Aim of this study was to examine the effects of aromatase inhibitors (AIs), which are used in every phase of breast cancer treatment, on the bone mineral density (BMD) of patients with early-stage breast cancer.
Material and methods: Menopausal female patients who were diagnosed with stages 1–3 breast cancer and who were planned for anastrazole or letrozole as adjuvant therapy were examined. After the patients' BMD was measured, 45 patients without osteoporosis were included in the study. Six months after AI therapy started, the patients' BMD was measured again.
Results: In this study, we tried to show that there was a statistical difference in the BMD of 45 patients before and 6 months after treatment. Among all measurements (femur and lumbar T-scores), the femur Z-score ($p = 0.52$) was the only score that was not statistically significant. Statistical significance ($p < 0.01$) was detected in comparative analysis of the other measurements. According to this analysis, a significant loss of BMD was seen even in the first six months after AI treatment was introduced.
Conclusions: Female patients with breast cancer are at higher risk for bone loss and fractures than healthy women. In this study, we showed the negative effects on BMD of aromatase inhibitor therapy, one of the main contributions to osteoporosis in women with breast cancer. This study is the first to quantify the short-term effect of AI treatment on BMD in postmenopausal women with breast cancer.

Key words: aromatase inhibitor, breast cancer, bone mineral density, osteoporosis.

Aromatase inhibitor treatment for breast cancer: short-term effect on bone health

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Introduction

Breast cancer (BC) is the most common type of cancer in women [1]. The life expectancy of patients with BC has increased in the last 10 years, linked to advances in imaging, diagnosis, and treatment. One of the most important reasons for the increase in life expectancy is the introduction of aromatase inhibitor (AI) use in treatment [2].

In menopausal women, circulating oestrogen is formed by the aromatisation of androgens to oestrogen in adipose, liver, and muscle tissue. The aromatase enzyme found in these tissues, a cytochrome p450 enzyme, catalyses the last stage of oestrogen synthesis. In addition, many breast tumour tissues have shown the presence of aromatase enzyme activity forming local oestrogen sources [3]. Aromatase inhibitor lowers oestrogen levels by blocking the cytochrome p450 enzyme. However, because AIs effectively deplete residual oestrogen levels, they are associated with accelerated bone loss and increased risk of fracture [4]. Although the type and duration of use are not clearly defined, AIs are recommended by standard treatment guidelines in one stage of adjuvant treatment of postmenopausal patients with breast cancer with positive hormone receptor (HR) [5].

Seventy-five per cent of the total bone density loss over a woman's lifetime occurs during the postmenopausal period. In the first 15–20 years of this period, 30% of the total bone density loss occurs [6]. Although 52% to 66% of this loss occurs due to oestrogen deficiency, the rest stems from aging [7]. An explicit decrease in bone mineral density (BMD) is observed along with a decrease in circulating oestrogen levels during the postmenopausal period due to the increased use of AI.

Intergroup exemestane studies (IES) [8] indicate that bone loss is relatively predictable, so the risk of developing osteoporosis while a patient is taking an aromatase inhibitor, before starting endocrine therapy, occurs after three years for women with normal BMD. In this study, in contrast to previous studies, we aim to show that the decrease in BMD related to AI treatment occurs even in the early stage of treatment.

Material and methods

The study population was selected from patients undergoing follow-up at the oncology department outpatient clinic of Kocaeli University Medical Faculty Hospital. The project was approved by the Kocaeli University Medical

Faculty Ethics Committee. Patients were informed about the tests, and written consent was obtained. In premenopausal women with breast cancer we prefer to use tamoxifen to protect the endometrium, but in postmenopausal women with breast cancer we use aromatase inhibitors. Postmenopausal patients with positive diagnosis of stage 1–3 breast cancer HR and planned AI (anastrazole, letrozole) adjuvant treatment were included in the study. Use of medications such as Coumadin, heparin, and steroids, metastasis found on second measurements, known rheumatic diseases, hyperthyroidism, severe chronic diseases or malabsorption, and bisphosphonate and calcium use for osteoporosis diagnosis were exclusion criteria. Patients' BMD was measured before AI treatment. Patients without known osteoporosis were included in the study, and AI treatment began. Fifty patients were included in the study. During this period, no patient was given calcium or vitamin D for any reason. During follow-up, some patients were excluded from the study: four patients developed metastases; one patient developed arthralgia linked to medication, and AI treatment was discontinued. The BMD of the 45 patients remaining in the study at the end of the 6-month treatment was measured to determine the short-term effects of the treatment on BMD.

Bone mineral density measurements

In this study, a DEXA device, Hologic Discovery A(S/N 81053) QDR 4500 series, was used. The working principle of the device is as follows: Radiation first passes through a calibration disk containing the absorption material, and then the patient. Then values from the patient are rated according to the values from the absorption material. Problems due to variations in the energy spectrum are resolved by the internal automatic reference system. Bone mineral density was measured with the patient supine, as recommended by the manufacturer. The BMD measurement results were presented as the BMD, *T*-score, and *Z*-score using statistical concepts. The *Z*-score is defined as the standard deviation between the patient's bone mass compared with normal reference values for her gender and age. The *T*-score is defined as the standard deviation between the patient's bone mass and that of a young

adult with peak bone mass. Bone mineral density is given as BMD g/cm^2. According to World Health Organization guidelines, a *T*-score between −1.0 and −2.5 standard deviation (SD) compared to young adults is accepted as osteopaenia while a *T*-score value of −2.5 SD or lower compared to young adults is accepted as osteoporosis.

Statistical analysis

Results were evaluated using the program Statistical Package for Social Sciences (SPSS) 16.0. To compare the patients' initial readings with those at the end of the 6-month treatment, the paired sample *t*-test was used. To evaluate the patients' prognosis and BMD loss, the chi-squared test was used. A $p < 0.05$ value was accepted as statistically significant.

Results

The demographic characteristics of the 45 women with BC included in the BMD study are given in Table 1. Although the initial BMD readings, *T*-scores, and *Z*-scores of 19 patients were within normal intervals (42.4%), 26 patients had values compatible with osteopaenia (57.8%). The patients were followed up during AI treatment. The second DEXA readings were taken six months after the AI treatment started. The femur and lumbar *T*-scores, *Z*-scores, and BMD readings after the six-month treatment were compared with the first readings. When the results were compared, the patients' lumbar BMD, *T*-score, and *Z*-score differed significantly ($p < 0.01$). In addition, the femur BMD and *T*-score differed significantly ($p < 0.01$). Of the readings, only the femur *Z*-score was not statistically significant, but it had decreased ($p = 0.052$) (Table 2). The decreases in the patients' femur and lumbar *T*-scores after AI treatment are shown in Fig. 1.
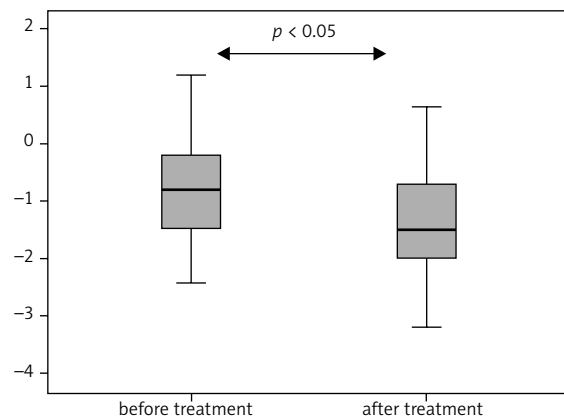
Table 1. Demographic characteristics of patients

Age (year)	58.1 ±8.8
BMI (kg/m²)	31.3 ±4.0
Age of menarche (years)	13.2 ±1.1
Duration of menopause (years)	9.5 ±7.5
Number of births	2.6 ±1.2

BMI – body mass index

Fig. 1. The decreases in the patients' femur and lumbar *T*-scores after AI treatment

Table 2. Bone mineral density values before and after treatment

	Lumbar *T*-score	Lumbar *Z*-score	Lumbar BMD (g/m²)	Femur *T*-score	Femur *Z*-score	Femur BMD (g/cm²)
Before treatment	−0.71 ±0.95	−0.01 ±1.02	1.011 ±0.161	−0.79 ±0.96	0.26 ±0.98	0.880 ±0.071
After treatment	−1.06 ±1.06	−0.30 ±0.15	0.947 ±0.023	−1.30 ±0.14	0.04 ±0.11	0.820 ±0.155
***P* value**	< 0.01	< 0.01	< 0.01	< 0.01	0.052	< 0.01

Table 3. Relationship between reduction in femur and lumbar BMD and prognostic factors

	Stage 1	Stage 2	P value	Grade 1	Grade 2–3	*P* value
Femur BMD	0.0622 ±0.070	0.0633 ±0.043	NS	0.0781 ±0.055	0.0530 ±0.067	NS
Lomber BMD	0.0684 ±0.073	0.0550 ±0.057	NS	0.0423 ±0.059	0.0785 ±0.072	NS

NS – not significant

Taking account of the patients' initial situation (normal, osteopaenia, osteoporosis), a McNemar analysis was conducted. According to the 6-month measurements for the 19 patients who had normal femur and lumbar *T*- and *Z*-scores on the initial measurements, 9 had developed osteopaenia and osteoporosis ($p < 0.05$). Of the patients with osteopaenia identified by the initial readings, seven had developed osteoporosis after six months of AI treatment ($p < 0.05$).

The relationship between the decrease in the patients' femur and lumbar BMD readings and prognostic factors is shown in Table 3. The increase in the patients' tumour stages and grades did not cause the decrease in the BMD measurements.

Discussion

The aim of this study was to show that osteoporosis develops in patients undergoing AI treatment for BC. This study showed that the patients' lumbar BMD, *T*-scores, and *Z*-scores decreased significantly. In addition, the patients' femur BMD and *T*-scores decreased significantly. In addition to showing the effect of AI treatment on the development of osteoporosis, as in previous studies, we demonstrated that even in the first six months of treatment there is a definite negative effect on bone health.

In recent years, many studies on the effects of BC on bones have been conducted. These studies have shown that BC has important effects on bone health. Many of the effects are due to chemotherapy (CT) and early induction of menopause due to ovarian ablation together with, in later periods, the start of AI treatment for HR-positive postmenopausal patients causing suppression of oestrogen after menopause. Bączyk *et al.* demonstrated that serum oestrogen levels have a protective effect on the BMD of postmenopausal women [9]. The imbalance between osteoclasts and osteoblasts leads to osteopaenia and, subsequently, osteoporosis. Oestrogen affects two receptors (ERα and ERβ) in osteoblasts, osteoclasts, and stromal cells of the bone marrow. In particular, oestrogen regulates osteoclasts [10] and inhibits the cytokines that activate bone resorption in osteoblasts and stromal cells in bone narrow [11]. We believe that aromatase inhibitors prevent the formation of oestrogen and lead to osteoporosis in this way.

Previous studies have shown that AI reduces BMD in postmenopausal women, but tamoxifen (TMX) had the opposite effect [12, 13]. Eastell *et al.*, in a study of patients with breast cancer after menopause, found that after two years of anastrazole and letrozole treatment hip and lumbar vertebra bone mineral density had decreased: the risk of hip fracture for women using anastrazole was 7%, and for women using letrozole 3.7%. The researchers concluded these results were linked to aromatase inhibition of residual circulating oestrogen in women after menopause and the removal of the antiresorptive effect of oestrogen on bone [14]. The Anastrazole, Tamoxifen, Alone or in Combination (ATAC) study showed the long-term effects (five years) of AI in women with breast cancer. That study compared anastrazole and tamoxifen [15]. In our study, we aimed to illustrate the negative effects of AI use on BMD in the light of previous studies. The measurements showed that the lumbar and femur BMD decreased, even within the first 6 months. When the BMD loss is evaluated with the patients' tumour stage and grade, we showed the decrease in the lumbar and femur *T*- and *Z*-score readings was independent of tumour stage and grade. These results support the view that the patients' bone loss was primarily due to AI treatment.

In this study, we observed that seven patients who had osteopaenia before AI treatment developed osteoporosis within six months. Based on these data, short-term AI treatment, especially in patients with osteopaenia, may cause osteoporosis. We also believe there is a definite increase in the incidence of fracture. Bajetta *et al.*, in a study of women with BC after menopause during three months of aromatase inhibitor treatment, found an increase in formation markers and resorption markers and showed that bone remodelling increased. This study supports the concern that letrozole, anastrazole, and exemestane use increases bone turnover markers and reduces BMD, increasing the risk of fracture [16]. Considering these data, especially for patients with osteopaenia, adding bisphosphonate to AI treatment is advantageous. The Austrian Breast and Colorectal Cancer Study Group (ABCSG) [17] and the Effect of monthly oral ibandronate on anastrozole-induced bone loss during adjuvant treatment for breast cancer (ARIBON) studies [18] on patients before menopause found that adding intravenous zoledronic acid [19], ibandronic acid, or risedronate [20] to anastrazole treatment preserved BMD and prevented bone loss. The most recent studies observed that even two years after ceasing bisphosphonate treatment, BMD was preserved in patients with BC [18]. Although similar studies state that bisphosphonate therapy is helpful for this patient group, another view for managing patients undergoing AI treatment has been proposed. Adequate intake of calcium and vitamin D, a healthy lifestyle, and regular (12–24 month) follow-up dual energy X-ray absorptiometry scanning should be routine. However, the role of prophylactic bisphosphonates is uncertain. The significance of the decrease in BMD due to AI treatment within the short period of our study (6 months) supports the proposal of applying bisphosphonate therapy to patients undergoing AI treatment.

In conclusion, this study is the first to quantify the short-term effect of AI treatment on BMD in postmeno-

pausal women with breast cancer. The most important point emphasised by this study is that the negative effect of treatment on bone health was definitively observed within the first six months. The severity of bone loss within this short period shows that more care must be taken in AI treatment of patients, especially regarding osteoporosis. For patients with osteopaenia, although adding bisphosphonate treatment from the beginning of treatment is known to reduce the risk of bone fractures, the topic is still controversial. All patients with BC should be carefully evaluated for osteoporosis. In particular, when AI treatment is to be started, patients' bone health should be more carefully examined. Patients with osteopaenia and osteoporosis should be closely monitored, and necessary treatment should be started as soon as possible to prevent the development of fracture risk in this patient group.

The authors declare no conflict of interest.

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