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The influence of chemotherapy on bone mineral density, quantitative ultrasonometry and bone turnover in pre-menopausal women with breast cancer

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ABSTRACT

Introduction: The effects of doxorubicin/cyclophosphamide (A/C; 6 cycles) chemotherapy on bone mineral density (BMD), quantitative ultrasonography (QUS) and bone turnover markers in pre-menopausal women with oestrogen receptor-negative breast cancer (BC) were compared with age-matched controls.

Methods: Among 106 women (BC = 53, controls = 53), BMD (spine and hip), QUS (calcaneus and phalanges) and bone marker levels were measured at baseline, 6 and 12 months. Correlations between parameters were determined by Spearman's rho.

Results: All BC patients became amenorrhoeic after chemotherapy and remained so for the duration of treatment. BC patients had significant bone loss at all sites ($P \leqslant .005$) and significant increases in bone turnover ($P \leqslant .05$). There were significant correlations between BMD, QUS and bone markers ($P \leqslant .05$).

Conclusions: Results confirm A/C's deleterious influence on bone health in pre-menopausal women with BC and established QUS's utility for monitoring bone effects. Large-scale longitudinal studies are needed to further understand and prevent bone changes following chemotherapy.

1. Introduction

Breast cancer and osteoporosis are two of the most common diseases in post-menopausal women, both of which result in reduced quality of life and a decreased life expectancy.[1,2] The risk of a 60-year-old woman sustaining a vertebral fracture is 18%, while the remaining lifetime risk of any fractures due to osteoporosis is 65%.[3] The incidence of breast cancer has progressively increased in the past few decades.[2] In 2007, it is estimated that there were 1.3 million new cases of breast cancer diagnosed worldwide.[4] Obesity, smoking, early menarche, late menopause, hormone replacement therapy and prolonged oestrogen exposure are risk factors for developing breast cancer, but these same factors, with the exception of smoking, protect against osteoporosis.[5] Because of the high rates of both breast cancer and osteoporosis, it is important to understand the correlation between these two diseases to prevent associated morbidity and mortality.

A number of cross-sectional and prospective studies have investigated the relationship between bone mineral density (BMD) and breast cancer. The results of the Framingham trial, the Fracture Intervention Trial (FIT) study, the Study of Osteoporotic Fractures (SOF) and the Marburg Breast Cancer and Osteoporosis Trial (MaBOT) suggest that at the time of diagnosis, women with breast cancer have higher BMD compared with healthy, matched controls.[5–9] Therefore a high BMD, which may be due in part to cumulative oestrogen exposure, has been considered a risk factor for breast cancer. Addition-

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ally, studies have shown that women with osteoporosis-related vertebral fracture had a 62% reduction in breast cancer risk, even after adjustment for age and BMD.[10]

Despite the increased BMD at the time of diagnosis, women with breast cancer have a 4–5-fold increased risk of fracture during the course of their disease.[11] A prospective analysis of more than 90,000 post-menopausal women enrolled in the Women's Health Initiative Observational Study (WHI-OS) revealed a 31% increase in the risk of fracture in breast cancer survivors.[12] Within the first few years after diagnosis of breast cancer, considerable loss of BMD has been attributed to the adjuvant chemotherapy used for treatment.[13] It is well known that chemotherapy-induced ovarian failure in pre-menopausal women can cause rapid bone loss; several recent studies have shown that chemotherapy may adversely affect osteoblasts directly.[14] Trials that have examined the influence of chemotherapy on BMD in pre-menopausal women with breast cancer have consistently shown a significant decrease in BMD in the first year after initiation of chemotherapy.[15–19] The current standard for measuring BMD is dual-energy X-ray absorptiometry (DXA); however, DXA is not readily available in many clinics in Europe.[20] Quantitative ultrasonometry (QUS), a new method for assessing the risk of fracture, has not been used in these studies. However, a large number of cross-sectional and prospective studies have established QUS as predictive of osteoporosis-related fractures independently of DXA-BMD.[21–25]

The aim of this 1-year, prospective, case-controlled study was to evaluate the effects of six cycles of chemotherapy with doxorubicin and cyclophosphamide on bone turnover in pre-menopausal women with oestrogen receptor-negative breast cancer compared with healthy, age-matched and body mass index-matched controls who did not receive chemotherapy. Bone turnover was assessed by measurement of BMD of the hip and spine and biochemical markers, with evaluation of QUS as a method to assess the effects of chemotherapy on bone.

2. Patients and methods

2.1. Patients

Pre-menopausal women between 24 and 47 years of age with histologically proven, oestrogen receptor-negative breast cancer were eligible for inclusion; all received chemotherapy with AC (doxorubicin and cyclophosphamide). Pre-menopausal women without breast cancer were enrolled as a control group and were matched for age (±9 years), height (±6 cm), weight (±11 kg) and body mass index (BMI; ±4 kg/m^2) to minimise the effects of confounders. Healthy control subjects were randomly selected from patients seen in an outpatient clinic for reasons other than breast cancer or osteoporosis. Women with metastatic breast cancer, post-menopausal women with breast cancer, women with osteoporosis-related fractures, women with a history of other malignancies and women who were receiving therapies known to affect bone turnover or with diseases known to affect bone mineral density were excluded from the study. The study was performed in accordance with the Declaration of Helsinki, and all women gave written consent for participation before enrolment in the study.

2.2. Study design

This was a prospective, case-controlled study. Upon enrolment in the study, all women completed a detailed questionnaire to assess risk factors for breast cancer and osteoporosis. Patients with breast cancer were scheduled to receive chemotherapy with intravenous (IV) doxorubicin 40 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks for 6 cycles. Patients were assessed before chemotherapy and at 6 and 12 months following chemotherapy with a physical exam, gynaecologic exam, assessment of menstrual status, assessment of risk factors, measurement of BMD at the spine and hip, QUS of the calcaneus and phalanges and assessment of bone turnover markers in serum. For this study, amenorrhoea was defined as cessation of menses for $\geqslant$6 months. Bone mineral density was measured by DXA using a Lunar Prodigy densitometer (GE/Lunar Healthcare Corporation, Madison, WI, USA) using a standard protocol for the hip and spine and by the same operator. The QUS measurements of the calcaneus were obtained using the Achilles device (GE Healthcare) while QUS measurements of the phalanges were obtained using the DBM Sonic Bone Profiler device (IGEA® Clinical Biophysics, Italy). The performance characteristics of these methods have been described in detail previously.[26,27] Short-term precision (coefficient of variation) of the Achilles device was assessed *in vivo* three times per day in healthy volunteers. During the study, daily quality control was performed using a standardised phantom. All measurements (DXA and QUS) were performed in a blinded manner, and were quantified by computer analysis of the data. Bone-specific alkaline phosphatase (BAP), N-terminal propeptide of type I procollagen (PINP) and C-telopeptide of type I collagen (CTX) levels were measured with routine, standardised assays at baseline, 6 months and 12 months after chemotherapy.

2.3. Statistical analysis

SPSS for Windows 11.0 (SPSS GmbH Software, Munich, Germany) was used for data analysis. The demographic data for patients in each group were analysed for normal distribution and compared after matching for all potentially significant confounding variables using the matched-pairs method. The data from baseline, 6 months and 12 months were compared by the Friedman Test with the Wilcoxon Test for post hoc analysis. Cases and controls were separately tested. The associations between parameters for measuring bone density and biochemical markers of bone turnover were analysed by Spearman's rho correlation. This was a pilot study. Because of the lack of results from trials of similar design, study size could not be determined by power calculation.

3. Results

3.1. Patient characteristics

Fifty-three pre-menopausal women with breast cancer and 53 healthy, pre-menopausal women were enrolled in this study. Patients and controls were matched for age, weight, height and BMI (Table 1), and there were no statistically significant

Table 1 – Patient baseline demographics (n = 106).

Mean	Healthy control group (n = 53)	Breast cancer + chemotherapy group (n = 53)
Age, years (range)	38 (24–47)	37 (24–47)
Weight, kg (range)	68 (52–100)	68 (50–96)
Height, cm (range)	165 (152–184)	166 (154–180)
BMI, kg/m^2 (range)	25 (19–37)	25 (18–35)
Bone mineral density, g/cm^2 ± SD		
Lumbar spine	1.195 ± 0.176	1.202 ± 0.174
Total hip	0.991 ± 0.106	0.987 ± 0.122
Femoral neck	0.937 ± 0.101	0.940 ± 0.122
QUS SOS, m/s ± SD		
Calcaneus	1539.8 ± 28.0	1542.8 ± 28.0
Phalanges	2008.4 ± 111.3	2052.1 ± 79.5

BMI, body mass index; SD, standard deviation; QUS, quantitative ultrasonometry; SOS, speed of sound.

between-group differences for baseline characteristics ($P > .05$ for all). All 53 patients with breast cancer received all 6 cycles of chemotherapy and had become amenorrhoeic by the 6-month assessment.

3.2. Analysis of BMD by DXA

The healthy pre-menopausal women in the control group had stable BMD as determined by DXA scans for the total hip, lumbar spine and femoral neck at the 6- and 12-month assessments (Fig. 1). In contrast, pre-menopausal women who received six cycles of AC for their breast cancer had a significant, progressive reduction in BMD for the total hip and lumbar spine over 12 months ($P < .001$ for all; Fig. 1). The BMDs of the femoral neck, total hip and lumbar spine were significantly lower at 12 months, with respective –2.79%, –4.02% and –5.17% mean percentage reductions in BMD from baseline ($P < .02$ for all).

3.3. Measurement of QUS

To assess the validity of QUS for measuring chemotherapy-associated bone loss, the percentage changes in QUS speed of sound (SOS) were determined in the same populations of women. The healthy, pre-menopausal women had stable ultrasound findings of the phalanges and calcaneus throughout the trial (Fig. 2). Patients with breast cancer who received AC chemotherapy had significant reductions in QUS SOS at both the phalanges and calcaneus ($P \leqslant .001$ at 12 months for both; Fig. 2). The mean QUS SOS for the phalanges had decreased by 2.18% at 12 months versus baseline ($P < .001$). In addition, the stiffness index for calcaneal bone had decreased by 4.3% during 12 months ($P \leqslant .001$).

3.4. Biochemical markers of bone turnover

Although changes in biochemical markers of bone turnover are not validated surrogates for clinical outcomes, they may provide early evidence of bone loss. Among patients in the control group, biochemical markers for bone turnover remained stable (Fig. 3). However, patients who received AC chemotherapy had a significant increase in bone turnover as determined by elevation in PINP, CTX and BAP levels at the 6- and 12-month assessments ($P \leqslant .05$ for all) (Fig. 3). Women who received AC chemotherapy experienced a 93% increase in PINP, a 33% increase in CTX, and a 37% increase in BAP during 12 months (Fig. 4).

3.5. Correlations between bone loss and bone turnover markers

Independently, each of the methods for measuring bone loss (i.e. DXA and QUS) demonstrated that women experienced significant bone loss during the first 12 months after receiving

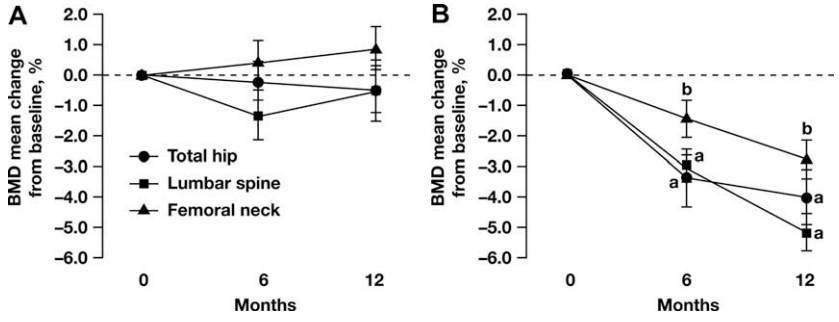

Fig. 1 – Percentage changes in bone mineral density (BMD) from baseline using dual-energy X-ray absorptiometry. Percentage changes in BMD were calculated at 6 and 12 months in (A) controls and (B) breast cancer patients receiving chemotherapy. Error bars represent the standard error of the mean. (a) $P < .001$ versus baseline; (b) $P < .02$ versus baseline.

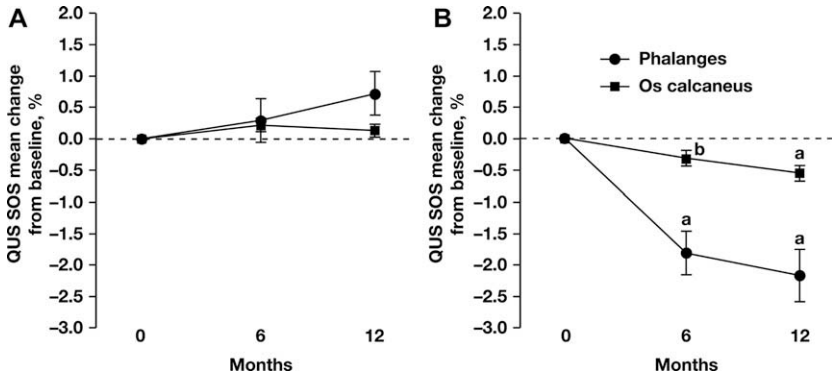

Fig. 2 – Percentage changes in the speed of sound (SOS, m/s) from baseline using quantitative ultrasonometry (QUS). Percentage changes in SOS at calcaneus and phalanges were calculated at 6 and 12 months in (A) controls and (B) breast cancer patients receiving chemotherapy. Error bars represent the standard error of the mean. (a) $P \leqslant .001$ versus baseline; (b) $P = .013$ versus baseline.

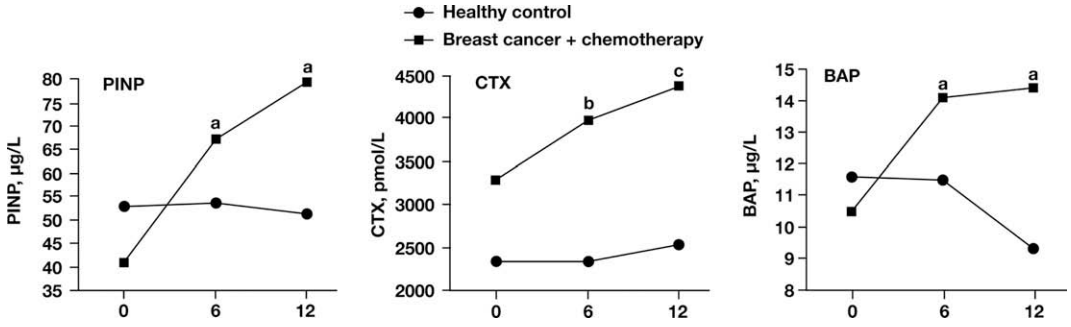

Fig. 3 – Biochemical markers of bone metabolism at baseline, 6 and 12 months. PINP, N-terminal propeptide of type I procollagen; CTX, C-telopeptide of type I collagen; BAP, bone-specific alkaline phosphatase. (a) $P \leqslant .001$; (b) $P \leqslant .05$ and (c) $P \leqslant .005$.

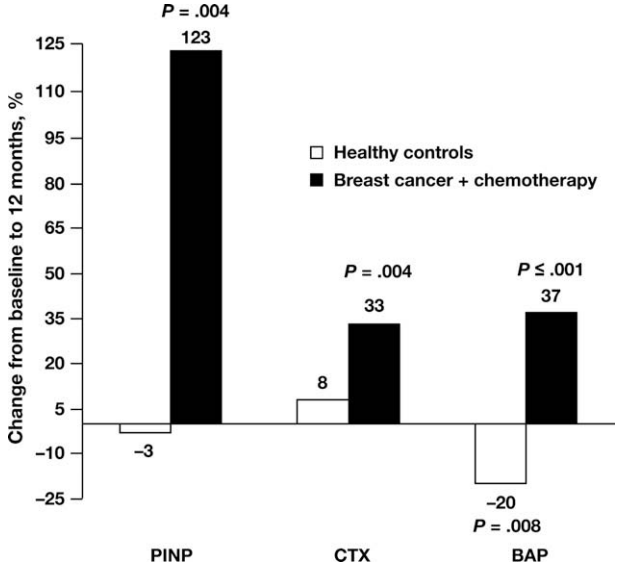

Fig. 4 – Percentage change in bone marker levels from baseline to 12 months. PINP, N-terminal propeptide of type I procollagen; CTX, C-telopeptide of type I collagen; BAP, bone-specific alkaline phosphatase. P values are for Wilcoxon test.

AC chemotherapy. Spearman's rank correlation coefficients (ρ_s) between DXA and QUS, and between DXA and bone marker levels revealed significant correlations (Table 2). Overall, an analysis that included all data from both healthy controls and women with breast cancer revealed that there were statistically significant positive correlations between the QUS SOS at the phalanges and DXA BMD measurements at the total hip ($\rho_s = 0.350$; $P < .01$), femoral neck ($\rho_s = 0.376$; $P < .01$) and lumbar spine ($\rho_s = 0.306$; $P < .01$; Table 2). In contrast, there were negative correlations between DXA BMD changes at each site and bone marker levels (PINP, CTX and BAP), indicating that bone marker levels were increasing as BMD was decreasing. Among women with breast cancer receiving AC chemotherapy, the correlations between QUS SOS at the phalanges and DXA BMD measurements were positive at baseline, 6 months and 12 months (Table 3). In addition, stepwise discrimination analyses indicate that QUS measurements were consistent with DXA measurements in the majority of patients (data not shown).

3.6. *Transitions between BMD categories*

Women in the study were categorised according to World Health Organisation clinical thresholds for normal BMD (*T*-score $\geqslant -1$), osteopaenia (*T*-score < -1 and > -2.5), and osteo-

Table 2 – Spearman's rank correlation coefficients (ρ_s) between DXA BMD and QUS SOS and bone marker measurements in healthy women and women with breast cancer.[a]

DXA BMD location	Phalanges, ρ_s (*P* value)	PINP, ρ_s (*P* value)	CTX, ρ_s (*P* value)	BAP, ρ_s (*P* value)
Total hip	0.350 (<.01)	–0.295 (<.01)	–0.329 (<.01)	–0.149 (.015)
Femoral neck	0.376 (<.01)	–0.186 (.014)	–0.280 (<.01)	–0.162 (.008)
Lumbar spine	0.306 (<.01)	–0.168 (.027)	–0.266 (<.01)	–0.144 (.018)

a For all measurements at all timepoints. DXA, dual-energy X-ray absorptiometry; BMD, bone mineral density; QUS, quantitative ultrasonometry; SOS, speed of sound; PINP, N-terminal propeptide of type I procollagen; CTX, C-telopeptide of type I collagen; BAP, bone-specific alkaline phosphatase.

Table 3 – Spearman's rank correlation coefficients (ρ_s) between DXA BMD and QUS SOS measurements in women with breast cancer.

DXA BMD location	QUS SOS phalanges, ρ_s (*P* value)		
	Baseline	6 months	12 months
Total hip	0.287 (.041)	0.245 (.083)	0.245 (.083)
Femoral neck	0.331 (.018)	0.321 (.022)	0.321 (.022)
Lumbar spine	0.302 (.031)	0.397 (.004)	0.397 (.004)

DXA, dual-energy X-ray absorptiometry; BMD, bone mineral density; QUS, quantitative ultrasonometry; SOS, speed of sound.

porosis (*T*-score $\leqslant$ –2.5)[28] using DXA (lumbar spine) and QUS (phalanges) data. In the healthy control group, the relative proportions of normal, osteopaenic and osteoporotic women remained relatively constant during the study (Fig. 5A and B). Among women with breast cancer receiving AC chemotherapy, the proportion of women with osteopaenic BMD increased from 23.5% at baseline to 39.2% at 12 months using DXA measurements (Fig. 5A), and from 35.3% at baseline to 56% at 12 months using QUS measurements (Fig. 5B). Although a larger proportion of women were categorised as osteopaenic or osteoporotic using the QUS method, both methods for measuring BMD identified approximately a 60% relative increase in the proportion of women with osteopaenia in the breast cancer group. Similar changes in *T*-scores over time were seen at the femoral neck and total hip, as well as at the calcaneus (data not shown).

4. Discussion

This study confirmed the deleterious effects of chemotherapy on spine and hip BMD as measured by DXA and for the first time demonstrated the adverse effects of chemotherapy on bone by QUS of the phalanges and calcaneus. Adjuvant AC chemotherapy was associated with a significant increase in markers of bone resorption and 5.2% and 4% decreases in BMD at the lumbar spine and total hip, respectively. Spearman's correlation analyses indicate that the bone loss measured by DXA correlates with the bone loss identified using QUS. Furthermore, both methods for measuring bone loss indicate that women receiving AC chemotherapy experience a shift from normal to osteopaenic *T*-scores within 12 months. These results, taken together suggest that premenopausal patients who receive chemotherapy for breast cancer may have an increased long-term risk for fractures and will require appropriate therapy to prevent bone loss.

Various factors may contribute to the bone loss observed in pre-menopausal women receiving cytotoxic chemotherapy for breast cancer. Chemotherapy-associated loss of ovarian function results in a rapid decline in circulating oestrogen levels, and chemotherapeutic drugs may exert direct negative effects on osteoblasts and osteoclasts. The direct effects of agents such as methotrexate, doxorubicin and cisplatin on bone turnover, particularly through effects on osteoblasts, have been demonstrated in animal models and *in vitro* studies.[14,29–32] Furthermore, the accelerated bone turnover associated with chemotherapy-induced bone loss has been demonstrated in a previous clinical study that monitored the effect of chemotherapy on biochemical markers such as PINP.[33] In this study, early increases in bone marker levels were predictive of BMD losses observed 12 months later. Our study confirms the adverse effects of AC chemotherapy on bone turnover as demonstrated by the significant increase in serum CTX, BAP and PINP levels during a 12-month period ($P \leqslant .05$ for all). Although bone markers have not yet been established as surrogates of bone loss during cancer therapy, their utility in monitoring bone resorption during the treatment of osteoporosis is well known.[34] With further study, bone markers may ultimately be used to direct antiresorptive therapy in patients with early breast cancer. Indeed, the ongoing BISMARK trial will examine bone marker-directed bisphosphonate therapy in women with breast cancer metastatic to bone.[35]

The results of the current study are consistent with prior studies that have examined the influence of chemotherapy on BMD. In a study of 35 pre-menopausal women with breast cancer who received either cyclophosphamide, methotrexate and fluorouracil (CMF) or cyclophosphamide with doxorubicin, patients experienced 7.7% and 4.6% decreases in lumbar spine and femoral neck BMD, respectively, after 1 year.[18] Bone mineral density losses of 6.8% and 1.9% at the spine and hip

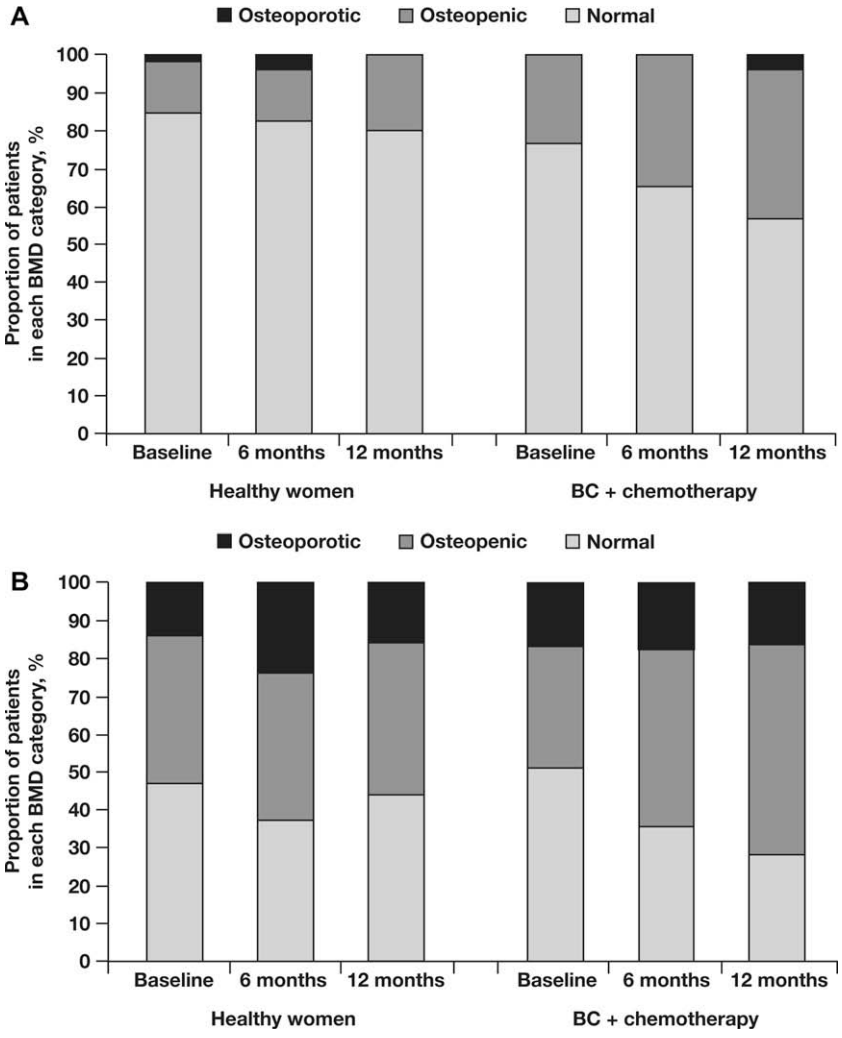

Fig. 5 – Proportions of patients who had normal, osteopaenic and osteoporotic BMD at baseline, 6 and 12 months. (A) T-score categories based on dual-energy X-ray absorptiometry bone mineral density (BMD) measurements. (B) T-score categories based on quantitative ultrasonometry speed of sound measurements. BC, breast cancer.

were reported in 22 pre-menopausal women with breast cancer who developed amenorrhoea after receiving CMF in the placebo arm of a trial examining clodronate for the prevention of bone loss.[17] In a large trial of bisphosphonate therapy for the prevention of bone loss, 155 women with breast cancer who received chemotherapy alone lost 1.9% in spine BMD after 2 years.[16] Moreover, hormonal therapy for breast cancer is known to cause significant bone loss, especially in pre-menopausal women, and the effects of adjuvant hormone therapy on bone appear to be just as dramatic and long-lasting as the bone loss associated with chemotherapy. For example, pre-menopausal women with breast cancer who received either CMF chemotherapy or goserelin, an agent that reversibly suppresses ovarian function, had dramatic bone loss.[15] After 2 years, lumbar spine BMD was significantly reduced in patients receiving goserelin as well as those receiving CMF (–10.5% and –6.5%, respectively; $P = .0005$ for between-group comparison). Although there was partial recovery of BMD associated with return of ovarian function in approximately 70% of goserelin-treated patients, no recovery of BMD was observed in patients who received CMF. Because many women with oestrogen receptor-positive breast cancer who receive chemotherapy also receive tamoxifen for up to 5 years, the effects of tamoxifen on bone loss are also important. In a trial of pre-menopausal women who received adjuvant chemotherapy followed by tamoxifen ($n = 88$) or no hormone therapy ($n = 23$), patients who received tamoxifen and retained ovarian function lost more BMD than patients who had lost ovarian function.[19] Overall, the available data suggest that both chemotherapy and hormonal therapy for breast cancer can have a negative influence on BMD, especially in pre-menopausal women. Given that the majority of women diagnosed with early breast cancer will survive for many years after completing treatment, it is important to address bone health during the initial chemotherapy.

In an effort to prevent the adverse effects of breast cancer therapy on bone, bisphosphonates have been studied in pre-menopausal women receiving cytotoxic chemotherapy. For example, one trial examined the efficacy of risedronate for prevention of bone loss in women with breast cancer and chemotherapy-induced ovarian failure. Bone mineral density at the lumbar spine was stable (0.3%) in patients receiving

risedronate for 1 year compared with a loss of 1.4% ($P = .018$) in patients who did not receive bisphosphonates.[36] In another trial, 73 women receiving CMF for breast cancer were randomised to receive oral clodronate or no bisphosphonate.[37] Patients in the control group had a 7.4% decrease in lumbar spine BMD at 3 years and a 9.7% decrease at 5 years, compared with baseline. Patients who developed chemotherapy-related ovarian failure had a much greater bone loss at 5 years than those who retained ovarian function (–10.4% and –1.3%, respectively).[37] Clodronate slowed bone loss in this study, but did not prevent it. These results suggest that oral bisphosphonates may reduce, but do not entirely prevent, chemotherapy-associated bone loss. Therefore, more efficacious IV bisphosphonates have been examined in this setting. The effect of zoledronic acid on bone loss was studied in 401 women enrolled in a study of the efficacy of endocrine therapy with tamoxifen or anastrozole in combination with goserelin for hormone-responsive breast cancer in pre-menopausal women.[38] At 36 months, a significant decrease in lumbar spine BMD was observed in patients receiving tamoxifen (–11.3%; $P < .0001$), but not in patients receiving tamoxifen and zoledronic acid (4 mg every 6 months). Similarly, patients receiving anastrozole had a 13.6% decrease in lumbar spine BMD that was not seen in patients receiving anastrozole and zoledronic acid. At a median follow-up of 60 months (24 months after ending adjuvant therapy), lumbar spine BMD had improved from the 36-month levels in patients receiving endocrine therapy alone, but remained significantly below baseline (–6.3%; $P = .001$; compared with baseline). In contrast, BMD at 60 months remained significantly better versus baseline in patients who received zoledronic acid in addition to endocrine therapy (+4%; $P = .02$; compared with baseline).[39] This study illustrates that concomitant treatment with zoledronic acid prevents on-treatment bone loss and improves BMD in long-term follow-up regardless of the type of hormone therapy. A second trial is investigating the efficacy of zoledronic acid (4 mg every 3 months) for prevention of bone loss among pre-menopausal women with breast cancer who develop ovarian failure because of adjuvant chemotherapy. In the first results from this study, lumbar spine BMD data were available for 166 patients who met the predetermined criteria for ovarian failure at 12 months.[40] Patients receiving chemotherapy alone ($n = 85$) had lower lumbar spine BMD (–6.6% on average) compared with baseline, whereas those receiving zoledronic acid in addition to chemotherapy ($n = 81$) had an average BMD increase of 2.2% ($P < .0001$ versus chemotherapy alone group). The inclusion of tamoxifen in the treatment regimen led to smaller BMD losses (BMD change from baseline at 12 months was –9.5% among patients receiving chemotherapy alone, versus –4.3% among patients receiving chemotherapy and tamoxifen), but could not completely prevent ovarian failure-induced decreases in BMD without the addition of zoledronic acid. Concomitant zoledronic acid treatment prevented such BMD loss and improved BMD above baseline in both groups.[40]

In conclusion, it is now clear that chemotherapy-induced bone loss constitutes a significant problem in pre-menopausal women with breast cancer. The dramatic loss of BMD and the associated long-term fracture risk underscore the need for preventive measures in this at-risk patient population. Although DXA is the current gold standard for assessing BMD, we have now established the utility of QUS for assessing changes in bone metabolism in these patients. Additionally, we have confirmed that biochemical markers of bone turnover can be useful surrogate measures to evaluate the detrimental effect of chemotherapy on bone. Zoledronic acid has been demonstrated to prevent bone loss in patients receiving hormonal therapy for breast cancer, and early results indicate similar efficacy in preventing bone loss among patients with chemotherapy-induced ovarian failure. It is likely that development of a strategy to manage chemotherapy-associated bone loss with bisphosphonates such as zoledronic acid will lead to better long-term quality of life for pre-menopausal patients with breast cancer.

Conflict of interest statement

Dr. Hadji has received honoraria, unrestricted educational grants, and research funding from the following companies: Amgen, AstraZeneca, Eli Lilly, GlaxoSmithKline, Novartis, Novo Nordisk, Organon, Pfizer, Procter & Gamble, Roche, Sanofi Aventis, Solvay and Wyeth. May Ziller, Carolin Maskow, Ute Albert and Mathais Kalder have no conflicts of interest.

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