Use of MR-based trabecular bone microstructure analysis at the distal radius for osteoporosis diagnostics: a study in post-menopausal women with breast cancer and treated with aromatase inhibitor

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Summary

Purpose. **Treatment with aromatase inhibitor (AI) is recommended for post-menopausal women with hormone-receptor positive breast cancer. However, AI therapy is known to induce bone loss leading to osteoporosis with an increased risk for fragility fractures. The purpose of this study was to investigate whether changes of magnetic resonance (MR)-based trabecular bone microstructure parameters as advanced imaging biomarker can already be detected in subjects with AI intake but still without evidence for osteoporosis according to dual energy X-ray absorptiometry (DXA)-based bone mineral density (BMD) measurements as current clinical gold standard.**
Methods. **Twenty-one postmenopausal women (62±6 years of age) with hormone-receptor positive breast cancer, ongoing treatment with aromatase inhibitor for 23±15 months, and no evidence for osteoporosis (current DXA T-score greater than -2.5) were recruited for this study. Eight young, healthy women (24±2 years of age) were included as controls. All subjects underwent 3 Tesla magnetic resonance imaging (MRI) of the distal radius to assess the trabecular bone microstructure.**
Results. **Trabecular bone microstructure parameters were not significantly (p>0.05) different between subjects with AI intake and controls, including apparent bone fraction (0.42±0.03 vs. 0.42±0.05), trabecular number (1.95±0.10 mm-1 *vs* 1.89±0.15 mm-1), trabecular separation (0.30±0.03 mm *vs* 0.31±0.06 mm), trabecular thickness (0.21±0.01 mm *vs* 0.22±0.02 mm), and fractal dimension (1.70±0.02 vs. 1.70±0.03).**
Conclusion. **These findings suggest that the initial deterioration of trabecular bone microstructure as measured by MRI and BMD loss as measured by DXA occur not sequentially but rather simultaneously. Thus, the use of MR-based trabecular bone microstructure assessment is limited as early diagnostic biomarker in this clinical setting.**

KEY WORDS: magnetic resonance imaging; osteoporosis; aromatase inhibitor; trabecular bone microstructure.

Introduction

Treatment with aromatase inhibitor (AI) is recommended for post-menopausal women with hormone-receptor positive breast cancer (1). However, AI therapy is known to induce bone loss leading to osteoporosis (2). Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing an individual to an increased risk of fracture (3). Osteoporotic fractures considerably reduce health related quality of life and are associated with an increased mortality later in life (4, 5). The assessment of osteoporosis associated fracture risk has traditionally relied on the assessment of bone mineral density (BMD) at the spine and hip by using dual-energy X-ray absorptiometry (DXA) (6). However, BMD values of subjects with and without osteoporotic fractures overlap (7). Therefore, it would be beneficial to establish early imaging biomarkers which could support clinicians in their treatment decision to prevent AI-induced bone loss, e.g. by antiresorptive therapies in conjunction with AI treatment (8).
High-resolution imaging techniques including high-resolution peripheral quantitative computed tomography (hr-pQCT), multi-detector computed tomography (MDCT), and magnetic resonance imaging (MRI) allow for an assessment of trabecular bone microstructure (9). Trabecular bone microstructure parameters have shown to improve the prediction of bone strength beyond DXA-based BMD (10). Furthermore, trabecular bone microstructure analysis revealed drug effects (e.g. teriparatide, alendronate, or risedronate) on bone strength which were partly not captured by BMD measurements (11-13). Due to these findings, it has been hypothesized that changes of trabecular bone microstructure might be already detectable in subjects who do not yet have evidence for osteoporosis according to DXA-based BMD measurements.
Therefore, the purpose of this study was to investigate whether changes of MR-based trabecular bone microstructure as advanced imaging biomarker could already be detected in post-menopausal women with hormone-receptor positive breast cancer, ongoing treatment with aromatase inhibitor, and no evidence for osteoporosis (defined by a current DXA T-score greater than -2.5).

Materials and methods

Subjects

The study was approved by the institutional Ethics Committee for Human Research. All subjects gave written informed consent before participation in the study.

Inclusion criteria were no history of fracture and no pathological bone changes like bone metastases, hematological or metabolic bone disorders. Twenty-one postmenopausal women (62±6 years of age) with hormone-receptor positive breast cancer, ongoing treatment with aromatase inhibitor (Arimidex®, Femara®, or Aromasin®), and no evidence for osteoporosis (current DXA measurement with T-score greater than -2.5) were recruited for this study. Eight, young, healthy women (24±2 years of age) were included as controls. No DXA measurements were available in the control cohort, since these measurements were not clinically indicated and therefore not approved by the institutional Ethics Committee for Human Research due to the radiation exposure.

MR Imaging

The left distal radius of all subjects was scanned by using a 3T MRI system (Philips Achieva, Eindhoven, Netherlands) and a four channel wrist coil (Medical Advances, Milwaukee, WI, USA). Subjects were positioned supine with the left forearm adjacent to the body and parallel to the magnet bore axis. Based on scout images in transverse, coronal, and sagittal planes, a 3D gradient echo sequence with a TE of 4.1 ms, TR of 11.9 ms, flip angle of 30°, matrix of 384 x 384, field of view (FOV) of 65 mm, in-plane resolution of 170 x 170 µm², and axial slice thickness of 340 µm was performed. Acquisition time amounted 7:00 min. Ninety-eight axial sections covering a range of 1.66 cm were acquired starting at the most proximal part of the distal joint line. A representative axial section of a 62 year old subject with AI intake is shown in Figure 1.

MR Image Analysis

MR images of the distal radii were transferred to a remote LINUX workstation. The distal radius was segmented using a fully automated, in-house developed seeded growing algorithm as previously described (14). Thus, the whole trabecular bone compartment excluding the cortical shell was segmented (Figure 2). Binarization of the MR images was required to calculate morphometric parameters of trabecular bone microstructure. For this purpose, a dual threshold algorithm was applied as outlined by Majumdar et al. (15). Four morphometric parameters were calculated in the segmented trabecular bone compartment in analogy to standard histomorphometry using the mean intercept length method (16): bone fraction (bone volume divided by total volume, BF=BV/TV), trabecular number (TbN; [mm^{-1}]), trabecular separation (TbSp; [mm]), and trabecular thickness (TbTh; [mm]). Parameters were labeled as apparent (app.) values, since they cannot depict the true trabecular bone microstructure due to the limited spatial resolution. Furthermore, fractal dimension (FD) as texture measurement of the trabecular bone microstructure was determined in the MR images using a box counting algorithm as previously described (14). Reproducibility errors for these trabecular bone microstructure measurements were reported previously and ranged from 0.38 to 5.80% (14).

Statistical Analysis

The statistical analyses were performed with SPSS (SPSS, Chicago, IL, USA). All tests were done using a two-sided

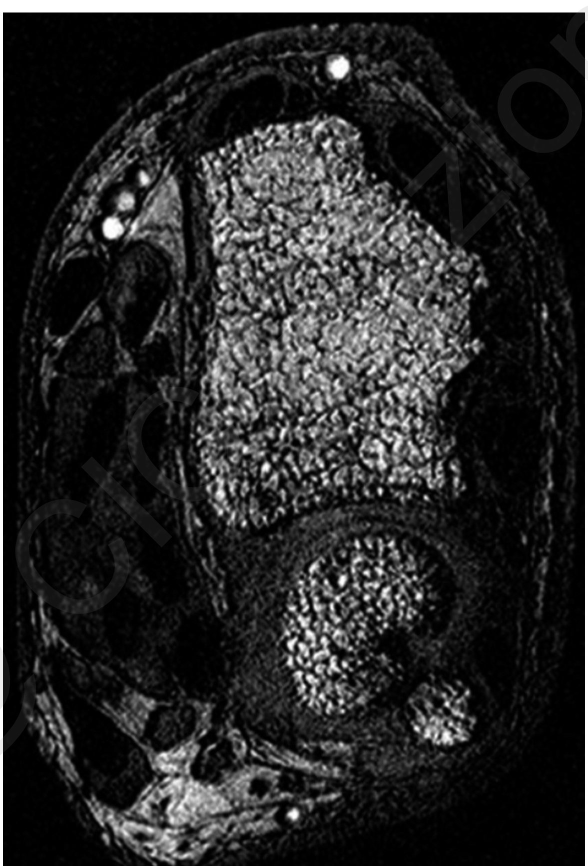

Figure 1 - Representative MR image of the distal radius of a 62-year-old subject with AI intake.

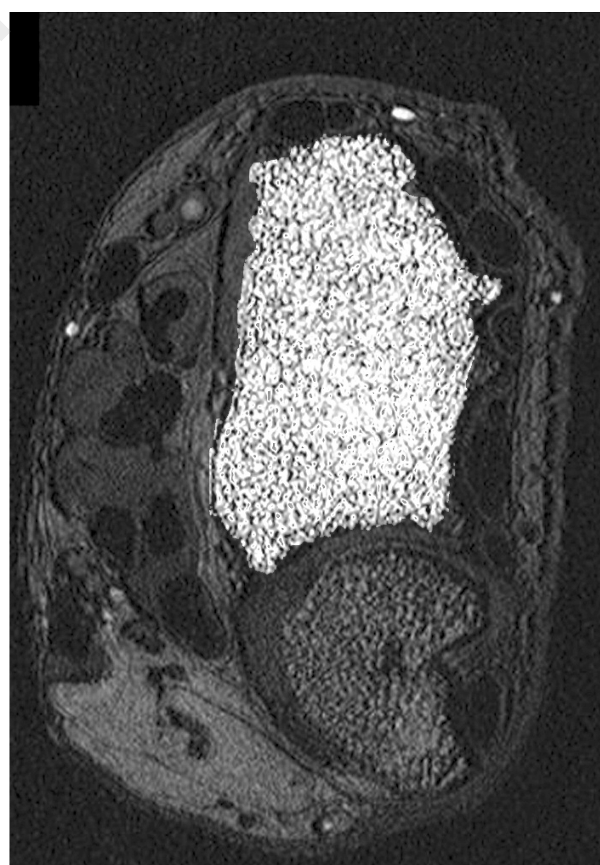

Figure 2 - Segmentation of the trabecular bone compartment of the distal radius based on a seeded growing algorithm (color-coded in white).

0.05 level of significance. The Kolmogorov-Smirnov test showed for most parameters no significant difference from a normal distribution (p>0.05). Therefore, trabecular bone microstructure parameters of the two groups were compared with t-tests. Additional adjustment for age and duration of AI intake by using multiple, logistic regression models did not change the p-values. Thus, only the p-values of the t-tests are reported in the results section. All values are represented as mean ± standard deviation. The association of bone microstructure parameters and duration of AI intake were determined with Pearson correlation coefficient r.

Results

The post-menopausal women had an ongoing AI treatment for 23±15 months. According to the lowest DXA-based T-score of the spine (L1-4), right and left hip, 5 postmenopausal women were classified as osteopenic and 16 post-menopausal women as normal. The averaged T-score of all post-menopausal women with AI intake amounted -0.8±0.8.

Differences between subjects with AI intake and controls were not statistically significant for app.BF (0.42±0.03 *vs* 0.42±0.05, p=0.796), app.TbN (1.95±0.10mm^{-1} *vs* 1.89±0.15mm^{-1}, p=0.185), app.TbSp (0.30±0.03 mm *vs* 0.31±0.06 mm, p=0.575), app.TbTh (0.21±0.01 mm *vs* 0.22±0.02 mm, p=0.101), and FD (1.70±0.02 *vs* 1.70±0.03, p=0.786) (Figure 3).

No significant correlations were observed between bone microstructure parameters and duration of AI intake (p>0.05).

Discussion

Post-menopausal women with hormone-receptor positive breast cancer, ongoing AI intake, and no evidence for osteoporosis according to DXA measurements showed no significantly different MR-based trabecular bone microstructure parameters at the distal radius compared to young, healthy controls.

AI therapy is known to induce bone loss leading to osteoporosis (2). DXA-based BMD values are commonly used by clinicians in their treatment decision to preserve AI-induced bone loss, e.g. by bisphosphonate prescription in conjunction with the AI (8). However, DXA-based BMD values of subjects with and without osteoporotic fractures overlap (7). Bone strength reflects the integration of BMD and bone microstructure (17). DXA-based BMD accounts for 60-70% of the variation in bone strength (18). However, BMD does not encompass bone microstructure. Clinical MRI systems are broadly available and allow for a non-invasive assessment of trabecular bone microstructure at the peripheral skeleton (10). MRI is advantageous comparted to hr-pQCT and MD-CT, since it lacks ionizing radiation. In previous studies, MR-based trabecular bone microstructure analysis at the distal radius improved the prediction of radial bone strength beyond DXA-based BMD (19, 20). Furthermore, these measurements significantly improved the diagnostic performance in differentiating postmenopausal women with and without osteoporotic vertebral fractures (21). Due to these findings, it has been hypothesized that subjects at high risk for bone loss may show changes of trabecular bone microstructure before DXA-based BMD loss can be detected. Post-menopausal women with breast cancer and AI intake represent such a patient population.

Therefore, this study investigated MR-based trabecular bone microstructure parameters at the distal radius in 21 post-menopausal women with breast cancer, ongoing AI intake, and no evidence for osteoporosis according to DXA. Trabecular bone microstructure measurements are known to be reproducible as reported previously (0.38 to 5.80%) (14). Compared to young, healthy controls, no significant differences in bone microstructure parameters were observed in subjects with AI intake. Thus, early changes of the trabecular bone microstructure could not be found in this study population with non-pathological BMD values. These findings reveal im-

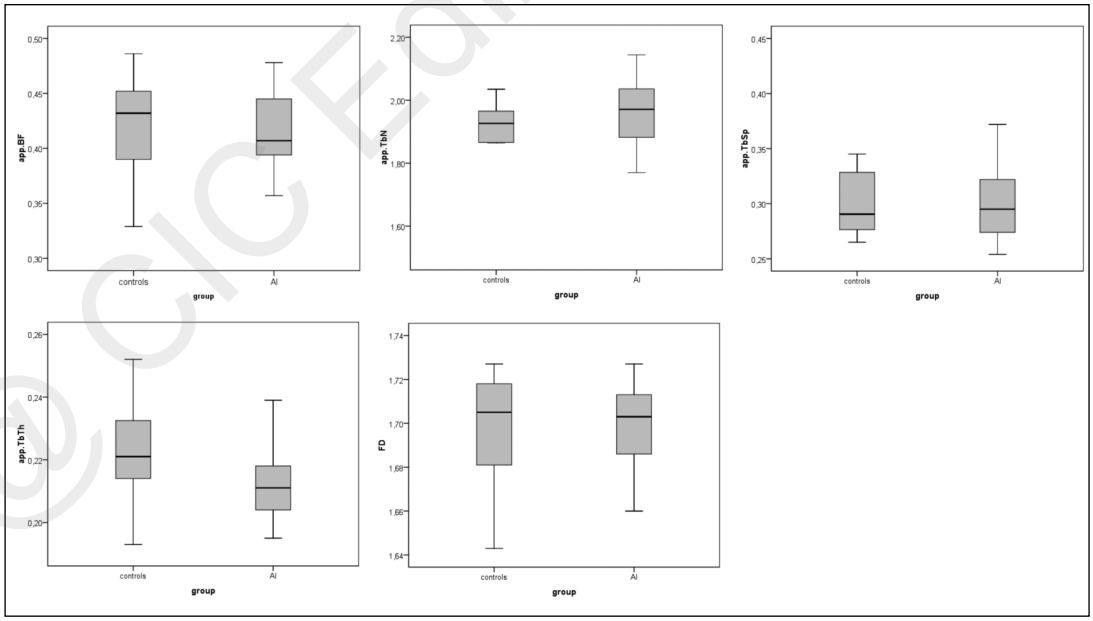

Figure 3 - Boxplots of apparent (app.) bone fraction (BF), trabecular number (TbN), trabecular separation (TbSp), trabecular thickness (TbTh), and fractal dimension (FD) in controls and subjects with aromatase inhibitor (AI) intake. Differences between the two groups were not statistically significant (p>0.05).

portant pathophysiological information about AI-induced osteoporosis. The present results suggest that initial deterioration of trabecular bone microstructure as measured by MRI and BMD loss as measured by DXA might not be occurring sequentially but rather simultaneously. To finally prove this hypothesis a longitudinal study would be needed to investigate changes of trabecular bone microstructure over time. The cross-sectional design is a limitation of our study. Our results suggest that MR-based trabecular bone microstructure analysis at the distal radius does not show advantages compared to DXA and therefore may not be suitable as early diagnostic biomarker in the clinical setting of subjects with AI intake but no evidence for osteoporosis according to DXA. These are important findings, since trabecular bone microstructure analysis has shown to be useful by revealing drug effects (e.g. teriparatide, alendronate, or risedronate) on bone strength which were partly not captured by BMD measurements (11-13).

In conclusion, early changes of the trabecular bone microstructure were not found in subjects with ongoing AI intake but still without evidence for osteoporosis according to DXA. Initial deterioration of trabecular bone microstructure as measured by MRI and BMD loss as measured by DXA might not be occurring sequentially but rather simultaneously. Future studies with longitudinal study design are needed to investigate this issue in more detail.

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Conflict of Interest

The Authors declare that they have no conflict of interest.

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