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Impact of Smoking Cessation on Bone Mineral Density in Postmenopausal Women

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ABSTRACT

Background: **Although clinical guidelines recommend smoking cessation to improve bone health, the impact of short-term smoking cessation (i.e., 1 year) on bone mineral density (BMD) is not known. We examined the effects of smoking cessation on BMD measurements, markers of bone turnover, and hormone profiles in postmenopausal women.**

Methods: **Postmenopausal women ($n = 152$) who smoked at least 10 cigarettes per day were randomly assigned to behavioral counseling and either nicotine or placebo patch for smoking cessation (3-month treatment with a 1-month taper) and followed for an additional year. The BMD at various sites (hip, spine, wrist, and total body), serum and urine biochemical markers of bone turnover, and sex hormones were measured at baseline and again 1 year after smoking treatment. Women who continuously abstained from smoking between the end of treatment and 1 year later (quitters) ($n = 42$) were compared with women who completed the study and continued to smoke ($n = 77$).**

Results: **Femoral trochanter BMD increased by 2.9% among quitters vs. 0.6% among continued smokers ($p = 0.02$). Total hip BMD increased by 1.52% among quitters vs. 0.43% among continued smokers ($p = 0.03$). Changes in BMD at the femoral neck, radius, spine, and total body did not significantly differ between groups. The effects of smoking cessation on bone were mediated in part by weight gain. Smoking cessation was also associated with an increase in bone alkaline phosphatase.**

Conclusions: **Smoking cessation, relative to continued smoking, increases BMD at the femoral trochanter and total hip in postmenopausal women.**

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INTRODUCTION

CIGARETTE SMOKING INCREASES the risk of developing osteoporosis, a major cause of disability and excess mortality.[1,2] Consequently, osteoporosis guidelines routinely recommend smoking cessation to improve bone health.[3] Although studies demonstrate that smoking accelerates bone loss,[4] we are not aware of any studies examining whether biochemically confirmed sustained cigarette abstinence improves bone mineral density (BMD).

Cross-sectional studies suggest that smoking cessation improves bone health. BMD measurements among self-reported former smokers are intermediate between those of smokers and nonsmokers.[5,6] One prospective study in older smokers found a significant dose-response relationship between the change in smoking status and hip BMD 16 years later.[4] Persons who quit smoking (by self-report) had a lesser decline in BMD compared with those who continued smoking. Although this study found that 16 years is sufficient to observe a measurable effect of smoking cessation on BMD, it is not known if the effects of smoking cessation on BMD could be observed in a shorter time period.

The best study design to examine the effects of smoking cessation on bone is to randomize smokers to either continued smoking or to smoking cessation; however, this study design is unethical. Consequently, we chose to perform secondary data analyses of the effects of smoking cessation on BMD from data obtained from a 1-year smoking cessation trial. Our study population includes postmenopausal smokers because an association between smoking and osteoporosis has been consistently reported in postmenopausal women.[1,7] We hypothesized that women who quit smoking for 1 year would have a slower decline in BMD of the hip compared with those who continued smoking. We also examined hormone profiles and markers of bone turnover to examine possible mechanisms by which smoking cessation could improve bone health.

MATERIALS AND METHODS

Study overview

The Institution Review Board at the University of Connecticut Health Center approved the study. Postmenopausal women participated in a clinical trial of behavioral counseling and either nicotine patch (21-mg patch for 3 months, 14-mg patch for 2 weeks, and 7-mg patch for 2 weeks) or placebo patch for smoking cessation. Participants were followed for an additional year after patch discontinuation. To examine the effects of smoking cessation on BMD, we performed analyses of the impact of 1-year continuous cigarette abstinence (confirmed by exhaled carbon monoxide [co]) on BMD measurements and biochemical measurements in women who completed this randomized trial. We here report on BMD and biochemical measurement changes in women who quit smoking relative to continued smokers. Other aims of the trial (i.e., to examine the short-term effects of nicotine *per se* on markers of bone turnover during the first 3 months of patch use) will be reported separately.

Subjects

Women interested in study participation were invited to a screening visit, where written consent was obtained and medical eligibility criteria were assessed. Women were eligible if they smoked at least 10 cigarettes per day and were postmenopausal (i.e., no menstruation for at least 1 year). Exclusion criteria included (1) taking oral corticosteroids, antiepileptics, or medication for prevention/treatment of osteoporosis other than estrogen replacement therapy (ERT), (2) untreated parathyroid or thyroid disease, multiple myeloma, or insulin-dependent diabetes mellitus, (3) a recent fracture, (4) an ionized calcium concentration >1.36 mmol/L, (5) consuming more than two alcoholic drinks per day, (6) using nicotine replacement or tobacco products other than cigarettes, and (7) an unstable psychiatric or medical condition. Figure 1 shows the number of subjects screened and outlines the frequency of participation by treatment group during the clinical trial.

Study visits and treatment

Subjects provided demographic information, a 4-day food diary, and Physical Activity Score for the Elderly (PASE) at the baseline visit (visit 1). The PASE is a 5-minute reliable and valid instrument for the assessment of physical activity in older persons.[8] Fasting blood and second void urine were collected. Height was measured using a stadiometer, and weight was measured on a bal-

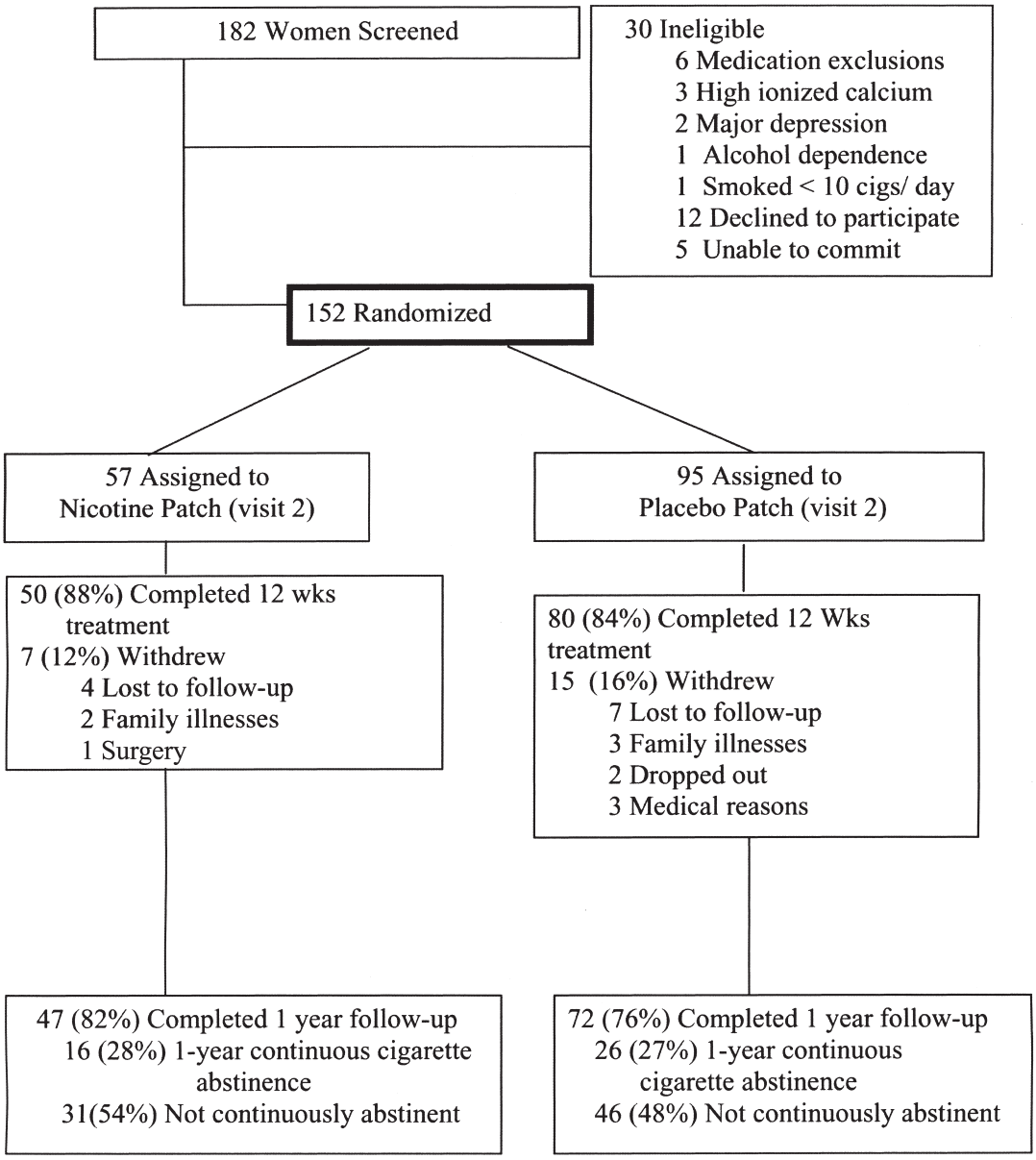

FIG. 1. Study participation.

ance beam scale. BMD was measured using dual energy x-ray absorptiometry (DEXA).

After the baseline visit, participants were enrolled in a 12-week treatment phase (visits 2–7). Participants received smoking cessation counseling and either a 21-mg nicotine patch or placebo patch (3:5 randomization) for smoking cessation. The last visit during the treatment phase (visit 7) occurred 12 weeks after initiating cessation. We provided participants with the booklet *Boning Up on Osteoporosis*,[3] discussed general preventive osteoporosis measures, and informed participants of the results of their BMD measurement. We encouraged subjects to discuss their BMD results with their personal physician so that an appropriate treatment plan could be devised for their ongoing medical care.

Visit 8 was scheduled 1 year after completion of the study medication (approximately 16 months after baseline visit). We repeated BMD measurements, a 4-day food diary, a PASE questionnaire, weight/height measurement, and blood and urine collection. Subjects who reported continuous cigarette abstinence from visit 7 to

visit 8 and who had an exhaled CO measurement of <8 ppm[9] at visits 7 and 8 were considered quitters for the purposes of analyses.

BMD was measured by DEXA (Lunar DPX-IQ, GE Lunar, Madison, WI). The coefficient of variation (CV) of BMD measurement, based on reproducibility scans completed at our center, are 1.8% for the greater trochanter, 1.3% for femoral neck, 1.1% for total hip, 1.7% for L1–2 spine, 2.2% for L2–4 spine, 3.7% for ultradistal wrist, 1.3% for radius, and 0.5% for total body.

We measured bone alkaline phosphatase (BAP) (Metra Biosystem Inc, Mountain View, CA) and urinary cross-linked N-telopeptides (NTx) (Ostex International Inc, Seattle, WA) using enzyme-linked immunosorbent assay (ELISA). Osteocalcin (OC) was measured by a sandwich ELISA using two antibodies (Biomedical Technologies, Inc., Stoughton, MA). The intraassay variability was 8% for NTx and 5% for BAP. We measured estradiol (E_2) and testosterone (T) using radioimmunoassay (RIA) and sex hormone-binding globulin (SHBG) using immunoradiometric assay (Diagnostic Systems Lab, Inc., Webster, TX). The detection limit of the E_2 assay is 2 pg/mL. Calciotropic hormones included intact parathyroid hormone (PTH) measured by sandwich ELISA Diagnostic Systems Labs, Inc.). The intraassay variability for all bone markers and hormones in the General Clinical Research Center Laboratory is <10%. The level of 25-hydroxyvitamin D was measured using competitive protein binding (Esoterix Inc., Calabasas, CA).

Statistical analyses

Baseline characteristics are computed, and means and standard deviations (SD) are reported. We used histogram and Q-Q plot to check the normality of distribution of markers of bone turnover, hormones, and BMD measurements. BMD measurements, SHBG, PTH, and 25-hydroxy vitamin D were normally distributed; however, the percent and absolute change of the following variables were highly skewed: NTx/CR, BAP, OC, E_2, and T. These skewed variables were transformed by the 0.2 power function to achieve normality. These transformed variables were used in all the analyses evaluating change over time.

Comparison of characteristics between groups was done using analyses of variance (ANOVA). To determine the effects of smoking cessation on BMD, the data were analyzed using linear regression models (SPSS version 12.0, Chicago, IL). Percent change in BMD (from baseline to visit 8) was the dependent variable. Variables were assessed in the model that could confound the relationship between smoking cessation and BMD (i.e., a variable that is associated with the predictor variable and causally related to the outcome variable). Baseline smoking rate (cigarettes/day), baseline BMD, body mass index (BMI), age, years postmenopause, randomization assignment to nicotine or placebo patch, ERT use during the study (i.e., number of months of use), and interaction between 1 year smoking abstinence and ERT use were evaluated as independent variables in the model that could confound the relationship between smoking cessation and BMD changes. Baseline smoking rate (cigarettes/day), BMI, age, years postmenopause, and randomization assignment to nicotine or placebo patch were removed because they did not significantly influence the parameter estimate for smoking cessation by >10%. We retained ERT use in the model as well as the interaction of months of ERT use with smoking cessation because of a planned analyses to determine if the effects of smoking cessation on BMD depend on ERT status.

Additionally, we evaluated the effects of potential mediators in the model (i.e., a variable on the causal pathway between smoking cessation and changes in BMD that could explain mechanisms by which smoking cessation influences BMD). Percent weight gain, calcium intake change during the study, and PASE score change were evaluated as potential mediators because, clinically, these could change as a result of smoking cessation. When evaluating the effects of smoking cessation on various BMD sites, we did not control for multiple comparisons, partly because many of the BMD sites and bone markers are not independent outcomes.

Pearson's correlation matrix for changes in bone density and markers of bone turnover and hormone profiles, as well as other changes that occurred during the study (i.e., changes in weight, changes in physical activity, changes in calcium supplementation and diet), were calculated to examine possible mechanisms by which smoking cessation could affect bone.

RESULTS

Table 1 shows the baseline characteristics of subjects who entered the study and of women who completed the study (i.e., quitters and continued smokers). Quitters, relative to continued smokers, smoked fewer cigarettes per day at baseline. Women were on average 12 years postmenopause (based on last menstrual period); however, excluding women with a history of hysterectomy, the average was 8 years postmenopause. The baseline (mean ± SD) BMD at the hip, wrist, and spine and total body for quitters and continued smokers were in the normal range (between −1 and 1 SD compared with young adults). All participants in the study were ambulatory. Of note, we also compared differences between women who completed the study and those who did not complete the study. There were no significant differences in any of the baseline demographic characteristics, BMD measurements, or bone markers between groups.

The results of the Women's Health Initiative (WHI) study were reported during our study,[10] which may have caused some women to discontinue ERT. During the follow-up period, 15 of the 73 subjects who were taking ERT at the beginning of the study discontinued it. Four subjects started ERT during the trial, and 5 subjects changed the dose of the ERT they were taking at study entry. Four subjects started treatment for osteoporosis during the study (alendronate). Two of these wo-

TABLE 1. BASELINE CHARACTERISTICS[a]

Variable	*All subjects* (n = 152)	*Quitters* (n = 42)	*Smokers* (n = 77)	p *value*[b]
Age (years)	55.6 ± 7.0	57.2 ± 7.4	55.0 ± 6.8	0.08
Years since menopause	12.4 ± 9.3	14.5 ± 10.1	10.6 ± 8.1	0.03
Body mass index[c]	27.0 ± 5.4	27 ± 5.6	26.9 ± 5.0	0.98
Calcium intake from diet (mg)	665 ± 347	639 ± 312	677 ± 361	0.55
Vitamin D from diet (IU)	125 ± 100	131 ± 101	123 ± 99	0.64
Number of cigarettes/day	21.4 ± 8.2	17.8 ± 4.9	22.9 ± 8.8	0.001
Number of years smoked	34.4 ± 10	33.5 ± 11.3	34.8 ± 9.6	0.46
Plasma cotinine (ng/ml)	246 ± 121.0	220 ± 98	256 ± 128	0.09
PASE score[d]	157 ± 80	171 ± 86	151 ± 77	0.18
Caucasian, %	89	86	90	0.22
>High school education %	72	72	72	0.75
Taking estrogen, %	49	49	49	0.94
Taking progesterone, %	23	21	27	0.47
On calcium supplements, %	35	37	35	0.78
On vitamin D supplements, %	10	12	10	0.78
Femoral neck (g/cm^2)	0.923 ± 0.136	0.910 ± 0.150	0.928 ± 0.131	0.50
Femoral trochanter (g/cm^2)	0.814 ± 0.136	0.801 ± 0.143	0.819 ± 0.133	0.45
Total hip (g/cm^2)	0.977 ± 0.146	0.959 ± 0.151	0.984 ± 0.144	0.36
Forearm radius 33% (g/cm^2)	0.684 ± 0.073	0.684 ± 0.075	0.690 ± 0.077	0.40
Spine L2–L4 (g/cm^2)	1.180 ± 0.193	1.170 ± 0.175	1.184 ± 0.201	0.78
Total body (g/cm^2)	1.173 ± 0.099	1.163 ± 0.102	1.178 ± 0.097	0.83
NTX/Cr (nM BCE per mmol/L)[e]	29.0 (21.6, 48.3)	26.5 (19.9, 39.0)	32.5 (21.7, 52.3)	0.12
BAP ($\mu g/dL$)[e]	22.2 (17.1, 27.4)	19.3 (15.3, 28.7)	22.5 (18.7, 27.3)	0.55
Osteocalcin ($\mu g/L$)[e]	7.1 (3.9, 14.0)	8.2 (4.4, 14.8)	6.9 (3.7, 12.3)	0.69
Estradiol (pg/mL)[e]	19.4 (12.4, 41.5)	18.2 (10.4, 47.6)	19.9 (13.1, 38.9)	0.82
Testosterone (ng/mL)[e]	0.33 (0.18, 0.66)	0.42 (0.25, 0.82)	0.29 (0.15, 0.56)	0.17
SHBG (nmol/L)	49.1 ± 31.9	50.4 ± 26.6	49.2 ± 31.7	0.84
Parathyroid hormone (ng/L)	58.7 ± 30.3	49.5 ± 19.9	52.5 ± 22.9	0.47
25-Hydroxyvitamin D (ng/mL)	21.5 ± 9.5	23.3 ± 9.8	21.0 ± 9.6	0.23

[a]Results are reported as mean ± SD.

[b]*p* value compares quitters to smokers using ANOVA for continuous variables (transformed variable was used for skewed variables) and chi-square for categorical variables.

[c]Calculated as weight in kilograms divided by the square height in meters.

[d]PASE, Physical Activity Score for the Elderly; BCE, bone collagen equivalents; SHBG, sex hormone-binding globulin; NTx, N-telopeptides of type 1 collagen; OC, osteocalcin; BAP, bone alkaline phosphatase.

[e]Median (25th percentile, 75th percentile) reported for skewed variable.

Table 2. Effects of 1-Year Continuous Cigarette Abstinence on BMD

Dependent variables	*Quitter*[a] *mean % change (95% CI)* (n = 42)	*Smoker mean % change (95% CI)* (n = 77)	p *value*
Femoral trochanter	2.89 (0.94 to 4.84)	0.60 (−1.08 to 2.28)	0.02
Femoral neck	0.75 (−0.69 to 2.19)	0.18 (−1.05 to 1.42)	0.69
Total hip	1.52 (0.26 to 2.77)	0.43 (−0.66 to 1.51)	0.03
Forearm radius 33%	0.28 (−0.95 to 1.5)	−0.59 (−1.7 to 0.49)	0.08
Spine L2-L4	−0.40 (−2.0 to 1.2)	−0.17 (−1.6 to 1.2)	0.55
Total body	0.07 (−0.70 to 0.84)	0.22 (−0.45 to 0.89)	0.32

[a]Two quitters did not have BMD measured at the hip because of hip replacement.

men were in the smoking cessation group, and 2 were in the continued smoking group.

The mean change ± SD in weight was 6.4 ± 4.9 kg among women who quit smoking compared with a 2.1 ± 3.8 kg weight increase among continued smokers ($p < 0.0001$). The mean change ± SD in PASE score was −8.4 ± 104 among quitters vs 7.7 ± 69 among continued smokers ($p = 0.32$). The mean change ± SD in calcium intake from diet was 33 ± 456 mg among quitters vs. −169 ± 446 mg among continued smokers ($p = 0.02$). Twelve percent of quitters stopped ERT vs. 16% for continued smokers ($p = 0.02$). Months of cigarette abstinence from baseline to end of study were 15.9 ± 0.1 months for the quitter group and 2.8 ± 3.8 months for the continued smoking group ($p < 0.001$). The mean change in cigarettes per day from baseline to end of study was −17 ± 6 in the quitter group vs. −5 ± 8 cigarettes per day in the smoking group ($p = 0.03$).

Smoking cessation had its greatest beneficial effect on % BMD change of the greater trochanter and total hip. The change was borderline significant at the forearm radius ($p = 0.08$) (Table 2). The effect of smoking cessation on % change in BMD was not statistically significant at the femoral neck, spine, or total body. We reanalyzed BMD changes excluding the 4 women who started alendronate during the study. Because the results were similar, they were included in the analyses. Table 2 displays unadjusted mean percent changes. Adjusted means were very similar to the unadjusted values, and statistical significance remained the same even after controlling for potential confounders.

The effect of smoking cessation on BMD after controlling for potential confounders is shown in Table 3. Baseline BMD and the interaction between estrogen and smoking cessation were independent predictors in the change in BMD. Standardized β coefficients are also included to show the relative importance of one predictor compared with other predictors in the model. Figure 2 shows the interaction between smoking cessation and ERT use on femoral trochanter and femoral total BMD. Women who used ERT for at least 8 months during the study were considered ERT users. Women who quit smoking and were

Table 3. Effects of Smoking Cessation on Percent Change in BMD, Controlling for Potential Confounders

Variables	*R-square*	*β coefficient standardized*	*β coefficient unstandardized*	*95% CI*	p *value*
Femoral trochanter	0.17				
Baseline BMD		−0.29	−8.36	−13.59 to −3.12	0.002
Estrogen use		+0.06	+0.03	−0.07 to 0.13	0.56
Smoking cessation[a]		**+0.25**	**+2.10**	**0.64 to 3.57**	**0.005**
Estrogen × cessation		−0.20	−0.11	−0.21 to −0.007	0.04
Total hip	0.11				
Baseline BMD		−0.17	−2.85	−5.96 to 0.25	0.07
Estrogen use		+0.09	+0.03	−0.04 to 0.10	0.36
Smoking cessation		**+0.19**	**+1.03**	**+0.09 to 1.97**	**0.03**
Estrogen × cessation		−0.19	−0.06	−0.13 to 0.002	0.06

[a]Bold type indicates parameter estimates and significance values for smoking cessation.

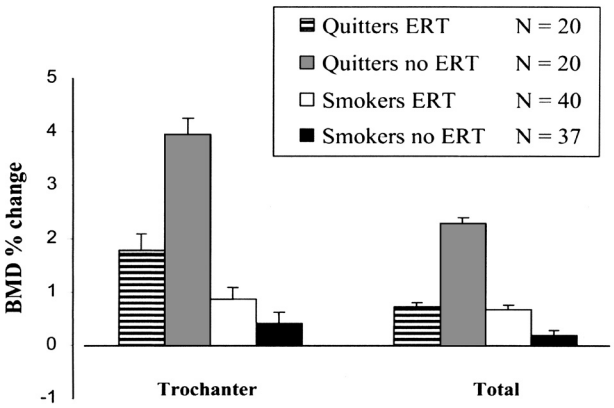

FIG. 2. This figure illustrates the interaction of smoking cessation and ERT use on femoral trochanter and total hip BMD. ERT use was defined as use of at least 8 months of estrogen during the study. Results are presented as mean % change ± SEM.

not taking ERT had a larger increase in BMD at the femoral trochanter and total hip compared with women taking ERT. Conversely, continued smokers not taking ERT had a relative bone loss compared with continued smokers taking ERT.

We also evaluated a model that includes known potential mediators of the effects of smoking cessation on BMD (Table 4). When each of these mediators was assessed independently in the model, only percent weight gain significantly altered the parameter estimate for smoking cessation.

The effect of smoking cessation on bone turnover and hormones is shown in Table 5. There was an increase in BAP in both groups that was small but significantly greater in the quitters vs. continued smokers. We conducted additional analyses of smoking cessation on hormones and bone turnover only in women who did not alter their use of ERT or start alendronate during the study ($n = 89$). The results were similar to values listed in Table 5.

Weight changes were correlated with percent changes in trochanteric BMD ($r = 0.28$, $p = 0.002$) and percent changes total hip BMD ($r = 0.19$, $p = 0.04$). Percent change in total hip BMD was also correlated with changes in cigarettes smoked/day ($r = -0.364$, $p = 0.0001$) and exhaled CO ($r = -0.247$, $p = 0.007$). Calcium intake, PASE scores, other hormones, and markers of bone turnover were not correlated with changes in BMD.

DISCUSSION

We found that 1 year of smoking cessation improved femoral trochanter and total hip BMD in postmenopausal women. No statistically significant BMD changes were observed at the femoral neck, radius, and spine or total body in quitters compared with continued smokers. We also found an interaction between ERT use and smoking cessation on hip BMD. The effects of smoking cessation on bone appear to be mediated in part by weight gain. Smoking cessation was also associated with an increase in BAP.

TABLE 4. EFFECTS OF SMOKING CESSATION ON PERCENT CHANGE IN BMD, INCLUDING POTENTIAL CONFOUNDERS AND MEDIATORS IN MODEL

Variables	*R-square*	*β coefficient standardized*	*β coefficient unstandardized*	*95% CI*	p *value*
Femoral trochanter	0.21				
Baseline BMD		−0.27	−7.80	−13.59 to −2.02	0.009
Estrogen use		+0.05	+0.03	−0.09 to 0.14	0.65
Smoking cessation[a]		**+0.12**	**+1.05**	**−0.68 to 2.79**	**0.23**
Estrogen × cessation		−0.19	−0.11	−0.21 to 0.003	0.06
Weight change		+0.26	+0.16	0.04 to 0.28	0.01
PASE score change		−0.04	−0.002	−0.01 to 0.008	0.71
Calcium change		+0.02	+0.000	−0.002 to 0.002	0.87
Total hip	0.13				
Baseline BMD		−0.16	−2.64	−6.16 to 0.89	0.14
Estrogen use		+0.14	+0.05	−0.03 to 0.12	0.21
Smoking cessation		**+0.12**	**+0.67**	**−0.46 to 1.80**	**0.24**
Estrogen × cessation		−0.14	−0.05	−0.12 to 0.03	0.19
Weight change		+0.14	+0.06	−0.02 to 0.13	0.16
PASE score change		−0.10	−0.003	−0.009 to 0.003	0.32
Calcium change		+0.04	+0.000	−0.001 to 0.001	0.58

[a]Bold type indicates parameter estimates and significance values for smoking cessation.

Table 5. Marker and Hormone Percent Changes after 1 Year Continuous Cigarette Abstinence[a]

Dependent variables	*Quitter mean (95% CI)*[b] n = 42	*Smoker mean (95% CI)* n = 77	p *value*
SHBG (nmol/L)	−0.9 (−18 to 17)	−1.8 (−17 to 13)	0.43
Testosterone (ng/mL)	2.4 (2.1 to 2.7)	2.3 (1.9 to 2.6)	0.36
Estradiol (pg/mL)	1.5 (1.3 to 1.7)	1.4 (1.2 to 1.6)	0.28
Intact PTH (ng/L)	26.2 (−2.6 to 55)	13.0 (−11 to 37)	0.59
25-Hydroxyvitamin D (ng/mL)	−16.9 (−35.4 to 1.7)	−18.0 (−33.5 to −2.6)	0.49
NTx/Cr (nM BCE/L)	1.5 (1.3 to 1.6)	1.6 (1.4 to 1.7)	0.39
OC (μg/L)	1.2 (1.0 to 1.3)	1.2 (1.0 to 1.3)	0.40
BAP (μg/dL)	1.7 (1.5 to 1.9)	1.5 (1.4 to 1.7)	0.009

[a]Adjusted for baseline value of a particular bone marker or hormone, months on estrogen, smoking cessation, and interaction between months on estrogen and smoking cessation.

[b]CI, confidence interval; SHBG, sex hormone-binding globulin; NTx, N-telopeptides of type 1 collagen; OC, osteocalcin; BAP, bone alkaline phosphatase.

Our findings agree with the only other longitudinal prospective study that we are aware of evaluating the effects of smoking cessation on BMD. In that study, older men and women had BMD tests at baseline and approximately 16 years later.[4] The most salient finding of this study was that the hip BMD was highest in never smokers at the 16-year follow-up, followed by subjects who reported quitting smoking before the study began, followed by subjects who reported quitting sometime within the 16-year study period, followed by continuous smokers. A slower decline in BMD was also observed in the midradius in women and in the spine in men who stopped smoking. One cross-sectional study in older women also suggested that the radius might be sensitive to changes with smoking cessation.[6] Although not statistically significant, we also found that smoking cessation may improve BMD at the forearm radius. Other cross-sectional studies in older persons have suggested that the calcaneous may be sensitive to the effects of smoking cessation.[5,11] We did not measure this site in our study. Consistent with epidemiological studies of smoking cessation on BMD, a meta-analysis of 86 studies enrolling over 40,000 subjects found that smoking is associated with lower BMD at all sites; however, the most pronounced deficit is at the hip site.[12]

In contrast to the findings from previous studies, we found that short-term smoking cessation significantly improves hip trochanteric and total hip BMD rather than halting bone loss. This finding is important, as decreased BMD at the total hip site is a risk factor for hip fracture.[13] Although we had anticipated continued bone loss in both groups, a possible explanation is that the study population was a number of years postmenopause when the rapid decline in BMD has stopped or leveled off. Moreover, many continued smokers quit for a period of time and relapsed or reduced their smoking, which may partially explain the lack of finding of bone loss at the hip site. For BMD sites other than the hip, the confidence intervals are consistent with a small decline in BMD in continued smokers. It is also possible that systematic variations in BMD measurements may have influenced our results. This does not negate our findings of between-group differences; however, a finding of a potential increase in BMD after smoking cessation needs to be replicated in future studies.

We observed a slightly higher weight gain in our clinical trial than has been observed in longitudinal cohort studies of smoking cessation (3.8–5 kg weight gain typically occurs in women after smoking cessation).[14,15] The hip is a weight-bearing site, and weight changes are an important determinant of hip BMD.[16] As smokers in general weigh less than nonsmokers, weight gain that occurs with smoking cessation is generally viewed as returning to a normal weight.[15] Including percent weight change in the model suggests that changes in weight mediate the beneficial effects of smoking cessation on bone. Changes in BMD in our study are not likely due to changes in calcium intake[17] or physical activity (PASE scores), as adding these variables to the model did not influence the results.

We are not aware of any studies examining the interaction between smoking cessation and ERT use on BMD. Other studies have examined interactions between smoking and ERT use in smok-

ers and nonsmokers. These studies suggest that ERT is more effective in increasing BMD in nonsmokers compared with smokers.[18,19] Moreover, smoking may increase the metabolism of oral estrogen.[18,20] Indeed, we had anticipated that the effects of smoking cessation on bone might be greater in ERT users because their exogenous estrogen may be more effective after smoking cessation. However, we found the opposite effect. A possible explanation for finding a smaller beneficial effect of smoking cessation in ERT users is that they are taking an antiresorptive agent, which may mitigate any potential beneficial effects of smoking cessation on bone gain. Similarly, ERT use may protect against bone loss with continued smoking. This rationale is supported by studies showing that bone resorption markers are higher in smokers than in nonsmokers.[21] We did not find an effect of smoking cessation on bone resorption markers; however, the power to detect changes in bone turnover in this study is limited. Our most consistent finding in bone markers was that smoking cessation was associated with an increase in BAP. This finding agrees with animal studies, which have shown that nicotine alone can influence bone formation.[22] BAP is a sensitive marker of bone remodeling that increases with age.[23,24] The changes we observed in BAP are consistent with removal of an inhibitory effect of smoking on bone formation. It is noteworthy that with multiple comparisons, particularly with bone markers and hormones, the results of smoking cessation on BAP may have been spurious. Future studies are needed to validate these findings.

Strengths of this study include its prospective design with biochemical verification of cigarette abstinence. We observed an 80% follow-up after 16 months of study participation. Limitations of the study include confounders (i.e., changes in hormonal status) that needed to be controlled for in the analyses. The error of the BMD test in a short-term study may be large even though our reproducibility at various BMD sites was excellent. A longer follow-up period may be needed to fully examine the effects of smoking cessation on BMD at all sites.

In summary, we found that smoking cessation for 1 year improves BMD at the trochanteric site, total hip, and possibly the radius. Future studies are warranted to replicate these findings and to examine the effects of smoking cessation in persons with low bone mass.

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