010-2552 Received November 2, 2010. Accepted February 11, 2011.
First Published Online March 2, 2011

Abbreviations: BMD, Bone mineral density; CTX, C-terminal telopeptide of type I collagen; CV, coefficient of variation; DKK1, Dickkopf-1; P1NP, N-propeptide of type I collagen.

DKK1 was recently recognized as a key player in joint damage of rheumatoid arthritis (17), whereas in ankylosing spondylitis, the bone formation-promoting factors functionally prevail, and this was at least partially attributed to decreased DKK1 (18).

Teriparatide (TPD, recombinant human PTH 1-34), a PTH analog with bone-anabolic actions, has been approved for osteoporosis treatment. Its daily administration at a low dose stimulates bone formation before a subsequent stimulation of the processes associated with bone resorption. The window between these opposing effects of PTH is thought to represent the period when PTH is maximally anabolic for bone (19, 20).

The ideal duration of TPD or PTH therapy remains an open question. At the moment, the recommended duration of treatment with TPD is of only 2 yr because its safety and efficacy have been evaluated over a mean of 22 months in the pivotal clinical trial in patients with severe postmenopausal osteoporosis (21). Data from several reports suggest that the effect of TPD on bone formation markers is exuberant during the first 6–12 months of administration and then begins to wane (22–27), even though a plateau in bone mineral density (BMD) changes cannot be clearly detected. A similar waning of bone formation markers was observed in patients with glucocorticoid-induced osteoporosis treated with TPD (28), but in these patients, BMD continued to increase between 18 and 36 months, possibly because the net balance of bone formation may still be greater than bone resorption (29).

Even though the exact signaling pathway responsible for the anabolic effect of PTH is not known, the Wnt-β-catenin pathway has generated interest due to a number of observations. Expression of the Wnt antagonist sclerostin is down-regulated by PTH (30), whereas suppression of osteocytic Sost and sclerostin appears to be implicated in PTH-induced bone gain (31). In addition, Guo *et al.* (32) have recently observed that PTH rapidly decreases the expression of DKK1 on bone explants. Association of these new findings might suggest that intermittent PTH treatment may be related to or followed by adaptive changes in the Wnt system by regulating bone formation.

The aim of our controlled prospective study was to evaluate the changes in serum bone turnover markers, DKK1, and sclerostin levels during long-term treatment with TPD.

Subjects and Methods

Study population

The study population include 55 women with severe postmenopausal osteoporosis, recruited at our osteoporosis center. Forty-five of these patients participated in multicenter, placebo-controlled international trials on the efficacy of sc TPD 20 μg daily. The remaining 10 patients were randomly assigned to treatment (seven patients) or a tablet of vitamin B1 as a placebo (three patients) with a ratio of 2:1 in an independent study carried out only in our center. All measurements and data were collected before the disclosure of the treatment assignment. When treatment assignment was disclosed, it became evident that 20 patients had received the placebo, and 35 had received TPD injections daily for 18 months. All patients were given calcium (800–1000 mg/d) and vitamin D (800 U/d) supplements.

Blood was collected at baseline and every 6 months thereafter for routine chemical analysis. Serum samples were stored at −50 C until being assayed for N-propeptide of type I collagen (P1NP, a marker of bone formation), C-terminal telopeptide of type I collagen (CTX, a marker of bone resorption), DKK1, and sclerostin in our laboratory.

The two bone turnover markers were measured by automated immunoassay with the ECLIA device from Roche Diagnostics, Monza, Italy. The coefficients of variation (CV) (interassays) in our laboratory were 5 and 8%, respectively. Serum DKK1 and sclerostin were measured by ELISA (Biomedica Medizinprodukte GmbH and Co. KG, Wien, Austria) with a sensitivity of 0.89 and 0.39 pmol/liter and intraassay CV of 7–8 and 5–6%, respectively. The interassays were assessed in four separate occasions in four serum samples, and the CV was 8.2 and 6.9% for DKK1 and sclerostin, respectively.

Median absolute changes from baseline in bone turnover markers within and between the two groups were compared using the Student's *t* test. Medians and interquartile ranges are reported for percent changes that were compared by Mann-

TABLE 1. Demographics and baseline characteristics of randomized patients

Characteristic	Control group (n = 20)	TPD group (n = 35)	*P* value
Age (yr)	64.5 ± 4.1	66.3 ± 6.2	NS
Height (cm)	157.45 ± 4.55	154.80 ± 6.83	NS
Weight (kg)	63.10 ± 9.40	61.54 ± 11.66	NS
Spine BMD (mg/cm^2)	695 ± 43	673 ± 90	NS
Spine BMD T-score (SD)	−3.2 ± 0.4	−3.4 ± 0.8	NS
Hip BMD (mg/cm^2)	696 ± 90	681 ± 124	NS
Hip BMD T-score (SD)	−1.9 ± 0.7	−2.1 ± 0.9	NS
P1NP (ng/ml)	41.27 ± 12.97	40.90 ± 19.72	NS
CTX (μg/liter)	0.52 ± 0.16	0.46 ± 0.22	NS
DKK1 (pmol/liter)	112.08 ± 52.56	106.07 ± 48.87	NS
Sclerostin (pmol/liter)	28.20 ± 14.90	27.14 ± 14.02	NS

NS, Not significant.

TABLE 2. Mean ± SD absolute values for biochemical parameters at all time points of study

Treatment group	Baseline	6 months	12 months	18 months
CTX (μg/liter)				
TPD	0.46 ± 0.22	1.23 ± 0.83[a]	1.28 ± 0.75[a]	1.09 ± 0.63[a,b]
Control	0.52 ± 0.16	0.44 ± 0.24	0.42 ± 0.19	0.41 ± 0.17
P1NP (ng/ml)				
TPD	40.90 ± 19.72	85.15 ± 40.33[a]	85.86 ± 40.36[a]	74.55 ± 35.63[a,b]
Control	41.27 ± 12.97	40.67 ± 13.93	40.98 ± 14.59	40.90 ± 15.02
DKK1 (pmol/liter)				
TPD	106.07 ± 48.87	110.82 ± 55.19	132.43 ± 67.32[a]	135.27 ± 65.89[a]
Control	112.13 ± 52.62	113.03 ± 44.89	101.43 ± 50.53	104.39 ± 46.55
Sclerostin (pmol/liter)				
TPD	27.14 ± 14.02	31.15 ± 16.11	30.35 ± 14.99	28.30 ± 12.25
Control	28.20 ± 14.90	28.96 ± 12.33	29.50 ± 13.47	31.28 ± 16.24

[a] $P < 0.05$ *vs.* baseline.

[b] $P < 0.05$ *vs.* 12 months.

Whitney *U* test. All statistical procedures were carried out using a computer program (SPSS version 13.0; SPSS Inc., Chicago, IL).

The study was approved by the institutional review board of the Medical School of Verona. All the women provided written informed consent for participating in the trial and for all the new measurements presented here.

Results

The main characteristics of the study population are listed in Table 1. The TPD and placebo groups were comparable for anthropometric and biochemical data at baseline. The TPD group was a little older (66 *vs.* 64 yr old) and with lower BMD values.

The mean absolute values for serum bone turnover markers, DKK1, and sclerostin at all time points are listed in Table 2. The percent changes were not normally distributed, and therefore, they are shown in Fig. 1 as median and 25 or 75% confidence interval. As expected, in TPD-treated patients, and not in those on placebo, both P1NP and serum CTX rose significantly by 112 and 170% within the first 6 months, respectively. At month 18, the mean values had decreased significantly with respect to month 12, but they were still significantly higher than baseline values (Fig. 1). Serum sclerostin remained stable over the entire study period in both groups. Serum DKK1 did not change during the first 6 month of treatment, but it rose significantly in the active group at months 12 and 18, at the same time when the pharmacological effect of TPD treatment was appeared to be declining (Fig. 1).

Discussion

We found that TPD 20 μg/d was associated with a significant increase of serum DKK1, but not of serum sclerostin after 12–18 months of treatment.

The results of a number of recent *in vitro* studies (33–35) showed that PTH might decrease the local concentrations or synthesis of both DKK1 and sclerostin, suggesting that the bone-anabolic effect of PTH may be related to a modulation of the Wnt signaling pathway, possibly accounting for the anabolic actions of PTH. Thus, the expected results would have been a decrease of DKK1 or sclerostin serum levels. The first serum sample was available only at 6 months, and we cannot exclude that an early transient decrease had taken place within the first months of treatment. In fact, a recent work showed that circulating sclerostin levels are reduced by short-term intermittent PTH therapy in postmenopausal women (36).

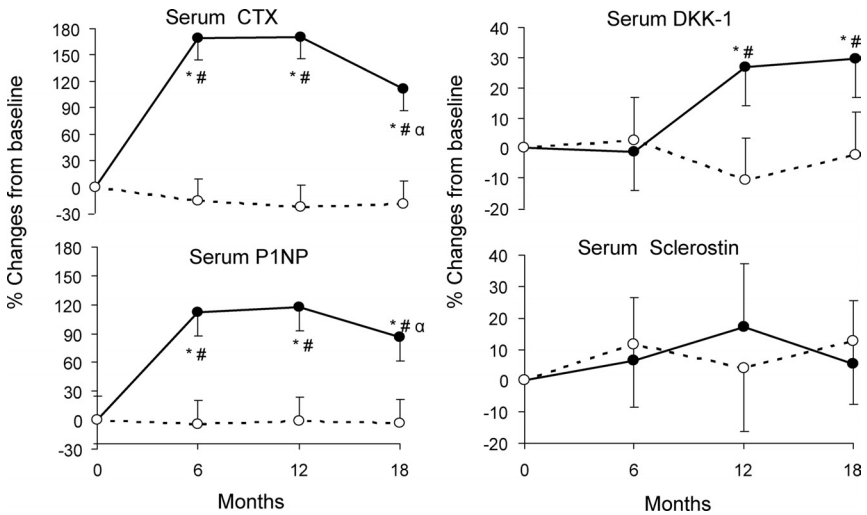

FIG. 1. Percent changes (median and 25th or 75th percentile) from baseline of serum CTX, P1NP, DKK1, and sclerostin in placebo group (*dashed line*) and in TPD group (*solid line*). *, $P < 0.01$ from baseline; #, $P < 0.01$ *vs.* placebo; α, $P < 0.01$ from 12 months.

The increase that we observed in serum DKK1 is also of some interest for its potential clinical implications. The anabolic actions of PTH involve direct effects on osteoblast lineage cells and indirect effects through the regulation of selected skeletal growth factors. IGF-I appears to be the most important of these growth factors, whereas its neutralization prevents the anabolic effect of PTH (37–39). Our observations suggest that chronic stimulation of the osteoblast lineage by PTH might trigger a homeostatic reaction by down-regulating its anabolic effects through an oversecretion of DKK1. This might explain the partial decline in P1NP that we and others (23, 25, 26) had observed during the second year of TPD treatment. The duration of the pivotal clinical trial and also the recommended duration of PTH or TPD treatment was limited to 2 yr. This was based exclusively on concerns for safety due to the occurrence of osteosarcomas in rats after long-term treatment. In some ways, this was a fortunate circumstance because our results suggest that any further extension of the clinical trial would have been associated with the appearance of a progressive declining pharmacological effect on bone formation markers. This does not imply a nullification of the clinical benefits. Indeed, in postmenopausal women with osteoporosis, increased duration of TPD *vs.* placebo treatment was associated with a progressive decrease in the rates of nonvertebral fragility fractures (40).

In conclusion, the results of this study indicate that long-term (>12 months) treatment with TPD is associated with significant increases in serum levels of DKK1 that might be associated with its declining pharmacological efficacy.

Acknowledgments

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Disclosure summary: None of the authors declare conflict of interest.

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