Predictive value of femoral head heterogeneity for fracture risk

E. Tancka⁎, A.D. Bakkerb, S. Kregtinga, B. Cornelissen a, J. Klein-Nulend b, B. Van Rietbergenc

Abstract

Osteoporosis (OP) is characterized by low bone mass and weak bone structure, which results in increased fracture risk. It has been suggested that osteoporotic bone is strongly adapted to the main loading direction and less adapted to the other directions. In this study, we hypothesized that osteoporotic femoral heads have 1) an increased anisotropy; 2) a more heterogenic distribution of bone volume fraction (BV/TV) throughout the femoral head; and, 3) a more heterogenic distribution of the trabecular thickness (Tb.Th.) throughout the femoral head, as compared to non-osteoporotic bone. To test these hypotheses, we used 7 osteoporotic femoral heads from patients who fractured their femoral neck and 7 non-fractured femoral heads from patients with osteoarthritis (OA). Bone structural parameters from the entire trabecular region were analyzed using microCT. We found that the degree of anisotropy was higher in the fractured femoral heads, i.e. 1.72, compared to a value of 1.61 in the non-fractured femoral heads. The BV/TV and Tb.Th. and their variations throughout the femoral head, however, were all significantly lower in the fractured group. Hence, the first hypothesis was confirmed, whereas the other two were rejected. Interestingly, the variation of Tb.Th. throughout the femoral head provided a 100% discrimination between the OP and OA groups, i.e. for the same BV/TV, all fractured cases had a less heterogenic distribution. In conclusion, our results suggest that bone loss in OP takes place uniformly throughout the femoral head, leading to an overall decrease in bone mass and trabecular thickness. Furthermore, the variation of Tb.Th. in the femoral head could be an interesting parameter to improve the prediction of fracture risk in the proximal femur.

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Introduction

Bone adapts its mass and micro-architecture to mechanical loading [1–6]. In normal situations, this adaptive process ensures a good balance between bone mass and strength: bone mass increases if the mechanical load increases by, for instance, physical activity [1], and decreases by immobilization.

In the case of osteoporosis (OP), the load adaptive process fails. Osteoporosis is an age-related skeletal disease that is characterized by low bone mass and a deteriorated bone structure. Especially, postmenopausal women are at risk to obtain OP. The estrogen deficiency in these women causes a loss in balance, i.e. an increased activation frequency, between resorption and formation, resulting in bone loss, reduced bone strength and, consequently, increased fracture risk. Patients with OP most often experience fractures at the hip, spine, and wrist. These fractures can occur without preceding trauma or in response to minimal trauma, indicating that bone strength is affected to a level that the bone cannot withstand normal loading conditions.

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The hypothesis would predict bone resorption in the compressive trabecular region from the femoral head to the femoral head. Since, force transmission mainly goes through a primary cylinder, as compared to non-osteoporotic bone. The amount of heterogeneity through the femoral head was measured in two ways. First, frequency plots were made to analyze the degree of anisotropy (DA), trabecular thickness (Tb.Th.), trabecular number (Tb.N.), and structure model index (SMI) were analyzed. The degree of anisotropy is a measure for the alignment of the trabeculae, which was determined from the mean intercept length, MILmax/MILmin [22]. The SMI determines whether the trabecular structure is rod-like or plate-like [23]. An ideal plate and rod have SMI values of zero and three, respectively.

Statistical analysis

For each femoral head, the average and standard deviation (SD) of the parameters of the bone cubes were calculated. When the parameters failed the normality test, the median and range were determined.

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Fig. 2. Example of a femoral head with OA (left) and a micro-CT slice in which the trabecular area was selected. The VOI was obtained by stacking the trabecular areas of all slices.
distributions of bone volume fraction and bone architecture for the entire trabecular region of the femoral head in OP and OA. From these frequency plots, the inter quartiles, i.e. the value of a bone parameter at the 75 percentile minus its value at the 25 percentile, were used as a measure of heterogeneity. This means that the larger the interquartile is, the more heterogeneous the distribution is as well. The second measure of heterogeneity was obtained from the ratio of a bone parameter between the primary compressive region, i.e. cylinder, and the total trabecular region of the femoral head, i.e. the average value of the cubes. A high ratio indicates a more heterogeneous distribution of a particular parameter as the difference between cylinder and total trabecular region is large, whereas a low ratio indicates more homogeneity.

Student’s paired t-tests were used to compare the bone parameters between the primary compressive trabecular region, i.e. cylinder, and the total trabecular region of the femoral head. Student’s t-tests were used to compare the bone parameters, including their inter quartiles, and their ratio (cylinder/total region) between patients with OP and OA. Significance was set at p < 0.05.

Results

The values of BV/TV (OP=0.25, OA=0.32) and Tb.Th. (OP=0.24 mm, OA=0.29 mm) were significantly lower in the OP cylinders than in the OA cylinders (Table 1). The DA, Tb.N. and SMI were not statistically significant between the OP and OA cylinders.

For the total trabecular region, i.e. average of the cubes, the average Tb.Th. was significantly lower in OP patients compared with OA patients, whereas DA was statistically higher in patients with OP (Table 1). Although the average BV/TV was lower in OP patients, the difference was not statistically significant from the OP patients. The average values of SM and Tb.N. were not statistically significant either between both groups.

Heterogeneity: cylinders versus total trabecular region

In both OP and OA patients, the average BV/TV in the cylinders was significantly higher than in the trabecular region of the total femoral head; BV/TVOP-cylinder =0.25; BV/TVOP-total region =0.14; BV/TVOA-cylinder =0.32; BV/TVOA-total region =0.18 (Table 1). In addition, the average DA and Tb.Th. were also significantly higher in the cylinders than in the trabecular region of the total femoral head, whereas the opposite was found for the SMI (Table 1). Furthermore, compared to the total region, the Tb.N. in the cylinders was significantly higher for OA patients, but not for OP patients. The average ratio between BV/TV in the cylinder and BV/TV in the total trabecular region of the femoral head was 1.7 for OP patients and 1.8 for OA patients (Table 2, p = 0.50). The average ratios for the other bone parameters were not statistically different either between OP and OA patients (Table 2).

Table 1

<table>
<thead>
<tr>
<th>Bone parameters of cylinders and total trabecular region in the femoral head in OP and OA patients</th>
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<tbody>
<tr>
<td>Cylinder (n=7)</td>
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<td>OP</td>
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<td>BV/TV</td>
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<td>Tb.Th (mm)</td>
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<td>Tb.N (mm)</td>
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<td>DA</td>
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*a* Significantly different from OP values at the same region using the Student’s t-test. Values refer to mean (SD). Significance was set at p = 0.05.

*b* Significantly different from the cylinder values within the patient group using the paired Student’s t-test. Values refer to mean (SD). Significance was set at p = 0.05.

Table 2

<table>
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<tr>
<th>Average ratios of bone parameters between cylinder and total trabecular region of the femoral head in OP and OA patients</th>
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<tr>
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Values refer to mean (SD). Significance was set at p = 0.05.

Heterogeneity: frequency plots

Differences in heterogeneity were found when the frequency plots were analyzed. The heterogeneities, i.e. inter quartiles, of BV/TV, through the femoral head were significantly lower in OP (0.13±0.04) compared with OA (0.18±0.04) (Fig. 3A). Also, the inter quartiles of Tb.Th. through the femoral head were significantly lower in OP (0.055±0.013) compared with OA (0.100±0.028) (Fig. 3B). The amount of heterogeneity of SMI, Tb.N. and DA did not differ significantly between patients with OP and OA (Figs. 3C-E); the inter quartile values were: SMI (OP): 1.25±0.20; SMI (OA): 1.61±0.46; Tb.N. (OP): 0.32±0.12; Tb.N. (OA): 0.34±0.07; DA (OP): 0.37±0.06; and DA (OA): 0.40±0.04.

Bone parameter versus average BV/TV

To further analyze the difference between patients with OP and without OA a fracture, we plotted the significant bone parameters of the total femoral head against the bone mass and performed Univariate Analysis of Variance. Hence, the average DA and Tb.Th. as well as the interquartile values of BV/TV and Tb.Th. were plotted against the average BV/TV of the femoral head (Figs. 4A-D). The graphs showed a substantial overlap in BV/TV values between the OP-patients with a fractured femur, and the OA patients without a fracture. Relative to BV/TV, the degree of anisotropy and the heterogeneity of BV/TV were not significantly different between OA and OP (p > 0.05) (Figs. 4A, C). In addition, relative to BV/TV both the trabecular thickness and the heterogeneity of Tb.Th. were significantly lower in the fractured group than in the non fractured group (p < 0.05) (Figs. 4B, D). For the heterogeneity of Tb.Th., this even resulted in a 100% discrimination between the fractured and non-fractured group: all interquartile-values below 0.078 belonged to the patients with a fracture (Fig. 4D).

Discussion

Our first hypothesis that osteoporotic femoral heads have an increased anisotropy as compared to osteoarthritic bone was confirmed for the total femoral head. Although the differences in morphological anisotropy between the groups were small, i.e. 0.11 U in anisotropy for the total trabecular area, it has been shown that such differences can be mechanically significant [12,24]. In addition, the degree of anisotropy was larger in the primary compressive regions, i.e. cylinders, compared to the total trabecular area. This nicely illustrates the adaptation of trabeculae to the primary loading direction. However, unexpectedly, the degree of anisotropy in the cylinders was similar between the OP and OA groups. This was not in agreement with other studies which have shown that the degree of anisotropy in OP is somewhat higher than in controls [11,12]. Hence, the hypothesis was not supported for the cylinder region when we used OA bone as a control.

Our second and third hypotheses that osteoporotic femoral heads have a more heterogenic distribution of the BV/TV and Tb.Th. as
compared to non-osteoporotic bone were both rejected. As expected, in both groups, the BV/TV was higher in the primary compressive region than in the total trabecular region, mainly due to thicker trabeculae. Furthermore, the BV/TV and Tb.Th. were lower in the fractured group. The variations of BV/TV and Tb.Th. throughout the femoral head were, however, also lower in the fractured group. When the BV/TV of the cylinder was divided by the BV/TV of the total trabecular area, the proportion was almost similar for both OP and OA (Table 2). This suggests that the percentage of both bone loss (in OP) and bone gain (in OA) takes place uniformly throughout the head. The results of the other bone parameters confirm this idea since no significant differences in proportion were found between OA and OP. These results are consistent with the results found by Snyder et al. [25]. In vertebral bodies, they found uniform bone loss in the trabecular area during aging, hence no preferential resorption of horizontal or vertical trabeculae.

Fig. 3. Frequency plots of the bone parameters in the femoral heads of patients with OA and OP; bone volume fraction (A), trabecular thickness (B), structure model index (C), trabecular number (D), and degree of anisotropy (E). Per interval the average of 7 femoral heads was taken.
The highest strength in the trabecular structure is mainly expected in the compressive region, i.e. in the cylinder, where bone encounters high loads. We found that the BV/TV, Tb.Th., and DA were indeed significantly higher in the cylinder than in the total femoral head, for both OP and OA patients. Furthermore, the SMI values were lower in the cylinder, meaning more plate-like structures which reflect high mechanical strength [26]. In addition, in osteoporosis, a transition from plate-like to rod-like architecture takes place [27]. In our study, the trabeculae in the OP femurs showed indeed a more rod-like structure than the trabeculae in the OA femurs, although this difference was not statistically significant.

Our results showed a substantial overlap between the BV/TV values of OP-patients with a fractured femur and the patients without fractures (Fig. 4). According to the World Health Organization (WHO), osteoporosis is defined as a bone mineral density (BMD) of 2.5 standard deviation below the average BMD of healthy 35-year-old women. Clinically, bone density is determined by DXA measurements. In our study, the BV/TV was used as an estimator of bone density as the sizes of the femoral head samples were too limited to perform accurate DXA measurements. Our results as well as studies by others have shown that bone density is a poor predictor of fracture risk for the individual patient [28–30]. This means that many individuals who fractured a bone as a result of moderate trauma will not be diagnosed as osteoporotic, whereas many individuals who are defined as osteoporotic will not fracture their bone(s). A reason why bone density alone is not a good predictor of fracture risk, is possibly related to the fact that the distribution of bone density and other bone parameters are not taken into account. In this perspective, our findings of the heterogeneity of trabecular thickness throughout the femoral head are of interest. The parameter was obtained by dividing the total trabecular area into cubes of which the interquartile value was determined. This heterogeneity parameter of Tb.Th., was able to discriminate the fractured from the non-fractured femora as all values below 0.078 belonged to patients with a fracture. It is, however, not yet possible to test and use this parameter clinically as the resolution of imaging systems have to be improved first. In addition, it should be realized that the absolute value of 0.078 can be different when subdividing the trabecular volume with different cube volumes or when using the standard deviation of the total trabecular area instead.

There are two additional limitations to our study that have to be considered. The analysis of the trabecular bone was restricted to the femoral head. According to Singh et al. [16], most of the age-related...
changes in the trabecular architecture occur in the femoral neck (grades 4–6). However, with increasing degrees of bone loss (grades 1–3), which they define as definite osteoporosis, they also found changed architecture and increased anisotropy in the center of the femoral head. Hence, the restriction of the analysis to the femoral head can be considered as relatively minor.

Second, the results should be interpreted in the perspective that OP femoral heads were compared to OA femoral heads and that no normal femoral heads were included. Collecting a set of normal femoral heads, which should be age- and sex-matched, is difficult as the definition of “normal” is questionable in the perspective of aging.

We chose to compare OP with OA. If anything, it is known that OP and OA are inversely correlated, and it has even been suggested that OP and OA have a common molecular origin, making them the two opposite end results of the same biological process [31]. This would be an argument in favor of comparing these two groups, as they represent two extreme ends of the same spectrum. Nevertheless, collecting and analyzing a set of normal femoral heads would be interesting for a follow-on study.

In conclusion, when compared to subjects with OA, this study did not generally confirm the presence of strong adaptation in the main loading direction and less adaptation in the other directions in osteoporotic femoral heads. While increased anisotropy in osteoporotic femoral heads was confirmed, we found less heterogeneity of the BV/TV and Tb.Th. in osteoporotic femoral heads as compared to OA bone. Hence, our hypothesis that in OP thick trabeculae would remain in the cylinder and trabecular loss would be found in the periphery, was not confirmed. The results suggest that bone loss in OP occurs uniformly throughout the femoral head, leading to an overall decrease in bone mass and trabecular thickness, in both cylinder and periphery. Finally, although not yet clinically applicable, the variation of Tb.Th. in the femoral head could be an interesting parameter to predict the variation of fracture risk in the proximal femur.

Acknowledgments

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References


