Randomized Trial of Pamidronate in Patients with Thyroid Cancer: Bone Density Is Not Reduced by Suppressive Doses of Thyroxine, But Is Increased by Cyclic Intravenous Pamidronate*

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ABSTRACT

Patients taking suppressive doses of T4 are thought to have accelerated bone loss and increased risk of osteoporosis. We therefore randomize 55 patients taking suppressive doses of T4 to treatment with pamidronate (APD) 30 mg iv every 3 months for 2 yr (APD/T4), or placebo (placebo/T4). Patients had measurements of bone mineral density (BMD) of the spine, hip, radius, and total body every 6 months for 2 yr. There was no significant bone loss at any site in the placebo/T4 group. Ninety-five percent confidence intervals excluded a rate of bone loss >0.89%/yr for the spine and >0.31%/yr at the total hip. When men were excluded from the analysis, there still was no significant bone loss for the placebo/T4 group, and confidence intervals did not change. The APD/T4 group showed increases in spine (4.3%, \( P = 0.0001 \)), total hip (1.4%, \( P < 0.05 \)), and trochanteric (3.0%, \( P = 0.0001 \)) BMDs. In conclusion, premenopausal women and men on suppressive therapy with T3 do not lose bone rapidly, and are not at increased risk of developing osteoporosis. A regimen of 30 mg APD given every 3 months for 2 yr causes significant suppression of bone resorption and increases in BMD, and may be an acceptable alternative treatment for osteoporosis in patients who cannot tolerate oral bisphosphonates. (J Clin Endocrinol Metab 83: 2324–2330, 1998)

HYPERTHYROIDISM impacts bone density adversely (1–3). Hyperthyroid patients have decreased enteral calcium absorption (1), increased bone resorption (4, 5), and accelerated bone loss (1, 6), all reversible with cure of the hyperthyroidism. Although this phenomenon is most obvious in patients with overt hyperthyroidism, some studies suggest that even mild subclinical hyperthyroidism associated with suppressed TSH is associated with increased bone resorption (7) and accelerated bone loss (8, 9). This observation is worrisome, because there are many patients who are treated with doses of T4 sufficient to suppress their TSH to treat thyroid conditions such as euthyroid goiter, thyroid nodules, or thyroid cancer. Patients with these conditions often are young women who are treated for years, raising the concern that therapy for their thyroid conditions may cause osteoporosis.

Because T4 excess accelerates bone loss by increasing bone resorption, we speculated that patients with subclinical hyperthyroidism might respond well to treatment with antiresorptive agents such as bisphosphonates. Studies in rats demonstrate that bisphosphonates decrease the excess bone loss caused by hyperthyroidism (10–13). Furthermore, short-term studies from our laboratory suggest that pamidronate (APD) prevents T3-induced bone resorption in humans (14). We therefore undertook a randomized, double-blind, placebo-controlled trial assigning patients on suppressive doses of T4 to concomitant treatment with either APD or placebo. Although APD had the expected beneficial effects on bone density, we found that patients on suppressive doses of T4 did not lose bone mineral density (BMD) faster than controls.

Subjects and Methods

Subjects

Charts of >300 patients with differentiated thyroid cancer from the practices of cooperating endocrinologists from the greater Boston area were reviewed. All patients received a letter from their endocrinologist.
encouraging them to consider participation in the study. All subjects were then contacted by phone by the principal investigator, and 55 patients taking suppressive doses of T4 agreed to participate in the study. The degree of suppression that was targeted depended on the endocrinologist and the patient, but patients were accepted only if chart review indicated that the goal of therapy was to suppress the TSH to below the normal range (<0.5 mIU/L). Subjects were eligible only if they had been on suppressive doses of T4 for at least 6 months. In addition, 29 normal hospital employees who were not taking thyroid hormone and were clinically and chemically euthyroid were recruited as controls. Subjects were excluded if they had a medical condition that might alter bone metabolism, such as Paget’s disease, hyperparathyroidism, hypoparathyroidism, myeloma, bony metastases, renal or hepatic failure, renal tubular acidosis, malabsorption, or Cushings’s syndrome. In addition, men with hypogonadism were excluded. Subjects were screened for these conditions by a history, physical examination, and measurement of serum chemistries and blood counts during a screening visit. Subjects were recruited without regard for racial, social, economic, or other status. This protocol was approved by the Beth Israel Hospital Committee on Clinical Investigations, and written informed consent was obtained in all subjects.

**Protocol**

Subjects were admitted to the Beth Israel Hospital Clinical Research Center (CRC) at study month 0 and a random urine sample was collected. Patients were kept NPO (except for water) from 2000 h until 0600 h. They were instructed to void and then drink 0.5 liter of water. At 0800 h on day 1, a blood sample and a 2-h fasting urine sample were obtained; the urine samples were used to measure biochemical markers of bone resorption, and the blood was used to measure serum chemistries, blood counts, and markers of bone formation. Patients who were unable to stay overnight in the hospital came to the hospital at 0800 h and followed the above-mentioned instructions as outpatients. After blood and urine were collected, subjects filled out questionnaires that allowed us to estimate their weekly exercise in kilocalories [according to the method of Paffenbarger et al. (15)] and their daily calcium intake (16). Subjects then underwent measurement of BMD at the spine, hip, forearm, and total body.

Subjects on suppressive doses of T4 were then randomized in a double-blinded fashion to receive either pamidronate (APD/T4) or placebo (placebo/T4). Subjects treated with APD received 30 mg in 500 ml 5% dextrose as an iv infusion over 4 h, and the placebo group received an identical placebo infusion consisting of 5% dextrose. Intravenous APD was chosen for use in this study because it is a U.S. Food and Drug Administration approved bisphosphonate that is highly effective in suppressing bone resorption related to Paget’s disease (17) and hypercalcemia of malignancy (18). In studies comparing it with etidronate, APD is more effective (19, 20) and is relatively free of the mineralization-inhibiting toxicity reported with etidronate (21).

Repeat admissions for measurement of biochemical indices of bone turnover and serum chemistries and blood counts occurred at 1, 2, 3, and 12 months. Repeat measurements of BMD were obtained at 6, 12, 18, and 24 months. Repeat infusions of APD occurred at months 3, 6, 9, 12, 15, 18, and 21. Repeat measurements of blood counts and chemistry profiles for monitoring for toxicity were done at 3, 6, 9, 12, 18, and 24 months, before to the repeat infusion.

**Measurements**

All assays were performed by a technician who was blinded regarding the subjects’ treatment assignment.

**Urine**

All specimens were frozen at −20 C after collection and were assayed at the end of the study to minimize interassay variability. Peptide bound N-telopeptide cross-links of type I collagen (NTX) in the urine were measured by enzyme-linked immunosorbent assay (ELISA) using a kit from Ostex International (Seattle, WA) by a method previously described in detail (22); using this method the intra-assay coefficient of variation (CV) is 5–19%. Creatinine was measured by standard automated methodology.

**Blood**

Automated blood counts and serum chemistry profiles were performed by Quest Diagnostics (formerly Bioran, of Cambridge, MA) by standard automated technology on blood immediately after collection of the samples. All other serum specimens were frozen at −70 C after collection and assayed at the end of the study to minimize interassay variability. PTH assays were performed with the Allegro immunoradiometric assay kit from Nichols (San Juan Capistrano, CA); the intra- and interassay CVs for this assay are 1.8–3.4% and 5.6–6.1%, respectively. 25-Hydroxyvitamin D was measured by RIA using a kit from INCASTAR (Stillwater, MN); the intra- and interassay CVs for this assay are 5.6–6.7% and 13.7–15.9%, respectively. Osteocalcin was measured by immunoradiometric assay (IRMA) using the Immutopics kit from Nichols, which measures both intact and the N-terminal-midfragment; the intra- and interassay CVs for this assay are 3.6–5.3% and 4.4–5.7%, respectively. TSH was measured by the TSH-3 assay, an automated two-site chemiluminescent third-generation assay using the ACS-180 automated chemiluminescent system from Chiron Diagnostics (Walpole, MA); the intra- and interassay CVs for this assay are 3.2–10.7% and 3.8–15.8%, respectively, and the normal range is 3.5–5.5 IU/mL. T4 and TBG were measured by RIA using a kit from Wallac Delfia (Gaithersburg, MD); the intra- and interassay CVs for this assay are both <10%. Free T4 index was calculated with the formula free T4 index = T4/ thyroxine binding globulin × 20, and the normal range in our laboratory was 4–10.

**BMD**

BMD was measured by dual energy x-ray absorptiometry using a QDR-2000 bone densitometer by Hologic (Waltham, MA). BMD was measured at the spine, hip, radius, and total body. The spine was measured in the PA projection, and results are reported for the total spine L1-L4. The hip was measured in the standard projection, and results were reported for femoral neck, trochanter, and total hip; the femoral neck was chosen to represent a site rich in cortical bone, and the trochanter to represent a site relatively rich in trabecular bone. The radius was measured in the standard projection, and results are reported for the ultradistal radius, the junction of the proximal two thirds and the distal one third of the radius (one third radius), and the total radius; the ultradistal radius was chosen as a site fairly rich in trabecular bone, whereas the one third radius was chosen as a site rich in cortical bone. In our laboratory, the CVs for the measurement of PA spine, total hip, and femoral neck BMDs are 1.5%, 1.2%, and 1.9%, respectively (23).

**Statistical analysis**

Results are reported as mean ± SEM. The significance of differences in continuous variables among the three groups was computed using ANOVA and multiple comparison testing if the data were normally distributed, and by Kruskall-Wallis test if the data were not normally distributed. The significance of changes in BMD and bone turnover over time were computed by paired t testing of baseline and subsequent values. In addition, changes in BMD over time for each individual were plotted, and the slopes computed by linear regression. The mean slope for each group was computed, and significance for differences among groups was determined using ANOVA and multiple comparison testing if the data were normally distributed, and by Kruskall-Wallis test if the data was not normally distributed. The results obtained using the mean slopes of the linear regression showed the same differences from baseline and among groups as those obtained using paired t testing, so results of paired t tests are reported. Ninety five percent confidence intervals for rate of bone loss were computed by multiplying the SEM for the rate of bone loss by the t statistic appropriate for the degrees of freedom. The significance of differences in dichotomous variables between groups was determined using the x-square test. All calculations were performed using the SAS statistical program (SAS Institute, Carey, NC).

Analyses were performed according to intention to treat. However, not all subjects adhered perfectly to the protocol, so a modified data set was reanalyzed in the most appropriate manner. As an example, one woman on suppressive doses of T4 decided to switch to replacement doses after 1 yr of the study. In the intention to treat analysis, we...
included all 24 months of BMD data. For the reanalysis on the modified data set, we included only the first 12 months of BMDs, during which time her TSH was suppressed. Results from the intention to treat analysis and those from the reanalysis showed the same differences from baseline and among groups, so results of the intention to treat analysis are reported.

Results

Baseline mean age, height, weight, calcium intake, vitamin D, and PTH levels were similar among the three groups as illustrated in Table 1. Similarly, the ratio of men/women and premenopausal/postmenopausal women was comparable in all three groups. Baseline serum osteocalcin and random urinary NTX/Cr were similar across the groups. Mean baseline BMD was slightly lower in the APD/T₄ group compared with the other two groups, but this achieved statistical significance only at the spine.

In the APD/T₄ group, 1 man dropped out of the study after month 12 because he moved away from the area, and 2 women remained in the study but discontinued the APD infusions (not related to adverse effects). In the placebo/T₄ group, 1 woman dropped out of the study after month 18 because she moved away from the area, and 1 woman decided to switch to replacement doses of T₄ after 12 months of study. Of the 28 subjects in the control group, 3 women remained in the study but discontinued the APD at month 12 because he moved away from the area, and 2 women on suppressive doses of T₄ therapy in the APD/T₄ and the placebo/T₄ groups compared with the other two groups, but this achieved statistical significance only at the spine.

Compliance with T₄ therapy in the APD/T₄ and the placebo/T₄ was good, as verified by serial measurements of TSH. An average of five measurements of TSH per individual were performed over the 2 yr of the study; 88% of the measurements were suppressed to below 0.5 mU/L, and 69% were below 0.1 mU/L. All TSH measurements in controls were in the normal range. Mean serum free T₄ index was significantly higher in the APD/T₄ and the placebo/T₄ groups than in controls (P < 0.01, Table 1). Ninety seven percent of the free T₄ index measurements in the APD/T₄ and the placebo/T₄ groups were in the normal range (4–10), while the remaining values were slightly elevated (in the 10–12 range). All free T₄ index values in controls were in the normal range. Mean T₄ dose for patients with thyroid cancer was 188 ± 6.5 μg/day or 2.47 ± 0.7 μg/kg per day.

Changes in BMD with suppressive doses of T₄

During the 2-yr course of the study, there was no significant bone loss for the placebo/T₄ group or for controls. Mean percent change of BMD for the placebo/T₄ group was -0.1%/yr (P = not significant) at the spine, and was positive (P = NS) for the other sites (Figs. 1 and 2). In addition, there was no significant difference in mean percent change of BMD at any site over the 24 months when the placebo/T₄ group was compared with controls.

To determine the confidence with which significant bone loss can be excluded among patients on suppressive doses of T₄, confidence intervals were computed for the rate of bone loss in the placebo/T₄ group (Table 2). Ninety five percent confidence intervals exclude a >0.89%/yr bone loss at the spine and a >0.31%/yr bone loss at the hip in patients on suppressive doses of T₄.

To determine whether the anticipated deleterious effects of suppressive T₄ on bone are limited to women, the data were analyzed separately for women. Mean percent change of BMD over 24 months for the women in the placebo/T₄ group was -0.2%/yr at the spine and -0.07%/yr for the ultradistal radius (P = not significant for both), and was positive (P = NS) for the other sites. Ninety five percent confidence intervals for our data exclude a >0.87%/yr bone loss at the spine and a >0.41%/yr bone loss at the hip in women on suppressive doses of T₄ (Table 2).

Changes in APD/T₄ group

After treatment with APD, 2-h fasting urinary excretion of NTX/Cr decreased significantly (Fig. 3). At 1 month, NTX/Cr fell 58% compared with baseline (P vs. baseline <0.0001), and by month 3 it was still 25% below baseline (P vs. baseline <0.01). Repeated doses of APD did not cause progressive suppression of NTX/Cr; urinary NTX/Cr at month 12 was 32% below baseline and not significantly different from the value at month 3.

Mean BMD of the hip and spine increased significantly in the group treated with APD/T₄, whereas BMD of the radius did not (Figs. 1 and 2). Over the 2 yr of the study, BMD of the spine increased by 4.3% (P = 0.0001). Similarly, BMD of the total hip and trochanter increased by 1.4% (P < 0.05) and 3.0% (P = 0.0001), respectively, although BMD of the femoral neck did not rise significantly. The increases in mean BMD in the spine and trochanter of the APD/T₄ group were significantly (P < 0.01) different from the minor changes in BMD in the other groups.

### TABLE 1. Mean ± SEM for baseline data on patient characteristics and bone density

<table>
<thead>
<tr>
<th>Parameter</th>
<th>APD/T₄</th>
<th>T₄</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>43 ± 2</td>
<td>45 ± 2</td>
<td>44 ± 2</td>
</tr>
<tr>
<td>Male/female</td>
<td>10/18</td>
<td>8/19</td>
<td>9/20</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78.1 ± 3.1</td>
<td>78.2 ± 3.9</td>
<td>76.8 ± 3.1</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169.0 ± 1.8</td>
<td>167.3 ± 1.7</td>
<td>168.6 ± 1.4</td>
</tr>
<tr>
<td>Calcium intake (mg/day)</td>
<td>898 ± 83</td>
<td>964 ± 109</td>
<td>1089 ± 139</td>
</tr>
<tr>
<td>Exercise (kcal/week)</td>
<td>2874 ± 498</td>
<td>3366 ± 545</td>
<td>3760 ± 673</td>
</tr>
<tr>
<td>25-OH vitamin D (ng/mL)</td>
<td>23.1 ± 2.6</td>
<td>23.2 ± 2.0</td>
<td>22.1 ± 1.8</td>
</tr>
<tr>
<td>PTH (ng/L)</td>
<td>39.1 ± 2.5</td>
<td>38.2 ± 2.7</td>
<td>39.6 ± 3.0</td>
</tr>
<tr>
<td>Osteocalcin (mg/L)</td>
<td>6.1 ± 0.4</td>
<td>5.6 ± 0.4</td>
<td>5.6 ± 0.3</td>
</tr>
<tr>
<td>NTX/Cr (nm BCE/mM)</td>
<td>27.7 ± 2.8</td>
<td>23.4 ± 2.8</td>
<td>28.4 ± 2.3</td>
</tr>
<tr>
<td>Free T₄ index</td>
<td>7.38 ± 0.30a</td>
<td>7.17 ± 0.33a</td>
<td>5.07 ± 0.15</td>
</tr>
</tbody>
</table>

a P < 0.05 vs. controls.
Adverse effects in APD/T₄ group

Subjects treated with APD or placebo were called several days after each infusion and questioned about potential side effects, such as fever and myalgias that have been reported after treatment with APD. Fever and myalgias were significantly more common after infusion of APD than after infusion of placebo; subjects complained of fever and myalgias after 12% of the APD infusions, and after 4.0% of the placebo infusions ($P = 0.001$ for the difference between APD and placebo). However, the incidence of fever and myalgias diminished significantly with subsequent infusions of APD; it was 45% after the first infusion, 21% after the second infusion, and 4% for the third through eighth infusions. The incidence of febrile side effects was significantly higher in the APD/T₄ group than in placebo/T₄ group only after the first and second infusions.
TABLE 2. Ninety five percent confidence intervals for annual percent change in bone density in patients taking suppressive doses of T4 but not APD

<table>
<thead>
<tr>
<th>Site</th>
<th>All patients</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total spine</td>
<td>−0.89%−+0.62%</td>
<td>−0.87%−+0.52%</td>
</tr>
<tr>
<td>Total hip</td>
<td>−0.31%−+0.62%</td>
<td>−0.41%−+0.86%</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>−0.48%−+0.97%</td>
<td>−0.67%−+1.27%</td>
</tr>
<tr>
<td>Trochanter</td>
<td>−0.39%−+0.74%</td>
<td>−0.57%−+0.90%</td>
</tr>
<tr>
<td>Total body</td>
<td>+0.17%−+0.02%</td>
<td>−0.04%−+1.18%</td>
</tr>
<tr>
<td>Total radius</td>
<td>−0.23%−+0.58%</td>
<td>−0.53%−+0.55%</td>
</tr>
<tr>
<td>Ultradistal radius</td>
<td>−0.37%−+0.55%</td>
<td>−0.63%−+0.49%</td>
</tr>
<tr>
<td>Distal 1⁄5 of radius</td>
<td>+0.21%−+0.28%</td>
<td>0%−+1.28%</td>
</tr>
</tbody>
</table>

Subjects complained of no other side effects that were judged to be related to APD.

Patients treated with APD were divided into those who had an initial febrile reaction to APD (n = 13) and those who did not (n = 15). Patients with febrile reactions had a trend for greater suppression of bone resorption with greater decreases in NTX/Cr and a greater increase in spine BMD at 2 yr. Mean suppression of urinary NTX at month 1 was 65% in the group that developed an initial febrile reaction and 52% in the group that did not. Furthermore, mean increase in spine BMD after 2 yr was 4.6% for the group that developed fever and 3.8% in the group that did not. Although there was a trend for APD to have a greater effect on NTX/Cr and BMD in subjects who became febrile after the first dose, there were no significant differences in ΔNTX/Cr or ΔBMD at any site between those with and those without febrile reactions.

Subjects treated with APD had no evidence of toxicity based on serial measurements of serum chemistries and blood counts, although some minor changes were noted in serum PTH, phosphate, and alkaline phosphatase. Although there was no change in serum calcium over the course of the study, at month 1 there was a 35% increase (P < 0.05) in serum PTH that was not apparent at months 2, 3, 12, or 24, so the rise in serum PTH was mild and transient. This rise in serum PTH was not accompanied by a decrease in serum phosphate. In addition, mean serum phosphate fell by 6.7% at month 3 (but not before, P < 0.05), and 9.6% at month 12 in the group treated with APD (P < 0.01), although at month 24 this decrease was no longer apparent. The decrease in serum phosphate was not accompanied by decreases in serum calcium or increases in serum PTH. Furthermore, no patient treated with APD had a serum phosphate lower than 2.1 mg/dL (normal range, 2.5–4.5 mg/dL), so there was no clinically significant hypophosphatemia, and even this mild hypophosphatemia was not significantly more common in APD/T4 (5.2%) group than in controls (3.4%). The mean serum alkaline phosphatase decreased by 12.9% by the end of month 12, and by 13.2% by the end of month 24 (P < 0.001). The fall in total alkaline phosphatase is likely caused by a fall in the bony fraction. There was no significant difference in mean values of white blood count, lymphocyte, eosinophil, platelet, hematocrit, or serum serum aspartate aminotransferase or serum alanine aminotransferase between the APD/T4 and placebo/T4 groups over the course of the study.

Discussion

Although the deleterious effects of hyperthyroidism on bone have been appreciated for many years, study of the effect of subclinical hyperthyroidism on the skeleton began approximately 10 yr ago when the sensitive TSH assay came into wide use. Many patients taking T4 who previously were thought to be euthyroid had been found to have a low TSH and subclinical hyperthyroidism. Mean BMD in these patients was 6–12% lower than that of controls (24–27). However, some of these cross-sectional studies were confounded by a distant history of hyperthyroidism in some of the patients. When patients with a history of hyperthyroidism were excluded from analysis, the deleterious effect of T4 suppression was attenuated (26, 27). However, other cross-sectional studies avoided the confounding history of hyperthyroidism by studying only patients who were intentionally treated with suppressive doses of T4 for euthyroid goiter or thyroid cancer; these patients had no history of hyperthyroidism. The early cross-sectional studies of patients with these conditions found that mean BMD in patients treated with suppressive doses of T4 was up to 20% lower than in controls (28–32), with postmenopausal women being affected more than premenopausal women (29, 30, 32). However, some of the more recent cross-sectional studies of patients with thyroid cancer did not find any difference in mean BMD in patients taking suppressive doses of T4 vs. controls (33–40).

Although it was presumed that longitudinal studies of bone loss in patients taking suppressive doses of T4 would help to clarify this issue, results have been mixed. Stall et al. (8) and Kung et al. (41) reported rapid bone loss in postmenopausal women on T4 suppression, whereas others did not (42–44). The only longitudinal series of premenopausal women published to date is that of Pioli et al. (9), who followed BMD in 15 premenopausal women with newly diagnosed thyroid cancer. Although they found no effect of T4 on loss of radius BMD, they found accelerated spinal bone loss of 2.6%/yr in the thyroid cancer patients compared with 0.2%/yr in controls. In the current study, we followed 27 patients with established thyroid cancer, of whom 17 were premenopausal women, for 2 yr. There was no significant bone loss in our thyroid cancer patients. When men were excluded from the analysis, there still was no significant bone loss at any site on our largely premenopausal group. The 95% confidence intervals for rate of bone loss exclude annual bone
loss of >0.89%/yr at the spine and >0.31% at the total hip (Table 2). The discrepancy between our results and those of Pioli is puzzling. One possible explanation is that Pioli’s patients were all newly diagnosed with thyroid cancer, and therefore newly treated with suppressive doses of T4. It is possible that there is a small nonsustained increase in bone loss briefly after initiating suppressive therapy with T4, followed by leveling off of the rate of loss. Furthermore, the initial dose of T4 used in Pioli’s study was 3 μg/kg per day, which was higher than the average dose required in our study (2.47 μg/kg per day). Alternatively, perhaps the fact that our subjects had a fairly high mean calcium intake (Table 1) might account for lack of bone loss (45). In any event, based on our data it is unlikely that men and premenopausal women treated conventionally with suppressive doses of T4 suffer a significant increase in long-term bone loss, but the effect of T4 suppression on postmenopausal women remains unclear.

When we initiated the present study early in 1992, virtually all of the published literature suggested that subclinical hyperthyroidism adversely affected bone. We therefore randomized patients with thyroid cancer to treatment with APD vs. placebo, in an attempt to prevent the anticipated bone loss. Although we did not find bone loss in placebo/T4 group, the APD/T4 group clearly benefited from the APD. BMD of the spine, trochanter, and total hip rose significantly by 4.3%, 3.0%, and 1.4%, respectively. The increase in BMD that we observed, although significant, was slightly less than that reported in previous studies of the effect of APD on BMD (46–49). We speculate that other studies observed greater increases in BMD because they studied postmenopausal women who tend to have high bone turnover (50), whereas we studied mostly premenopausal women, who tend to have low bone turnover. Because the rise in BMD with antiresorptive therapy is usually greater in patients with high bone turnover than in patients with low turnover (51, 52), we had less impressive increases in BMD in our relatively low-turnover group. Perhaps this explanation accounts for the fact that we observed no increase in radius BMD, whereas some (49, 53), but not all (47), other authors have observed increases in radius BMD after bisphosphonate therapy in postmenopausal women with osteoporosis.

The expected changes in bone turnover were observed after therapy with APD. Two-hour fasting urinary NTX/Cr fell by 58% by 1 month after the first dose of APD, and was 25% lower than baseline by month 3. This suggests that the dosing schedule of APD infusion suppressed bone turnover significantly (52). The effects had not totally dissipated by the time the patient received the next infusion 3 months later (Fig. 3), suggesting that this regimen of APD should be effective in treating osteoporosis. However, the best evidence that our regimen of APD every 3 months was effective was the significant rise in BMD on this regimen. This finding is clinically relevant, because bisphosphonate therapy has been shown to improve BMD (54) and reduce fracture risk (55) in women with osteoporosis. Although these studies were done with the oral bisphosphonate alendronate, it is reasonable to assume that an iv regimen of APD that achieves a similar degree of suppression of bone turnover and increases in BMD will result in similar benefits. In patients with osteoporosis who are unable to tolerate oral alendronate or who are unable to comply with the dosing instructions, iv APD every 3 months provides a reasonable and attractive alternative.

We observed some of the minor febrile reactions that have been previously reported with APD (14, 56–59). These reactions were mild and self-limited, and no one discontinued the study because of these side effects. Moreover, we observed that the incidence of the mild febrile side effects diminished greatly after the first infusion, as has been previously reported (17, 49, 60). We did not observe any of the mild decrease in leukocytes and lymphocytes described by others (14, 56, 57, 61), perhaps because this fall occurs within days after the infusion and then promptly resolves (14).

In summary, patients with thyroid cancer on suppressive doses of T4 did not lose bone significantly over 2 yr. These data suggest that men and premenopausal women on suppressive doses of T4 do not lose bone rapidly, and should not have an increased risk of osteoporotic fractures. These data may not apply to postmenopausal women who have higher bone turnover than premenopausal women or men. Finally, the regimen of parenteral APD that we used has beneficial effects on bone resorption and on BMD and could be considered for use in women with osteoporosis who are unable to tolerate oral bisphosphonates.

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