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Original Article

Bone Mineral Density Values Using Radiofrequency Echographic Multi-Spectrometry in Premenopausal Breast Cancer Patients Receiving Tamoxifen Therapy

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ABSTRACT

Background: Breast cancer (BC) is the most prevalent malignancy in women. Tamoxifen produces varying effects on the bone according to menopausal status. This study was performed at Adam Malik Hospital to analyze the risk factors for osteoporosis, focusing on bone mineral density (BMD) and length of tamoxifen therapy in premenopausal breast cancer patients. This research also used radiofrequency echographic multi-spectrometry (REMS) to evaluate BMD as a potential alternative to dual x-ray absorptiometry (DXA) in the diagnosis of osteoporosis patients.
Methods: This case-control study analyzed and interviewed 20 premenopausal breast cancer patients who received at least one year of tamoxifen therapy. The stadium of cancer, type of tamoxifen therapy, and BMD of each patient were determined using REMS.
Results: The study of 20 breast cancer patients showed a mean age of 50.4 ± 5.61 years. The average length of tamoxifen therapy was 2.65 years, with a standard deviation of 1.13 years. Most patients presented with osteopenia status, namely 16 patients (80%), whereas three patients (15%) of the total sample presented with osteoporosis. REMS showed excellent accuracy in distinguishing between various tissue types, providing detailed information on tissue composition and structure.
Conclusions: Based on the conducted research, it was determined that the use of tamoxifen for more than four years in premenopausal breast cancer patients influenced the incidence of osteoporosis. REMS shows potential as an alternative to DXA for the diagnosis of osteoporosis.

Keywords: Bone mineral density, Breast cancer, Human and medicine, Radiofrequency echographic multi-spectrometry, Tamoxifen

INTRODUCTION

Breast cancer is the most prevalent form of malignancy in women. Deaths due to breast cancer have also significantly increased in women. Globally, 2.3 million women had a new diagnosis of breast cancer in 2020, and 685,000 of those instances resulted in death. The incidence of breast cancer varies by region but is continuously increasing. Based on the present trajectory of breast cancer's morbidity and death, an estimated 2.64 million cases of breast cancer and 1.7 million deaths from the disease will occur by 2030, correspondingly. Age-standardized incidence rates in wealthy nations were 66.4/100,000 and in developing nations, 27.3/100,000. The prevalence of breast cancer is rising quickly, and the incidence rate has grown at 0.5% annually over the last 30 years, or 57.8%. Numerous factors may lead to breast cancer. Elements include hormone levels, environment, behavior, lifestyle, and genetics.[1,2]

The Indonesian Ministry of Health conducted national health research focused on cervical pre-cancerous lesions and breast tumors in 2016.

A total of 38,749 participants participated, with a response rate of 62.5% of the planned 70,000. The incidence of breast cancer was 8.1% (95% CI 7.4-8.8%). A greater prevalence was observed among women aged 35 to 44 years, who were employed, had never married, and held a higher education.[3] The prevalence of breast cancer at a young age in Adam Malik Hospital in 2013-2017 was 234 patients (15.2%), while at an old age was 1,309 patients (84.8%) with the conclusion that the prevalence of breast cancer at a young age is lower than breast cancer at an old age.[4]

One of the long-term consequences of breast cancer treatment is osteoporosis, which affects up to 80% of patients with bone density reduction. Women diagnosed with breast cancer, regardless of bone metastases, exhibit an elevated risk of developing new fractures compared to age-matched women without breast cancer.[4] Osteoporosis is diagnosed by evaluating bone mineral density (BMD) in the lumbar spine and femoral neck. Dual X-ray absorptiometry (DXA) is a technique frequently used to confirm the diagnosis of osteoporosis. Nonetheless, DXA possesses numerous limitations, such as a significant risk of false negative outcomes, the necessity for operation by a skilled individual, limited equipment portability, substantial costs, the requirement for specific patient positioning, and regulatory and legal obligations concerning ionizing radiation.[5] There are other limitations to DXA as well; according to a 2015 research, 90% of DXA tests included mistakes (including setup problems for the patient's location information, positioning issues, and analysis errors). For instance, osteoarthritis (OA), the most common cause of artifacts when using DXA, mainly in older patients; vertebroplasty, especially when it involves two or more lumbar vertebrae, limits the ability to obtain an adequate assessment of BMD using DXA; and aortic calcification can result in an overestimation of bone mineral density.[6]

A novel echographic method for the diagnosis of osteoporosis, Radiofrequency Echographic Multi-Spectrometry (REMS), has been recently developed and clinically validated in a single-center study. REMS exhibits a significant correlation with the associated BMD values, and the precise DXA values for each parameter are regarded as the current gold standard reference.[7] REMS is a portable technology free of radiation that can assess osteoporosis at the central regions including the femoral neck and lumbar vertebrae and presents potential advantages over DXA and other modalities. The automatic accounting for artifacts resulting from calcifications, osteophytes, vertebral fractures, metal structures, etc. is one of REMS's advantages of REMS over DXA and could result in more precise BMD measurements.[8]

Tamoxifen is among the most commonly used medications for endocrine therapy. It is a selective estrogen receptor modulator that could induce osteoporosis by causing estrogen insufficiency in premenopausal women while also providing a preventive effect in postmenopausal patients.[9] Tamoxifen produces varying effects on the bone according to menopausal status. Tamoxifen elevates bone density (about 1-2% annually) in postmenopausal women whereas it induces bone density reduction (around 1-2% annually) in premenopausal women.[10] For this reason, researchers are interested in examining premenopausal breast cancer patients who receive tamoxifen therapy at Adam Malik Hospital because there are no data on the BMD value of premenopausal breast cancer patients who receive tamoxifen therapy at Adam Malik Hospital.

MATERIAL AND METHODS

Study Design and Sampling

This study used a cross-sectional design and descriptive observational approach. Data were obtained from medical records and interviews that satisfied the inclusion criteria. The participants were patients who satisfied the inclusion criteria, namely premenopausal women with ER(+) and PR (+) having a history of breast cancer at Adam Malik Hospital, patients who had a history of tamoxifen

therapy for more than one year, and patients who provided informed consent for this research. The exclusion criteria for research subjects were patients with osteoporosis or bone metastases before starting tamoxifen therapy, patients with a history of using hormone replacement therapy, patients with routine vitamin D and calcium supplementation intake, patients with impaired kidney function, and patients with impaired parathyroid gland function. Ethical approval for this study was obtained from the Health Research Ethics Commission of the Faculty of Medicine at Universitas Sumatera Utara.

Data Collection

The study sample comprised breast cancer patients who sought treatment at the Adam Malik Hospital and fulfilled the inclusion and exclusion criteria. Sample collection was performed using consecutive sampling techniques. The collected data included the age, gender, education, working status, body mass index, and menopause status of the patients. Data were collected from February to April 2023 using a consecutive sampling technique. The stadium of the cancer and type of tamoxifen therapy administered to each patient were determined. Radiofrequency echographic multispectrometry (REMS) was performed to determine each patient's bone mineral density (BMD). The examination was performed using an REMS device. A probe with a thin layer of ultrasound gel was gradually moved along the axis of the spine starting from L1 to L4 for approximately 20 s, and the movement from one vertebra to another was signaled visually and audibly by the device. Data were then collected, tabulated, and statistically analyzed. The Lemeshow formula was used to determine the sample size used in this study, with the minimum sample being 17 patients.

Statistical Analysis

Data were analyzed descriptively to examine the frequency distribution of the research subjects according to the characteristics of the research sample. Univariate analysis was conducted, and the results are displayed in the frequency distribution table for each variable. Bone mineral density (BMD) levels are reported as Mean + SD when the data follows a normal distribution; if the data deviates from normality, it is expressed as median (min-max) for each group. The data analysis was conducted utilizing SPSS 22.0 (IBM SPSS Statistics, New York, USA).

RESULTS

Of the 33 identified premenopausal breast cancer patients who had received tamoxifen therapy, 13 were excluded: seven had a history of bone metastases before tamoxifen therapy, two had kidney impairment, and four had taken tamoxifen less than one year before the research started. As the study employed the Lemeshow formula with at least 17 patients, 20 patients who met the inclusion criteria were included.

The Shapiro-Wilk test for normality analysis revealed that age, height, and BMI were normally distributed, whereas BW was not normally distributed. The mean age was 50.4 ± 5.61 years. The median body weight was 63 kg, with the lowest value being 40 kg and the highest being 69 kg. The height was 155.86 ± 5.43 cm. The mean BMI was 23.57 ± 3.52 kg/cm2. In the categorical analysis of patients, most of the study samples were in the ideal group, namely, 12 people or 60%. Most patients, 18 (90%), had a high school education or) with 18 (90%) working as housewives. The average length of tamoxifen therapy in patients was 2.65 years, with a standard deviation of 1.13 years. Most patients were treated with a length therapy of two years followed by three years, seven patients and five patients, respectively (Table 1).

In this study, the clinical parameters of the study samples were analyzed descriptively. The study samples were from breast cancer patients treated with tamoxifen. At the Adam Malik Hospital, all patients underwent chemotherapy with a single tamoxifen regimen. REMS was performed to assess

BMD, and the bone density status of each patient was determined. REMS showed excellent accuracy in distinguishing between various tissue types, providing detailed information on tissue composition and structure.

In the data distribution analysis, both BMD and T-scores were not normally distributed in the Shapiro-Wilk test. The mean BMD was 0.83 ± 0.07. The mean T score was 2.03 ± 0.61, while the mean Z score was 0.94 ± 0.56. Most patients presented with osteopenia status, namely 16 patients (80%), and three patients, or 15% of the total sample, had osteoporosis (Table 2).

Bivariate statistical analyses were performed to evaluate the impact of the length of therapy on patient diagnosis. Considering that the length of the treatment variable was normally distributed with the length of therapy as an independent variable of more than two categories, the chi-square test was chosen to assess significance. It was found that there was a significant variation between the diagnosis of patients whose therapy was long, including recent starts (e.g., 1 year) with a p-value = 0.022 and Chi-Square Test were 17.91 (Table 3).

A bar chart was created to visualize the data, showing a decrease in the frequency of osteopenia over time, but the emergence of a diagnosis of osteoporosis as the length of therapy progressed (Figure 1). This indicates an increase in the incidence of osteoporosis as the duration of tamoxifen therapy continues.

Table 1. Demographic characteristics of the study participants

Parameter	Results
Age	50.4 ± 5.61 years
Length of therapy	2.65 ± 1.13 years
1 year	3 (15%)
2 years	7 (35%)
3 years	5 (25%)
4 years	4 (20%)
5 years	1 (5%)
Body weight	63 (40-69) kg
Body height	155.86 ± 5.43 cm
BMI	23.57 ± 3.52 kg/cm²
Underweight	3 (15%)
Ideal body weight	12 (60%)
Overweight	5 (25%)
Obesity	0 (0%)
Education	
Primary school	0 (0%)
Junior high school	0 (0%)
Senior high school	18 (90%)
Bachelor	2 (10%)
Job	
Housewife	18 (90%)
Non-housewife	2 (10%)
Total	20 (100%)

Table 2. Clinical characteristics of the study sample

Parameter	Results
Bone Mineral Density	0.83 ± 0.07
T-score	-2.03 ± 0.61
Z-score	-0.94 ± 0.56
Diagnosis, n (%)	
Normal	1 (5%)
Osteopenia	16 (80%)
Osteoporosis	3 (15%)
Total	20 (100%)

Table 3. Effect of length of tamoxifen therapy

Length of therapy	Normal	Osteopenia	Osteoporosis	p-value	X^{2*}
1 year	1 (5%)	2 (10%)	0 (0%)	0.022	17.91
2 years	0 (0%)	7 (35%)	0 (0%)		
3 years	0 (0%)	5 (25%)	0 (0%)		
4 years	0 (0%)	2 (10%)	2 (10%)		
5 years	0 (0%)	0 (0%)	1 (5%)		

*Chi Square Test

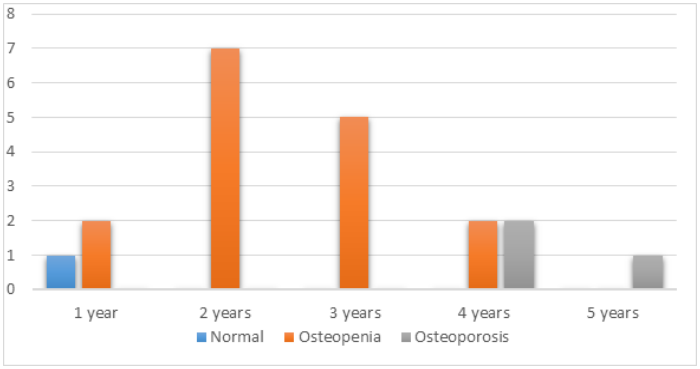

Figure 1. Bar chart length of tamoxifen therapy

DISCUSSION

The mean age of the samples in this research was 50.4 ± 5.61 years. The mean age at menopause was 46.93 ± 5.02 years. This aligns with studies conducted in Iran by Alizadeh et al., which indicated that the average patient age was 46.76 ± 1.19 years.[11] Breast cancer is the most prevalent form of malignancy in women with nearly 1.7 million new cases each year; approximately 25% of all cancers in women and 12% of all new cancer cases. Over the last 50 years, the spread of breast cancer worldwide has been mainly due to changes in human lifestyles. The prevalence of advanced-stage cancer treatment and the elevated mortality rate among diagnosed patients can be attributed to the absence of screening tests that enable early diagnosis. Screening mammography is essential for decreasing breast cancer mortality. Identifying a fraction of malignancies discovered before clinical manifestation increases the likelihood of therapies leading to long-term survival.

Tamoxifen is a prevalent adjuvant therapy for ER+ breast cancer. Tamoxifen is administered as a prodrug and requires hepatic metabolism to produce an active metabolite that exerts its estrogen antagonist activity. Thus, it is categorized as a selective estrogen receptor modulator (SERM) that inhibits estrogen binding to estrogen receptors and diminishes cell growth and viability. Consequently, tamoxifen is the mainstay hormonal treatment for premenopausal individuals with HR+ breast cancer.[12]

In this study, the mean BMD was 0.83 ± 0.07. The mean T score was 2.03 ± 0.61, while the mean Z score was 0.94 ± 0.56. Most patients presented with osteopenia status, namely 16 patients (80%), whereas three patients (15% of the total sample) had osteoporosis. This aligns with the findings of Cha et al., which indicated that after a three-year follow-up, tamoxifen adjuvant therapy reduced BMD with an SMD of 0.79 at the lumbar spine and 0.38 at the hip.[13] Patients undergoing a combinatorial treatment with chemotherapy or ovarian function suppression (OFS) demonstrated decreased bone density reduction at the lumbar spine in contrast to those receiving tamoxifen monotherapy.

This corresponds with two forthcoming clinical trials using a restricted cohort of patients (under 40 years old premenopausal women), which indicate that tamoxifen induces premenopausal women's bone density to decrease overall or at the lumbar spine. Tamoxifen administration had varying effects on BMD during short-term follow-up (<3 years), according to subgroup analysis: SMD = 0.03 to 0.41, in contrast to long-term follow-up (>3

years): SMD = 1.06. After three years follow-up, tamoxifen adjuvant therapy resulted in a decrease in bone mineral density with SMD = 1.17 at the lumbar spine and 0.66 at the pelvis.[4]

Tamoxifen may enhance or maintain bone density and reduce the incidence of fractures in postmenopausal women. Nonetheless, after two years of tamoxifen treatment, the advantage does not endure upon transitioning to aromatase inhibitors, suggesting a rebound effect. The cessation of tamoxifen treatment, along with the swift decline in estrogen levels induced by aromatase inhibitors, may accelerate BMD loss after the transition. McCaig et al. indicated that discontinuing tamoxifen and initiating an aromatase inhibitor led to a markedly larger enhancement in bone turnover compared to commencing an aromatase inhibitor in tamoxifen-naive patients.[10]

This study also shows, in accordance with research conducted by Iwaszkiewicz and Leszczyński, that radiofrequency echographic multi-spectrometry can be used as an alternative examination to evaluate BMD. The REMS examination, which focuses on the interaction of ultrasonic waves with bone tissue, facilitates assessment of BMD in grams per square centimeter (g/cm^2). This denotes a densitometric evaluation comparable to DXA. BMD evaluation using REMS was performed at the hip and lumbar spine. In the femoral neck, the diagnostic sensitivity and specificity of REMS for osteoporosis were 91.5% and 91.8%, respectively. In the lumbar spine, it was 91.7% and 92.0%, respectively. REMS demonstrated a substantial diagnostic concordance with DXA, with rates of 88.2% in the femoral neck and 88.8% in the lumbar spine.[5]

REMS is a portable technology free of radiation that can assess osteoporosis in the cen¬tral regions, including the femoral neck and lumbar ver¬tebrae, and presents potential advantages over DXA and other modalities. The automatic accounting for artifacts resulting from calcifications, osteophytes, vertebral fractures, metal structures, etc. is one of the advantages of REMS over DXA and could result in more precise BMD measurements. REMS also offers several notable advantages over DXA, particularly in terms of safety, non-invasiveness, and diagnostic versatility. Unlike DXA, which involves exposure to low doses of ionizing radiation, REMS utilizes high-frequency ultrasound and radiofrequency waves, ensuring a completely noninvasive and radiation-free procedure. This significantly reduces the potential risks for patients, particularly in those requiring frequent monitoring, such as children or pregnant women. Additionally, REMS provides detailed real-time imaging and comprehensive analysis of tissue composition, including fat, muscle, and bone structures, allowing for more accurate and dynamic assessments. In comparison, DXA primarily focuses on bone mineral density, limiting its diagnostic scope. Therefore, REMS presents a more comprehensive, safer, and versatile approach to assessing a wide range of medical conditions.[8] However, further research is needed to establish its diagnostic accuracy, long-term efficacy, and clinical validation compared to DXA. Therefore, while REMS is a promising tool, it currently serves more as a supplementary diagnostic method than as a complete replacement for DXA in diagnosing osteoporosis.

The disadvantage of this study is its single-center research model. A multicenter study can capture this phenomenon more comprehensively. Another drawback of this study is the research model, which is a descriptive analysis, and we did not have the BMD values of patients before receiving tamoxifen therapy. Bivariate statistical analysis of patients not taking tamoxifen can capture the phenomenon that occurs more definitively.

CONCLUSION

Based on the conducted research, the study was dominated by premenopausal breast cancer patients who received tamoxifen therapy with a mean age of 50.4 years. The mean BMD was 0.83 ±

0.07, mean T score was 2.03 ± 0.61, and mean Z score was 0.94 ± 0.56. It was determined that the use of tamoxifen for more than four years in premenopausal breast cancer patients influenced the incidence of osteoporosis. REMS shows potential as an alternative to DXA for the diagnosis of osteoporosis. A multicenter study with an analytic model is needed to obtain more comprehensive, holistic, and reliable results.

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DATA AVAILABILITY

Due to privacy restrictions, raw data cannot be made publicly available. However, aggregated and anonymized data are available from the corresponding author upon request.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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