



# The Open Orthopaedics Journal

Content list available at: [www.benthamopen.com/TOORTHJ/](http://www.benthamopen.com/TOORTHJ/)

DOI: 10.2174/1874325001610010382



## RESEARCH ARTICLE

# Preoperative Bone Mineral Density and Bone Turnover in Women Before Primary Knee Arthroplasty

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Received: March 24, 2016

Revised: April 26, 2016

Accepted: April 28, 2016

### Abstract:

#### Purpose:

The preoperative prevalence of osteoporosis and/or osteopenia and overall bone quality in prospective total knee arthroplasty (TKA) patients may affect the postoperative outcome after prosthetic insertion into the bone. The purpose of this study is to determine the baseline bone mineral density (BMD) and bone turnover in preoperative, female, primary TKA patients.

#### Methods:

We prospectively measured the lumbar spine and hip BMDs using dual-energy X-ray absorptiometry (DEXA) scans in a cohort of 119 knees (107 patients) one day before surgery. We also assessed bone turnover using urinary levels of N-telopeptide (NTX), a type I collagen crosslinker, normalized to creatinine.

#### Results:

The prevalence of osteoporosis by DEXA scan (T-score  $\leq -2.5$ ) among the TKAs was 12% in the spine and 10% in the hip. Eighty-three knees (70%) had osteopenia or osteoporosis of either the spine or hip. The mean T-score of the spine was  $-0.7$  (SD 1.6), which is within normal limits, and of the hip was  $-1.2$  (SD 1.0), which is defined as osteopenia. The mean Z-scores of  $0.9$  (SD 1.4) in the spine and  $0.6$  (SD 0.9) in the hip were positive. The median urinary NTX/creatinine ratio was elevated at 58.1 (interquartile range: 13.7 to 188.4).

#### Conclusion:

Based on Z-scores, the TKA patients had higher spine and hip BMDs than the age-matched general population. Elevated NTX levels may suggest a systemic or local abnormal bone turnover. Further study is needed to determine whether such turnover, as a type of patient-related medical systemic disorder, affects postoperative clinical outcomes.

**Keywords:** Bone turnover, Dual energy x-ray absorptiometry, Osteoarthritis, Preoperative bone mineral density, Urinary N-telopeptide, Total knee arthroplasty.

## INTRODUCTION

Osteoarthritis and osteoporosis, which are common diseases in women over the age of 65, can be present simultaneously, especially in patients with chronic arthritis [1], though the prevalence depends on patient age, lifestyle, and environment. Several papers [2 - 4] have reported the prevalence of osteoporosis in patients with advanced knee osteoarthritis who are undergoing total knee arthroplasty (TKA). However, the preoperative bone quality and bone turnover are not both routinely assessed during pre-TKA planning.

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Many recent studies on TKA surgery have examined implant design and relatively few have assessed the quality of the bone into which the implants are inserted [5]. Clinically, the most common cause leading to revision knee arthroplasty is the aseptic loosening of components [6, 7] that occurs when periprosthetic bone is resorbed because of surgeon-related factors such as malalignment, patient-related factors such as bone quality, or implant-related factors such as cemented or cementless fixation or design, among others [6]. The results of two studies demonstrated that bisphosphonates, which prevent bone resorption, significantly reduce the rate of revision surgery [8] and increases the T-score hip bone mineral density (BMD) after TKA [9]. Conversely, several studies did not find any beneficial effects of bisphosphonate treatment [10 - 12].

Based on these studies, assessing the baseline BMD and bone turnover preoperatively in women before primary TKA may help surgeons obtain better clinical outcomes by providing information for them to preoperatively develop strategies for approaching any patient-related negative factors. The aim of this study was to prospectively characterize the bone quality of a cohort of women patients before primary TKA and to determine the prevalence of osteoporosis in the arthroplasty population.

## MATERIALS AND METHODS

The protocol for this study was approved by the Research Board of the Healthcare Corporation Ashinokai, Gyoda, Saitama, Japan, and informed consent was obtained from all patients. Between October 2009 and November 2014, 107 primary OA, postmenopausal women patients (119 knees) undergoing TKA were evaluated. Twelve patients had scheduled staged bilateral TKA with an average interval between the first and second surgery of 17 months (range: 6 to 40). The mean age at the time of surgery was 72 years (range: 55 to 88). The preoperative diagnosis for all patients was osteoarthritis, and the mean body mass index was 27 (SD 4). Mean preoperative HSS Score showed 42 (SD 10) [13], and all osteoarthritis grades revealed IV using the Kellgren and Lawrence radiographic grading scale [14]. Twenty two patients took medication for osteoporosis. The exclusion criteria were diagnosis of rheumatoid arthritis and patients who were undergoing revision surgeries. One patient undergoing a bilateral total hip surgery was excluded during the study period. Each patient completed a questionnaire recording demographic data, medical history, and drug history.

### Bone Mineral Density

BMD was measured by dual-energy x-ray absorptiometry (DEXA) scanning using a Lunar Prodigy Primo densitometer (GE Healthcare Lunar, Madison, WI, USA) on the day before surgery. The preoperative scans of the anteroposterior spine and the total hip were performed using the settings and patient positioning recommended by the manufacturer. The scanning precision was calculated as the coefficient of variation (% CV) between scan BMD values. In this series, the precision of the measurements was 1.9% in the lumbar spine (L1–L4) and 1.7% in the total hip. The results are expressed as the spine and total hip BMD, T-Score, and Z-Score. The T-score is the number of standard deviations from the mean BMD of the young adult population, and the Z-score is the number of standard deviations from the age-matched mean BMD. Osteoporosis is defined by a T-score of  $-2.5$  or less, and osteopenia is defined by a T-score between  $-2.5$  and  $-1$  in the lumbar and total hip region, according to the World Health Organization international reference standard [15].

### Urinary N-Telopeptide

NTX is a cross-linker for mature type I collagen that is specific to bone and is released into the circulation during the process of bone resorption. It is excreted unmetabolized in urine, making it a sensitive and specific marker of bone resorption during osteoporosis [16]. NTX was measured using an enzyme-linked immunosorbent assay (ELISA) using an Osteomark<sup>®</sup> kit (Alere Inc., Waltham, MA, USA) one day before surgery. For normalization, creatinine (Cre) was measured using the second morning void urine samples as a baseline before surgery. The precision was calculated as the coefficient of variation (% CV: 3.8%) in this series. According to the guidelines of the Japanese Osteoporosis Society, the reference ranges for Cre-normalized urinary NTX have been established using a commercially available enzyme immunoassay as: 9.3 to 54.3 nmol bone collagen equivalent (BCE)/nmol•Cre in premenopausal females, 14.3 to 89.0 nmol BCE/nmol•Cre in postmenopausal females, and 13.0 to 66.2 nmol BCE/nmol•Cre in males [17]. In addition, NTX values can suggest bone diseases ( $>54.3$ ), metastatic bone tumor ( $>89.0$ ), or abnormal calcium metabolism ( $>66.2$  nmol BCE/nmol•Cre). Finally, the cutoff level of NTX that indicates high risk of fracture is 54.3 nmol BCE/nmol•Cre [17].

## Statistical Analysis

The prevalence of osteoporosis and osteopenia between the spine and hip was compared using the  $\chi^2$  test. The Spearman's correlation of rank coefficients was used to evaluate the relationships between the T- and Z-scores and NTX. The strength of the correlation of the rank coefficients was defined as strong for values of 0.7–1.0, moderate for 0.4–0.7, and weak for 0.2–0.4. The statistical analyses were performed using SPSS software (ver. 14.0 J; SPSS, Tokyo, Japan). P-values less than 0.05 were considered statistically significant.

## RESULTS

The T-scores of the spine and hip were normally distributed within the study population (Table 1). The normality of the data was verified by inspecting the histogram and performing Kolmogorov–Smirnov test of normality. The mean BMD values of spine and hip were 1.023 (SD 0.187) and 0.788 (SD 0.122) respectively. The mean T-score of the spine was  $-0.7$  (SD 1.6), which is within the normal range, and of the hip was  $-1.2$  (SD 1.0), which is defined as osteopenia. The mean Z-scores of 0.9 (SD 1.4) in the spine and of 0.6 (SD 0.9) in the hip were positive.

**Table 1. Patient characteristics.**

	Female
Patients/ Knees	107/119
Mean (SD) age (years)	72 (7)
BL	149 (6)
BW	59 (10)
Mean (SD) BMI	27 (4)
Preoperative HSS Score*	43(10)
Osteoarthritis Grade**	IV: 119
Medication for Osteoporosis	22

SD: standard deviation; BL: body length; BW: body weight; BMI: body mass index;

\*HSS: Hospital for Special Surgery score [13].

\*\*Osteoarthritis grade was evaluated using the Kellgren and Lawrence radiographic grading scale [14].

The prevalence of osteoporosis (T-scores  $\leq 2.5$ ) within the cohort was low. The rate of osteoporosis defined by DEXA scan was 12% (14/119) in the spine, 10% (12 of 119) in the hip, and 18% (21 of 121) in either the hip or spine. However, the rate of osteopenia (T-scores from  $-1.0$  to  $-2.5$ ) was much higher, with 70% (83 of 119) of patients displaying osteoporosis or osteopenia of either the spine or hip (Table 2). There was no significant difference in the prevalence of osteoporosis or osteopenia between the spine and total hip (Table 4). Of the patients with DEXA-defined osteoporosis of the spine or hip, only five of the 21 (24%) were being treated for osteoporosis.

**Table 2. Distribution of spine and hip T-Scores.**

Values	-3.5	-3	-2.5	-2	-1.5	-1	-0.5	0	0.5	1	1.5	2.0	2.5	3	3.5	Total
Spine (L1-4)	2	3	9	12	14	18	17	8	12	13	1	3	0	5	2	119
Total Hip	2	3	7	13	25	20	18	18	7	4	1	1	0	0	0	119

**Table 3. Baseline bone mineral density (BMD).**

Mean (SD) BMD values [No. Patients/Knees]	Mean (SD)
<b>Spine [107/119]</b>	
BMD (g/cm <sup>2</sup> )	1.023 (0.187)
T-score	-0.7 (1.6)
Z-score	0.9 (1.4)
<b>Hip [107/119]</b>	
BMD (g/cm <sup>2</sup> )	0.788 (0.122)
T-score	-1.2 (1.0)
Z-score	0.6 (0.9)

SD; standard deviation.

**Table 4. Prevalence of osteoporosis and osteopenia.**

Total (N=119): number (%)	Osteoporosis	Osteopenia	Osteoporosis or Osteopenia
Spine	14(12)	44(37)	58(49)
Hip	12(10)	58(49)	70(59)
Hip or Spine	21(18)	74(62)	83(70)

Osteoporosis:  $\chi^2=0.173$  p=0.835, Osteopenia:  $\chi^2=30363$  p=0.089, Osteoporosis or Osteopenia:  $\chi^2=2.434$  p=0.153.

The median urinary Cre-normalized NTX level was elevated at 58.1 (range: 13.7 to 188.4; interquartile range: 43.5 to 73.9) compared with the normal range (reference range: 14.3 to 89.0). The distribution of NTX/Cre was skewed to the right (Table 3). The NTX/Cre ratio was higher than the upper bound of the reference range in 18% (21 of 119) of the study population, and values more than 54.3, defined as a high fracture risk group [17], were found in 59% (70 of 119) of the study population (Table 5).

**Table 5. Distribution of NTX/Cre nmol BCE/nmol•Creatinine.**

≤ Values	20	30	40	50	60	70	80	90	100	110	120	120<
Numbers (119)	3	11	11	15	28	20	10	9	4	1	2	5

The BMD values in the study cohort were normally distributed. The mean Z-scores.

Correlations between the continuous variables, the T-scores of the spine and hip and the NTX/Cre ratio, were assessed using Pearson's rank correlations. The Pearson's tests showed no correlation between either the spine T-score ( $r=-0.072$ ,  $p=0.4355$ ) or hip T-score ( $r=-0.188$ ,  $p=0.0411$ ) and NTX/Cre.

## DISCUSSION

The results of this study suggest three main findings. First, the prevalence of DEXA-defined osteoporosis among this cohort of knee arthroplasty patients was low, but that 70% of the patients had osteopenia or osteoporosis in either the spine or hip. Second, the median NTX/Cre ratio was elevated to the 'high fracture risk' range in the majority of the women, and there was a large variation in the NTX/Cre ratios, with abnormally elevated levels in over 18% of the patients. Finally, no correlation was found between the NTX/Cre ratio and the T-scores of either the spine or hip.

This study had a number of limitations. First, only women were included in the study population. We recognize the necessity of further studies that evaluate male patients. Second, this study was conducted on Japanese women aged  $\geq 55$  years who were postmenopausal. Thus, the results may not be applicable to other populations, such as younger patients who are premenopausal or patients with different ethnicities. Third, further investigations are needed to clarify the clinical significance of the results. Despite these limitations, the results of the present unique and prospective study show that we were able to evaluate baseline BMD, as was previously reported [2 - 4], but also the bone turnover in women preoperatively before primary TKA.

Because only 12% of the spines and 10% of hips in this study cohort showed DEXA-defined osteoporosis, defined by a total hip T-score  $\leq -2.5$ , the prevalence of osteoporosis in the patients undergoing knee arthroplasty was low. Kanis *et al.* [18] estimated that the prevalence of femoral neck osteoporosis in the Swedish female population aged between 65 and 69 years was 20.2%. Recently, James *et al.* [5] reported similar values as those found in the present study, namely an overall prevalence of hip osteoporosis up to 9.3% in preoperative hip and knee arthroplasty patients. In addition, osteoporosis was defined as a BMD of less than 70% of the peak bone mass, according to the criteria of the Japanese Society for Bone and Mineral Research (JSBMR) [19]. Osteoporosis was defined in women as a BMD  $< 0.708$  g/cm<sup>2</sup> at the lumbar spine and as a BMD  $< 0.604$  g/cm<sup>2</sup> in the total hip. The prevalence (%) of osteoporosis according to the JSBMR criteria, classified for Japanese women aged 70–79 years, was 29.8% in the lumbar spine, which was evaluated at L2-L4, and 25.9% in the total hip [20]. In the present study, only 6% (7/119) of hips and 0% of lumbar spines satisfied these criteria.

The BMD values in the study cohort were normally distributed. The mean Z-scores in the lumbar spine and hip were positive, which suggests that knee arthroplasty patients have, on average, higher BMDs than the similarly-aged general population. Although the mean spine T-score was within the normal range, the T-scores of the hip all showed osteopenia (range:  $-1.0$  to  $-2.5$ ). A decrease in the direct load-bearing of the proximal femur as compensation for severe knee pain and disuse of the affected limb before surgery might have greatly affected the hip BMD, while the spine BMD remained relatively unaffected. The results of two other papers [21, 22] support the results presented here

and the effect of loading on the BMD of the proximal femur in osteoarthritic patients. Im *et al.* [21] conducted a cross-sectional study to determine the relationship between the severity of radiographical knee osteoarthritis and the degree of osteoporosis in the ipsilateral proximal femur, controlling for body mass index, in a population of Korean women. They concluded that a higher Kellgren–Lawrence (K–L) grade [14] was significantly associated with a lower BMD in the proximal femur, but the BMD of the lumbar spine was not similarly associated. Ishii *et al.* [22] compared the BMD in the contra- and ipsilateral hips pre- and post-TKA surgery. They reported an improvement in the hip BMD postoperatively and concluded that the increase in patient mobility and hip loading after TKA may explain the increase in BMD.

The median NTX/Cre levels in the study group were elevated to 58.1 (range: 13.7 to 188.4), indicating a high fracture risk. Two types of potential factors may have induced the increased levels of bone resorption. One type is systemic factors that are derived from an overall reduction in physical activity, and the second type is local factors that are derived from the decreasing loads on the proximal femur because of the severe knee pain that usually occurs before TKA surgery. Because the age, lifestyle, and environments of each patient are different, the contribution of systemic vs. local factors may vary by person. Neither the spine nor the hip DEXA values were correlated with the NTX/Cre ratios in the present study. Two other cohort studies [23, 24] reported high levels of urinary NTX/Cre in patients with advanced osteoarthritis. According to a cross-sectional study on a cohort of the knee osteoarthritis survey in Japan, approximately 80% of the women subjects in the highest urinary NTX quartile also had radiological knee osteoarthritic changes ( $\geq$  K-L [14] Grade II) [24]. In addition, the bone resorption, as assessed by urinary NTX, was increased in patients with progressive knee osteoarthritis, according to the longitudinal results from the Chingford study [23].

Regarding the prevalence of high bone resorption, 59% of the study population had elevated NTX/Cre ratios ( $> 54.3$  nmol BCE/nmol•Cre), while nearly 18% had higher than normal ratios ( $> 89.0$  nmol BCE/nmol•Cre). This finding indicates abnormal bone turnover and increased resorption in a large proportion of the TKA patients. Furthermore, because osteoporosis therapies, including bisphosphonates, selective estrogen receptor modulators, and active vitamin D3 can significantly improve NTX/Cre levels and no adjustment was made for patients taking medications, these results may underestimate the prevalence of abnormal bone resorption.

The results of the present study provide potentially important preoperative information on the baseline BMD and bone turnover of women patients before undergoing TKA. Because these variables are recognized as some of the patient-related preoperative systemic factors that can influence the postoperative clinical outcomes, along with other medical systemic disorders such as cardiovascular, respiratory, liver, and renal function, among others, this information may help preoperative planning. Despite their importance, few studies have reported these baseline preoperative values [9]. We recognize that further study is needed to understand the clinical significance of the results for each patient, including the TKA outcomes such as prosthetic loosening and periprosthetic or other bone fractures. From those results, we may be able to determine whether the preoperative detection and treatment of osteoporosis or osteopenia in female patients is routinely necessary.

## CONCLUSION

In conclusion, the prevalence of osteoporosis in female patients undergoing TKA is low. Patients undergoing TKA generally have higher BMDs than is average for their age. Additionally, a marker of bone resorption was elevated in knee arthroplasty patients.

## ETHICAL REVIEW COMMITTEE STATEMENT

The local institutional review board approved this study. All patients provided informed consent.

## CONFLICT OF INTEREST

Each author certifies that he or she has no commercial associations (*e.g.*, consultancies, stock ownership, equity interest, patent/licensing arrangements, *etc.*) that might pose a conflict of interest in connection with the submitted article.

## ACKNOWLEDGEMENTS

Declared none.

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