Longitudinal Follow-up Study of Bone Mineral Density in Adult Survivors of Solid Pediatric Cancers

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Abstract

To investigate the hypothesis that abnormal bone mineral density in pediatric solid tumor survivors persists into early adulthood, a follow-up study to our original cross-sectional study was undertaken in two parts. In Part I, the original cohort of 38 patients was updated to include 3 additional patients. The results showed a 34% prevalence of osteopenia and a 12% prevalence of osteoporosis in at least one site.[1] The part II study cohort consisted of 14 of the original 38 patients who returned more than 5 years later for repeat dual energy x-ray absorptiometer (DEXA). Overall, during the 5-year interval, 100% of the part II patients showed a decrease in bone mineral density (BMD) at one or more sites and 28.5% showed decreased total body BMD. Statistically significant ($p<0.05$) overall declines in BMD were seen in the right femoral neck and left distal radius. Young survivors of childhood tumors do not exhibit normal bone mineral density progression and warrant consideration of early preventative intervention.

Key Words: Bone mineral density, lymphoma, Wilm's tumor, sarcoma, DEXA, pediatric tumors, chemotherapy, osteopenia, osteoporosis

INTRODUCTION

Specific subgroups of children who survive treatment for childhood malignancies have been shown to develop relative osteopenia following treatment and are felt to be at risk for developing osteoporosis later in life due to their inability to reach peak bone mass during childhood.[1] In earlier work, our group has shown in a cross-sectional study that approximately 50% of pediatric solid cancer survivors have at least regional low bone mineral density (BMD).[1] Prior to this work, solid tumor survivors had not been known to be among the groups at higher risk for development of low bone density. Subsequent studies have shown pediatric osteosarcoma survivors in particular to be at increased risk for low bone density.[2-4] A rare solid tumor survivor subgroup that appears to be exempt from the risk of developing low bone density is that of pediatric Hodgkin's lymphoma.[5]

The purpose of this study was two-fold. First, the addition of more patients to our original cross-sectional study allowed us to re-examine the prevalence of decreased bone density among solid pediatric cancer survivors with slightly greater statistical power. Second, the longitudinal follow-up study was undertaken to determine whether these survivors of solid malignancies, managed by their local physicians and through continued follow-up in surveillance cancer survivor clinics, would show increasing BMD over their early adult lives, as would be expected to occur among their healthy counterparts, or whether they would fail to progress in developing improved bone density. We hypothesized that their chemotherapy will have rendered them unable to continue to increase their BMD, leaving them at an even greater risk for the subsequent complications of osteopenia or osteoporosis.

METHODS

All research subjects were obtained through the institutional long-term survivor Kids Now Off Therapy (KNOT) clinics. The original cohort included pediatric subjects diagnosed with lymphoma or solid tumors who were younger than age 16 at time of treatment initiation and less than 40 at time of study recruitment. Excluded were subjects treated for acute lymphoblastic leukemia or those with cranial irradiation, total body radiation, or non-autologous bone marrow transplant (all groups already known to be at high risk). Institutional Review Board approval was obtained and all patients provided their informed consent.

The original study methods have been previously described.[1]

Subjects

In Part I of this study, the original data set was reviewed and updated. Since publication of the initial cross-sectional study consisting of 38 subjects, three additional patients had been recruited and data collected as per the original study protocol and using the same GE Lunar DPX-IQ dual energy x-ray absorptiometer (DEXA) located in the Institute for Human Performance. With the data for these three additional patients added, a new contingent of 41 subjects (23 male, 18 female) resulted. The most common diagnoses were lymphoma (19), sarcoma (9), Wilm's tumor (5), and neuroblastoma (4).[Fig. 1] Mean age was 21.7 years (range, 12.6 to 32.4). Mean height was 145.2 cm (range 143.2 to 160.6), mean weight was 68.6 kg (range 43.2-127.8), and mean body mass index (BMI) was 32.0 kg/m^2 (range 24.0-50.0).

Mean age at time of diagnosis was 9.4 ± 5 years (range, 0 to 17.5). All diagnoses occurred between November 1981 and March 1997. Time from diagnosis of underlying cancer to study enrollment averaged 18.1 years (range, 11.1 to 26.5). Thirty-nine of the 41 subjects received chemotherapy for an average duration of 38.8 ±17 weeks (range, 12.9 to 75.2). The remaining 2 patients received only surgery/ radiotherapy. Twelve of the 38 original subjects received methotrexate and eight received prednisone.[1] No additional information regarding the details of radiation could be obtained for the 3 additional subjects, so the data regarding radiotherapy remains the same as previously reported. Briefly, 18 of the 38 original subjects received radiotherapy to one or more fields; seven of these received additional courses of radiation to more than one field during their treatment course.[1] Total radiation doses ranged from 1,050 cGy for Wilms Tumor to 4,494 cGy for hepatoblastoma.[1] Mantle irradiation was the most common therapy (six patients), and the total dose ranged from 2,100 to 4,025 cGy.[1] Two subjects, both with nodular sclerosing Hodgkin's disease, received only radiotherapy without chemotherapy.[1]

Staging of the tumors was done by conventional criteria, and the most common types of tumors diagnosed in this study group were staged as follows. Of the 19 patients with lymphoma, two were stage I, eight were stage II, eight were stage III, and

one was stage IV. Subjects with Wilms Tumor were staged based on the National Wilms Tumor Study Group clinicopathologic staging system: one was stage I, two were stage II, one was stage III, and one was stage V (bilateral). Those with neuroblastoma were staged according to the International Neuroblastoma Staging System: two were stage 3 and two were stage 4S. Bone tumors, including five osteosarcomas and one Ewing sarcoma, were stage IIA or IIB, according to the Musculoskeletal Tumor Society (MSTS). Using the American Joint Committee on Cancer (AJCC) TNM staging system, the five osteosarcomas classify as stage IIA or IIB. Staging of the second Ewing sarcoma in the study population could not be determined. The two rhabdomyosarcomas were determined to be in clinical group 3, one in IIA, one in IIIB, according to the Intergroup Rhabdomyosarcoma Study Group. The only Triton tumor was stage IIB by the MSTS system.

In Part II of this study, all patients from Part I were recruited again for follow-up DEXA analysis a minimum of five years later. Fourteen (5 male, 9 female) patients were seen for follow-up visits. Letters requesting follow-up visits were mailed on two separate occasions. We attempted to reach all 41 patients using their most updated addresses and phone numbers. The patients we failed to contact were no longer residing at their former residence. None of the patients were confirmed to be deceased. Diagnoses included lymphoma (8), Wilm's tumor (2), sarcoma (1), yolk sac carcinoma (1), ovarian germ cell tumor (1), and Triton tumor (1).[Fig. 2] Mean age was 29.4 years (± 4.2 years). Mean height was 146.7 cm (± 8.1 cm), mean weight was 68.1 kg (± 11.5 kg), and mean body mass index (BMI) was 23.7 kg/m^2 (± 3.7 kg/m^2)

Mean age at diagnosis was 11.2 years (± 4.5 years), all of which were diagnosed between March 1987 and January 2001. Mean time from diagnosis of underlying cancer averaged 18.1 years (± 4.4 years). Twelve of the 14 subjects received chemotherapy for an average duration of 36.2 weeks (± 14.9 weeks) weeks. The other two patients were treated with surgery and radiotherapy alone. Six of the 14 subjects received frontline radiotherapy, three of whom received additional radiation later in their treatment. Mantle radiation was the most common field (three subjects). The total radiation dose ranged from 2,100 cGy for Hodgkin's lymphoma to 4,025 cGy, also for Hodgkin's

lymphoma. Only one patient, with nodular sclerosing Hodgkin's disease, underwent radiation therapy without chemotherapy. Eleven patients had surgery in addition to their radiation and/or chemotherapy. At the time of this follow-up study, none of the patients have any evidence of disease.

Staging of the tumors was determined in the same manner as it was for the original paper. One patient with lymphoma was stage I, three were stage II, and four were stage III. Of the two Wilms tumors, one was stage I and one was stage II. The stages of the sarcoma, yolk sac carcinoma, ovarian germ cell tumor, and Triton tumor could not be determined based on the patient's records.

Densitometry Technique

Bone mineral density measurements were made on the aforementioned DXA. The same operator using standard quality assurance checks against a calibration phantom made all measurements.

Definition of Low Bone Mineral Density (BMD)

Subjects were classified as osteopenic or osteoporotic based on their Z-scores, as defined by a simplification of the WHO classification, which is recommended by the International Society for Clinical Densitometry (ISCD). A Z-score of less than or equal to -1.0 but greater than -2.0 was considered "osteopenia" while a score of less than or equal to -2.0 was considered "osteoporosis" in order to remain consistent with the definitions used in our original manuscript.[1]

Metabolic Markers

Bone-specific alkaline phosphatase (BSAP) and N-telopeptides (NTx) were used as serum markers of bone metabolism. . For both the initial study and the follow-up, peripheral blood was collected via venipuncture on the morning of the respective DXA scan. Blood was collected into additive-free Vacutainer tubes (Becton Dickson, Franklin Lakes, NJ). Within 30 minutes of collection, the blood specimens were centrifuged for 10 minutes at 3200xg, serum was collected, aliquoted and stored frozen at -80°C until assay. Serum bone-specific alkaline phosphatase levels were measured by enzyme-linked immunosorbent assay (MicroVue BAP ELISA, Quidel Corp. San Diego, CA) as an indicator of skeletal anabolism. Serum cross-linked N-telopeptides of type I collagen were measured by an enzyme-linked immunoassay (Osteomark NTx EIA,

Inverness Medical Innovations Inc., Princeton, NJ) as an indicator of skeletal catabolism. All serum samples were assayed simultaneously and each aliquot was subject to only one freeze-thaw cycle from collection to assay. Assays were performed without modification of manufacturer's recommended instructions. Serum levels were interpolated to a curve of known standard concentrations, and expressed as units per liter (BAP) or nanomolar concentration (nM, NTx). To facilitate direct comparison between the original study and our current report, serum samples from the original study were re-assayed in parallel with the respective serum sample collected at follow-up.

Statistical Analysis

Data were analyzed using IBM-SPSS Statistics for Windows, Version 19, by our statistician (W.D.G.) Initial data reduction included development of distribution statistics. Comparisons were undertaken using unpaired t-tests with all significance assessments made at a minimum of alpha <0.05 using two-tailed analyses.

Each body region scanned by DXA was analyzed separately. These included total body, lumbar spine, right total hip, right femoral neck, left total hip, left total femoral neck, right ultra distal radius, right 33% radius, left ultra distal radius, and left 33% radius.

RESULTS

Part I. Of the 41 patients in this cohort, 36% (15/41) of them had osteopenia or osteoporosis in at least one site using The World Health Organization's classification criteria. More specifically, 4.9% (2/41) had decreased total body BMD, 9.8% (4/41) had decreased BMD in the lumbar spine (L2-L4), 12% (5/41) had decreased BMD in the right hip, 7% (3/41) had decreased BMD in the left hip, 12% (5/41) had decreased BMD in the right femoral neck, 4.9% (2/41) had decreased BMD in the left femoral neck, and 14.6% (6/41) had decreased BMD in the upper extremity.

Part II. Using The World Health Organization's classification criteria for osteopenia and osteoporosis for any one or more areas including total body, lumbar spine (L2-L4), total hip, femoral neck, ultra distal radius, or 33% radius, 9 of the 14 subjects (64.2%) examined after a subsequent interval of greater than five years exhibited osteopenia. None of the patients

were osteoporotic at any site, even using the definition we had employed in our earlier report.[1]

Twelve of fourteen subjects (85.7 %) of patients showed a further decrease in BMD, as measured by the Z-scores, at one or more sites during the 5-year interval following their initial DXA evaluation. Not all 14 patients received scans of all sites on their follow-up visit, so only those patients for whom we have comparative data were included. Total body BMD decreased in 35.71 % (5/14) of patients. Lumbar spine BMD decreased in 35.71% (5/14) of patients. Right femoral neck BMD decreased in 80.00% (8/10) of patients, left femoral neck BMD decreased in 72.73% (8/11) of patients, left total hip BMD decreased in 53.55% (6/11) of patients, and right femur BMD decreased in 50.00% (5/10) of patients. Right ultra distal radius BMD decreased in 50.00% (3/6) of patients, right 33% radius decreased in 50.00% (3/6) of patients, left ultra distal radius BMD decreased in 30.00% (3/10) of patients, and left 33% radius BMD decreased in 20.00% (2/10) of patients.

Statistically significant overall decreases in mean bone mineral density over the 5-year interval for the longitudinal follow-up cohort of 14 subjects were observed in the right femoral neck (right $p< 0.05$) and the ultra distal ($p < 0.05$) and 33% ($p < 0.05$) radius.[Fig. 3] Mean overall decreases in total body, spine, and total hip failed to show statistical significance.

The anatomic distribution of sites of osteopenia changed over time [Table 1]. Comparing the 14 patients to their original BMD classification, 1 more patient had osteopenia in the total hip region, 2 more in the right femoral neck, 1 more in the left femoral neck, and 2 more in the left 33% radius. Moving in the opposite direction, 3 fewer patients had osteopenia in the spine and 4 less in the right 33% radius region. The incidence of osteopenia in the right and left ultra distal radii remained unchanged.

Blood levels of BAP and NTx for the 14 follow-up patients were collected and compared to their original values, with an average follow-up interval of 5.5 years. Mean BAP decreased over time from 30.49 U/L to 28.48 U/L ($p = 0.60$), and mean NTx decreased over time from 14.00 nM to 11.23 nM ($p = 0.06$). Patients with decreased BMD in the upper extremity, as well as those patients with decreased BMD in the

lower extremities, exhibited lower mean BAP and NTx values compared to those with normal BMD.

DISCUSSION

The literature now clearly shows that survivors of pediatric solid malignancies are at risk for having premature osteopenia/ osteoporosis, particularly those with pediatric bone sarcomas.[2-4] Results of Part I of this paper further underscore that fact. However, prior to the current report, the vast majority of published data in this patient population has been cross-sectional. Only scant longitudinal data with limited bone mineral density measurement sites is available to determine the direction of the trajectory in these patients.[6] Based upon the longitudinal data presented herein, the hypothesis that young adult survivors of pediatric solid tumors do not follow normal bone mass progression is supported. The demonstrated decreases in BMD in numerous sites, including total body, spine, total hip, femoral neck, ultra distal radius and 33% radius, at an age when BMD should be increasing, suggest altered normal maturation of bone density in this patient population. Bone development, as measured by BMD, generally reaches its peak at age 31.[7] Therefore, increasing bone mineral density in our longitudinal study population (mean age 29.4 years) would have been the norm if they had not received treatments for cancer. The opposite phenomenon is occurring, however, with 100% (14/14) of patients showing a decrease in BMD in at least one of the measured sites and more than half of the patients exhibiting a decrease in BMD in the lumbar spine, total hip, and femoral neck sites.

A longitudinal study examining bone mineral density of solid tumor survivors showed low bone mass at the first examination (3.7 ± 4.6 years from therapy completion) in 30.5% (n=36) of those individuals.[6] In contrast to our study, Muszynska-Roslan et al. also report that three years later (6.9 ± 4.6 years from therapy completion), BMD was comparable to that of healthy children.[4] Our differences may in part be due to the methods used to collect the BMD data; we analyzed density in myriad anatomic regions, including total body, spine, femur, and radius, while Muszynska-Roslan et al. present data that is limited to total body and spine BMD.

Survivors of ALL and individuals who have received cranial irradiation have been previously identified for their increased risk

of low bone density.[8-10] Gunes et al., found that 44% of their 70 children had osteoporosis and 42% had osteopenia.[8] Moreover, 12% of the individuals had a history of fracture, all of which occurred within the first two years after completing their chemotherapy.[8] This is particularly worrisome in light of Muszynska-Roslan et al.'s study, which found that the total number of survivors with low BMD was higher in solid tumor subjects compared to ALL and Hodgkin disease (HD) subjects.[7] If solid tumor survivors are at risk for even worse outcomes than ALL and HD patients, as Muszynska-Roslan et al. suggest, particular attention must be paid to this population to ensure the proper follow-up and treatments are provided.

Osteosarcoma survivors have been targeted in the literature, as they seem to have a particularly high risk of developing low bone density.[2-4,12] In a similar cross-sectional study as ours but restricted to osteosarcoma survivors, longer follow-up revealed a higher prevalence of decreased BMD, suggesting that these patients fail to increase their BMD as normal young adults do.[2] In addition, Müller et al. found that of the 46 children and adolescents in their cross-sectional study, 28.3% presented with Z-scores below -1 and 2.2% presented with a Z-score below -2 following neoadjuvant chemotherapy.[10]

The limitations of our study include the small sample size, due to the difficulty in obtaining long-term follow-up of the original 41-patient cohort, which limits our ability to achieve significance. Moreover, though DXA scans were performed bilaterally on every body site analyzed during Part I of the study, some patients only received partial scans on their subsequent visits. Therefore, our comparison of some regions, most notably the upper extremities, is limited. Although planar DXA remains a powerful tool in assessing one's bone mineral density, it may not be entirely accurate in portraying subtle changes in bone quality that may exist in this patient population. Despite the limitations of this small patient population, based on these results, young adult survivors of pediatric solid tumors do not exhibit normal bone mass progression over time and warrant close follow-up and consideration for early treatment.

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Figure Legends

Figure 1. Diagnoses of the 41 patients at time of original cross-sectional study.

Figure 2. Diagnoses of the 14 patients at time of follow-up longitudinal study.

Figure 3. Mean percentage decrease in bone mineral density for 14 patients during the 5-year interval between the original cross-sectional study and the follow-up longitudinal study.

Table 1. Presence of osteopenia/osteoporosis according to DXA study for 41 patients at time of original study and for 14 patients at time of follow-up study.

Table 2. Bone metabolic parameters for the 14 follow-up patients grouped by normal or low bone mineral density in the upper and lower extremities.

Fig. 1

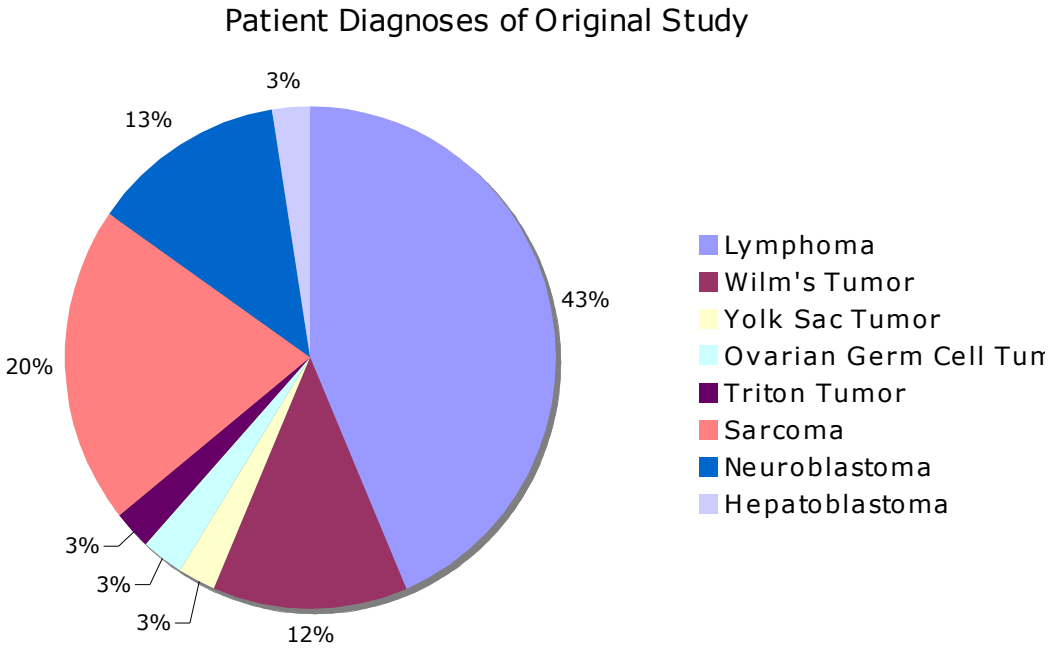

Fig. 2

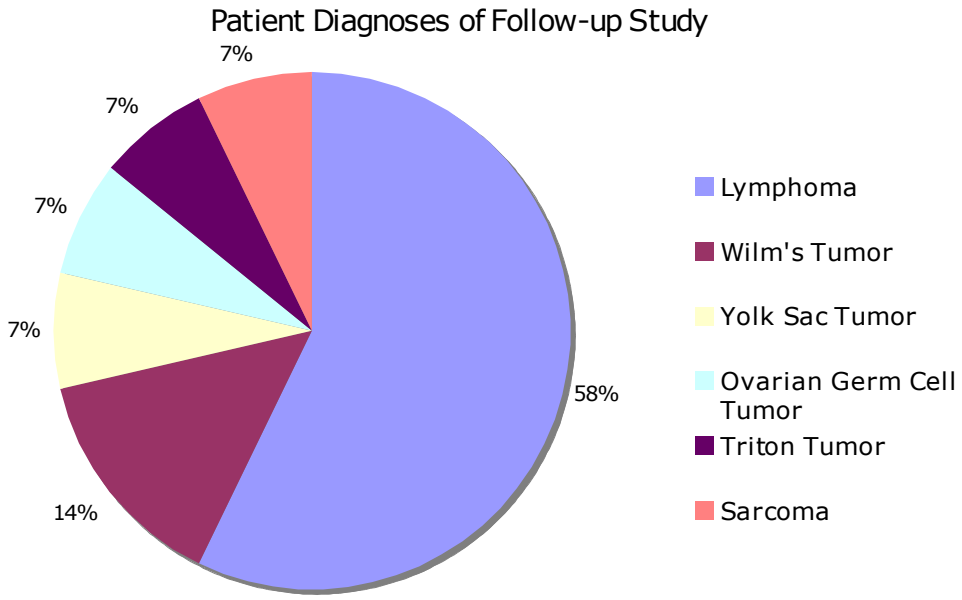

Fig. 3

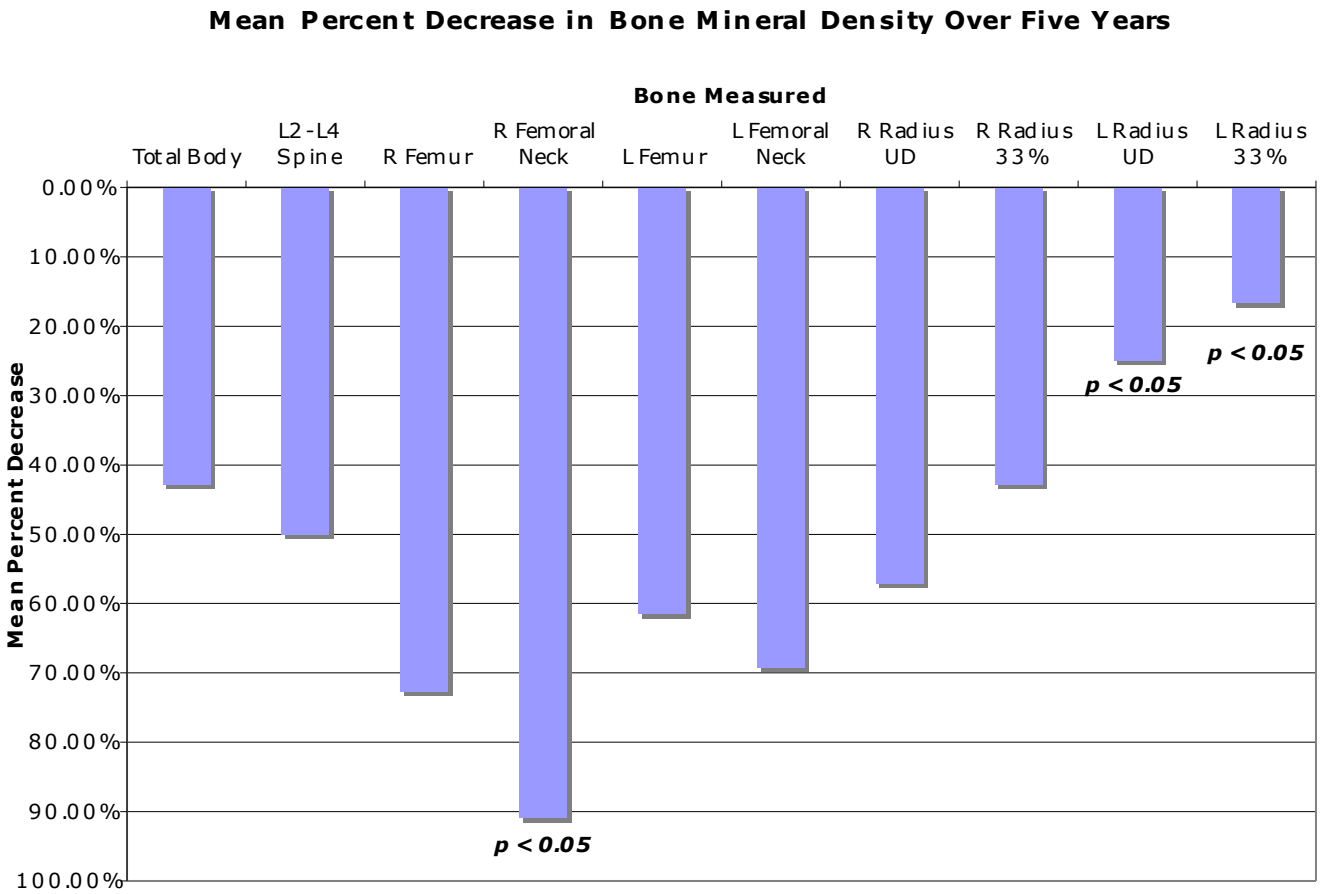

Table 1

Presence of Osteopenia/Osteoporosis According to Body Area Examined During DXA Study

DXA Site	Z-Scores for subjects without osteopenia/osteoporosis Mean (SD) [Number]	Z-Scores for subjects with osteopenia/osteoporosis Mean (SD) [Number]	p Values (pooled T-tests)
Part I			
Total Body	0.73 (0.84) [39]	-1.50 (0.00) [2]	0.001
Spine-Osteopenia	0.37 (0.86) [34]	-1.40 (0.47) [7]	<0.001
Hip, total (right)	0.13 (0.79) [18]	-2.02 (0.69) [5]	<0.001
Hip, total (left)	0.32 (0.89) [21]	-1.77 (0.91) [3]	0.001
Femoral neck (right)	0.19 (0.74) [19]	-1.74 (0.62) [5]	<0.001
Femoral neck (left)	0.20 (1.01) [22]	-1.70 (0.42) [2]	0.016
33% radius (right)	0.07 (0.41) [9]	-1.26 (0.46) [11]	<0.001
33% radius (left)	0.14 (0.51) [11]	-0.98 (0.63) [13]	<0.001
UD radius (right)	1.26 (0.84) [9]	-0.74 (0.89) [11]	<0.001
UD radius (left)	1.05 (0.83) [11]	-0.92 (0.93) [13]	<0.001
Part II			
Total Body	0.57 (0.46) [13]	-1.50 (-----) [1]	0.001
Spine	-0.12 (0.53) [14]	*	-----
Hip, total (right)	0.30 (0.54) [10]	-1.20 (0.28) [2]	0.04
Hip, total (left)	0.38 (0.67) [12]	-1.00 (-----) [1]	0.072
Femoral neck (right)	0.20 (0.44) [10]	-1.20 (0.28) [2]	0.002
Femoral neck (left)	0.46 (0.73) [12]	-1.00 (-----) [1]	0.081
33% radius (right)	-0.26 (0.76) [5]	-1.10 (-----) [1]	0.372
33% radius (left)	0.00 (0.74) [8]	-1.22 (0.18) [5]	0.005
UD radius (right)	0.32 (0.59) [5]	-1.20 (-----) [1]	0.079
UD radius (left)	0.26 (1.41) [10]	-1.37 (0.21) [3]	0.08

*No patients fit this criteria

Table 2

Bone Metabolic Parameters Grouped by Presence of Normal or Decreased BMD in Upper and Lower Extremities

	Subjects with normal UE BMD (n=8)	Subjects with low UE BMD (n=6)	p Value	Subjects with normal LE BMD (n=11)	Subjects with low LE BMD (n=3)	p Value
Bone-specific Alkaline Phosphatase (U/L)	30.74	25.47	0.48	29.94	23.12	0.44
N-Telopeptides (nM)	12.48	9.81	0.23	11.50	10.20	0.65
BAP/NTx ratio	2.56	2.56	1.00	2.60	2.40	0.73