High-resolution MRI and micro-FE for the evaluation of changes in calcaneal bone mechanical properties in postmenopausal women after one year of idoxifene treatment

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Introduction

Current methods for the assessment of fracture risk in osteoporosis are primarily based on bone mineral density (BMD) measurements. The mechanical properties of bones, however, are not only related to its density, but also to its internal architecture and its tissue properties. A non-invasive measurement of bone mechanical properties that accounts for the in-vivo bone internal architecture would be of great value for improving the assessment of fracture risk and for the evaluation of the efficacy of drug treatments in osteoporotic patients. Accounting for bone architecture is a prerequisite for a better evaluation of cancellous bone mechanical properties. Recently, new micro-finite element (μFE) techniques have been introduced to directly quantify cancellous bone mechanical properties as they relate to its trabecular architecture, which is accessed by high-resolution 3D magnetic resonance (MR) images (van Rietbergen et al., 1998). Recent studies demonstrated that such analyses can provide very detailed information about in-vivo bone anisotropic mechanical properties and can identify differences between osteopenic and healthy groups in cross sectional analyses (Newitt et al., 2001, 2001b).

The purpose of this study was to investigate if μFE analyses based on in-vivo MR images can detect significant changes in cancellous bone mechanical properties during long-term longitudinal clinical studies that are aimed at evaluating the efficacy of drugs for the treatment of osteoporosis.

Methods

The drug investigated in this study was idoxifene, a selective estrogen receptor modulator that reduces bone turnover in osteopenic postmenopausal women (MacDonald et al., 2000). A subset of 56 subjects participating in a large randomized double blind multicenter study investigating the effect of idoxifene on lumbar spine BMD, were recruited for MR imaging and DEXA BMD measurement of the calcaneus. All subjects in the subset were postmenopausal and received 500 mg/day of elemental calcium and either a placebo (n=18), 5mg/day (n=23) or 10 mg/day (n=15) of idoxifene. MR-images were acquired at baseline and after one year of treatment with a 1.5 Tesla whole-body scanner using special coils and a high-resolution modified fast gradient echo sequence (Ouyang et al., 1997). Spatial resolution for the heel images was 195 microns in-plane and 500 microns in slice direction. Using a fully automated procedure, a Volume of Interest (VOI) of cancellous bone of 19x19x10 mm was selected at the center of the calcaneus (Fig. 1). A reference threshold criterion based on fat and bone regions intensities was determined as a starting point for image segmentation and to calculate a reference volume fraction BV/TV of the VOI. An iterative threshold

Fig. 1 Overview of the micro-FE approach.
procedure (Ulrich et al., 1998) was then used to segment the images such that a well connected reconstructions results with a BV/TV matching the reference value. Segmented reconstructions were converted to FE-models from which the orthotropic elastic properties of the VOI's were calculated (van Rietbergen et al., 1996). Elastic properties were quantified by the 3 longitudinal moduli (E, E2, E3), the 3 shear moduli (G12,G13,G23) and the 3 anisotropy ratios (E2/E1, E3/E1, E3/E2) and sorted such that E3>E2>E1. A paired Wilcoxon signed rank test was used to investigate if significant changes from baseline could be detected after the treatment period of one year for the treated groups and for the placebo group. A Kruskal-Wallis test was used to test if significant differences between groups could be detected.

Results

There were no significant differences between the mean changes in the treated groups and the placebo group for any of the investigated parameters. There were, however, significant changes from baseline within groups after one year of treatment, but only for the treated groups (Fig. 2). Values at one year for the placebo group were not significantly different from baseline for any parameter. For the treated groups, changes significantly different from baseline were found for the highest longitudinal modulus E1 in the 5 mg group and for the lowest modulus E3 in the 5 mg and 10 mg group. Significant changes from baseline were also found for all shear moduli in the 5 mg group and for G23 in the 10 mg group. Predominant changes for the treated groups were found for the smallest longitudinal modulus E3, which increased by 20-31% and for the shear moduli in the third direction that increased by 14-24%.

No significant changes were found for the BMD values measured from the DEXA scans of the calcaneus nor for changes in the reference BV/TV determined from the MR-images on which the micro-FE models were based (Fig. 3). One-year values for anisotropy ratios were significantly different from baseline for all groups, including the placebo group (Fig. 4). In all groups the anisotropy ratio was reduced after one year of treatment, with the largest reduction for the placebo group. A dose responsive change in anisotropy ratios was seen with the smallest reduction being seen in the 10 mg cohort.

Discussion

Significant changes in mechanical parameters were obtained for the treated groups whereas no significant change in bone mass was found. Consequently, the application of these techniques may increase the clinical significance of these trials. In addition, the methods can provide direct and very detailed information about mechanical parameters, which are the most relevant parameters given the fact that it is the decreased bone strength caused by the pathophysiological changes of osteoporosis that leads to bone fractures. The fact that no significant changes were found between the treated groups and the placebo group for any of the investigated parameter is likely due to the sample size, the large heterogeneity in the placebo group, the relatively short follow-up period of one year and the small effect of idoxifene on systemic

![Fig. 2 Changes in FE-calculated elastic properties after one year of treatment](image1)

![Fig. 3 Changes in BMD and BV/TV after one year of treatment](image2)
bone loss after one year (approximately 2% increase from placebo at the lumbar spine, MacDonald et al, 2000).

The trend to an increase from baseline for the mean of the BV/TV calculated from the MR images for all groups is unexpected, given the osteopenic subjects, and is not supported by the calcaneal DEXA BMD measurements that show a trend to a reduced bone mass. This trend to increased BV/TV, however, is likely due to the fact that changes in BV/TV and mechanical parameters were close to the limit of reproducibility of the method (Newitt et al., 2001a) and thus might reflect an overestimation of bone mass for the one-year images. However, since groups were randomized and all treated in the same way, the results for all groups would be affected to the same extent and this effect would not affect our main conclusion with regard to the improved significance of the results. Since the calculated elastic constants are dependent on the bone volume fraction calculated from the MR-images (BV/TV), the changes in elastic constants show the same trends as those in the BV/TV. The elastic anisotropy ratios, however, being dimensionless parameters, are much less dependent on (uncertainties in) the volume fraction. It can be seen that these parameters show a dose dependent response (Fig. 4). The fact that the anisotropy ratios are not much dependent on the bone volume fraction can also explain why significant changes in the elastic anisotropy ratios can exist for groups in which no significant changes in elastic moduli could be detected.

The finding that there was much more spread in the data for the placebo group than for the treated groups could suggest that the idoxifene treatment inhibits drastic changes in the trabecular architecture and thus may have beneficial effects on an individual as well as a population level. This suggestion would be supported by the fact that changes in bone anisotropy were smaller in the treated bone than in the placebo group. Given the limited population size, however, we can only speculate at this point. The present study is the first demonstration that longitudinal changes in bone mechanical properties due to trabecular micro-architectural changes may be quantified in long-term clinical studies. Important advantages over analysis methods based on BMD are that the approach presented here provides information about changes that are specific to cancellous bone regions and that the parameters detected in the micro-FE analyses provide a direct measure of bone mechanical properties.

**References**


MacDonald B et al. *Proceedings of the ASBMR*, 2000


Newitt DC et al. (in preparation) 2001b


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