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ORIGINAL ARTICLE

Low bone mineral density at femoral neck is a predictor of increased mortality in elderly Japanese women

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Abstract
Summary This study aimed to determine whether low bone mineral density (BMD) at the femoral neck independently predicts all-cause mortality in elderly Japanese women. A prospective cohort study of 271 women aged 67–89 years was conducted. A Cox proportional hazard model was used to examine independent associations between BMD and total mortality. During a 12-year follow-up period, the mortality risk (as measured by hazard ratio [HR]) was significantly increased in the three categories of baseline BMD (diagnostic criteria of osteoporosis, tertile of BMD, and quartile of BMD). After adjusting for major potential confounding variables for mortality, significantly increased mortality risks were found in subjects with osteoporosis (HR=2.17, p=0.032), in subjects in the lowest tertile (HR=2.57, p=0.007), and in subjects in the lowest quartile (HR=3.13, p=0.014], respectively. Our findings suggest that preventive strategies should be considered to increase and maintain high BMD at the femoral neck in the elderly women not only to prevent hip fractures but also probably to reduce mortality risk.
Introduction Several longitudinal studies with Caucasian subjects have suggested that osteoporosis is associated with increased mortality. This study aimed to determine whether low bone mineral density (BMD) at the femoral neck independently predicts all-cause mortality in elderly Japanese community-dwelling women.
Method A prospective cohort study of 271 women aged 67–89 years was conducted. A Cox proportional hazard model was used to examine independent associations between BMD at both the femoral neck and the trochanter and total mortality.
Results During a 12-year follow-up period, 81 of 271 women (29.9%) died. An independent and significant relationship was found between baseline BMD at the femoral neck and mortality risk. The mortality risk (as measured by HR) was increased by 2.80-fold (95% confidence interval [CI] 1.55–5.06; p<0.01) in the subjects with osteoporosis or by 2.94-fold (95% CI 1.64–5.26; p<0.001) in subjects in the lowest tertile or by 3.61-fold (95% CI 1.77–7.41; p<0.001) in subjects in the lowest quartile of BMD, respectively. After adjusting for major potential confounding factors for mortality such as age, body mass index, blood pressure, blood variables, medical history, alcohol drinking, and smoking status, those in the subjects with osteoporosis (HR=2.17 [95% CI 1.07–4.41], p=0.032), in the lowest tertile (HR=2.57 [95% CI 1.29–5.15], p=0.007), or in the lowest quartile (HR=3.13 [95% CI 1.26–7.73], p=0.014] had a significantly increased risk of mortality. BMD measurement at the trochanter showed similar but weaker results.
Conclusions Our findings suggest that preventive strategies should be considered to increase and maintain high BMD at the femoral neck in elderly subjects not only to prevent osteoporosis and its associated fractures but also probably to reduce mortality risk.

Keywords BMD · Elderly women · Femoral neck · Mortality

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Introduction

Aging of the population results in an increased number of individuals with osteoporosis and associated fractures, partic-

ularly in women. Significant morbidity and mortality associated with osteoporotic fractures have led to the recognition of osteoporosis as an important public health problem [1]. Among these osteoporotic fractures, hip fractures have been reported to not only decrease activity in daily living and quality of life but also to increase mortality [2–5]. Several longitudinal studies have also suggested that osteoporosis is associated with increased mortality [6–10]. Furthermore, excessive mortality following hip fracture has been shown in many studies [11–14]. It is well known that the incidence of hip fractures is reported to vary from one geographic area to another. Although the bone mass of Japanese women is lower than that of Caucasians even after adjusting for body size [15, 16], the incidence of hip fractures is remarkably low in Japanese women compared with that in Caucasians [17–19]. However, the relationship between bone health and all-cause mortality among elderly Japanese women is unclear. To test whether bone mineral density (BMD) is associated with mortality, we prospectively studied a cohort of elderly community-dwelling women and assessed mortality rates during 12 years of follow-up. BMD measurements were obtained from the proximal femur, i.e., the femoral neck and trochanter, because it is easier to calculate BMD without any degenerative changes and also to predict both hip fracture and mortality among the elderly [13, 14, 20, 21].

Materials and methods

Study population

The source of data for this study was derived from the Longitudinal Interdisciplinary Study on Aging, conducted by the Tokyo Metropolitan Institute of Gerontology (TMIG-LISA). TMIG-LISA, a long-term prospective study on aging and health in elderly Japanese people residing in many communities which aimed to identity the risk factors for those with geriatric diseases or chronic medical conditions and to determine which factors accelerate or decelerate the aging process, was carried out in representative samples of the population. The detailed framework and sampling methods have been described elsewhere [22, 23].

This study aimed to prevent osteoporosis and its associated fractures among the elderly women and was conducted in a rural and mountainous area in northern Japan (Nangai Village, Akita Prefecture). The total population of this village in 1994 was about 5,100 and the proportion of residents aged 65 and older in the population was approximately 20%. A baseline survey of this study was carried out in 1994–1995, and 791 (319 males and 472 females) elderly persons aged 67 and older were community dwelling and eligible. Because of a higher prevalence of osteoporosis and fractures in the elderly women, the subjects included in this study were only elderly women. Of all the community-dwelling women aged 67 years or older, 334 ambulatory women among 472 eligible women (70.8%) were invited to participate in the survey which was conducted at a health examination center. The remaining 138 elderly women took part in a home-visit interview survey only. Of the 334 women, 299 (89.5%) were interviewed and underwent medical examination including BMD measurement of the hip. The remaining 35 women had difficulties during BMD measurement, either with mobility or with the instrumentation used. Study participants were followed up until August 2007. Of the original 299 women in the cohort, one had missing BMD values and another 27 had missing data relating to the covariates. The final sample size which was used for analysis was 271. The Tokyo Metropolitan Institute of Gerontology Review Committee approved the study protocol, and informed consent was obtained from all participants.

Data collection

Baseline interviews and medical examinations included demographic details, medical history including vertebral and limb fractures in the preceding 2 years, smoking habits, alcohol intake, anthropometry, standard blood pressure measurement, and collection of blood specimens.

BMD was measured at the femoral neck and trochanter using dual-energy X-ray absorptiometry (DXA), with the Hologic QDR-1000 densitometer (Hologic, Waltham, MA, USA), and was used as a mobile DXA [24]. The coefficient of variation for hip BMD was 1.6% for the femoral neck and 1.5% for the trochanter [25]. Due to a greater coefficient of variation for BMD at Ward's triangle (3%), we did not adopt this measurement in our study.

Blood pressure was measured twice using a sphygmomanometer, after the participant had been seated and rested for 5 min, and the lower value of the two readings was used for analysis.

Blood samples were centrifuged at the examination sites, and the resulting serum samples were kept at 4°C until analysis. Total cholesterol, high-density lipoprotein cholesterol, hemoglobin A_{1c}, albumin, and hematologic values were measured using standardized procedures.

Body mass index was calculated as weight in kilograms divided by height in squared meters. Medical history included the self-report of physician-diagnosed stroke, heart disease, type 2 diabetes mellitus, hypertension, and major osteoporotic fractures such as hip fractures and vertebral fractures. The participants were also asked whether they had suffered either a vertebral or limb fracture in the previous 2 years (after the age of 65 years).

Current smokers were defined as those who reported "yes" to the question "do you smoke cigarettes now"? Self-report alcohol intake was divided into three categories: no intake, previous intake, and occasional or regular intake.

Mortality data were obtained through a comprehensive surveillance system which has been used successfully since the initiation of TMIG-LISA. Current residence in Nangai Village in August each year was determined from the municipal registration files for this village. All deaths were ascertained by checking local registries. However, this system does not allow the identification of causes of death.

Statistical analysis

Means and standard deviations (for continuous variables) along with proportions (for categorical variables) were calculated for all participants. Differences between alive and dead were assessed using *t* test for continuous variables and the chi-squared tests for categorical data. Differences of cumulative mortality rates among three categories were assessed by the chi-squared tests. Differences among tertile of BMD at the femoral neck were assessed by one-way analysis of variance for continuous variables and by the chi-squared test for categorical data.

Calculation of Pearson's correlation coefficient (r) was carried out to confirm the correlation between BMD at the femoral neck and at the trochanter. The results showed a high and significant intercorrelation of these two BMD measurements (r=0.792, p<0.0001). Because of a significant high intercorrelation (r) between BMD at the femoral neck and the trochanter region, only femoral neck BMD was adopted for the analysis of baseline characteristics of the subjects. We used both BMD measurements separately as an independent variable for the Cox's proportional hazard regression model. The independent role of BMD at the femoral neck as a predictor of total mortality was evaluated using Cox proportional hazards regression models, with adjustments for age, history of disease including osteoporotic fractures, and other major potential confounding factors selected on the basis of previous literature findings. These factors included body mass index, systolic blood pressure, total and high-density lipoprotein cholesterol levels, albumin level, hemoglobin A_{1c} level, and smoking and alcohol drinking status (current, former, or never), which were entered into the models as continuous variables, except those for smoking and alcohol status which were entered as dichotomous data. Preexisting or a history of diseases including physician-diagnosed stroke, heart disease, hypertension, type 2 diabetes mellitus, and major osteoporotic fractures were each entered into the models as dichotomous data (present vs absent). In these analyses, predictive values of BMD at the femoral neck and at the trochanter for total mortality were evaluated using adjusted relative risks in the following three categories of baseline BMD, i.e., (1) diagnostic criteria including osteoporosis, osteopenia, and normal, (2) tertile of BMD, and (3) quartile of BMD. The diagnostic criteria defined by the Japanese Guideline for the Prevention and Treatment of Osteoporosis (2000 revision) was used only in the femoral neck BMD because of a lack of criteria at the trochanter. Cumulative survival up to the end of the follow-up period using these three categories of baseline BMD at the femoral neck were also calculated using Cox's proportional hazard regression model with multiple adjustments. All data analyses were performed using a statistical software program (SPSS version 14.0 for Windows; SPSS Inc, Chicago, IL, USA).

Results

Eighty-one women (29.9%) died during the 12-year follow-up period. The baseline characteristics of the women (n=190) who had survived and of the women (n=81) who had died during a mean follow-up period of 7.14 years are shown in Table 1. There were significant differences between the women who survived and those who had died for mean age (p<0.0001), systolic blood pressure (p=0.005), serum albumin level (p=0.011), and BMD at the femoral neck (p<0.0001) and at the trochanter (p=0.007). We observed a graded relationship between BMD at the femoral neck and total mortality in all three categories of baseline BMD, i.e., in the diagnostic criteria, tertile (Fig. 1), and quartile (Fig. 2). The cumulative mortality rates during the 12-year follow-up period according to the three categories of baseline BMD are shown in Table 2. In these three categories, the highest mortality rates in each were found in the subjects with osteoporosis, in subjects in the lowest tertile, and in the lowest quartile. There were clear differences in the survival curves among the three categories, and the mortality rate was linearly associated with BMD with p values less than 0.001 at the femoral neck and 0.01 at the trochanter. BMD at both the femoral neck and the trochanter was significantly lower in women who had died compared with women who had survived.

Women who died were significantly older (by about 3 years) and significantly more likely to have higher systolic blood pressure and a lower serum albumin concentration. There was no significant prevalence of common or lifestyle-related diseases including osteoporotic fractures between women who had and had not survived.

Baseline characteristics of the women according to tertile of BMD at the femoral neck, as one of the representative examples in this study, are shown in Table 3. Compared with the highest tertile of BMD, women in the lowest tertile were significantly older (by 4 years, p<0001) and had a lower mean body mass index (BMI; p<0001). No significant differences in the three tertile groups were observed for systolic blood pressure, blood variables (five items), medical history with the exception of diabetes mellitus (four items),

Table 1 Characteristics of 271 elderly women aged 67–89 years at baseline survey in 1994–1995 according to vital status by 2007 in the TMIG-LISA

Status	Alive (n=190)	Dead (n=81)	Significance (p value)
Age (years), mean (SD)	71.9 (4.4)	75.0 (5.2)	<0.0001[a]
BMD (g/cm$^{2)}$, mean (SD)			
At femoral neck	0.600 (0.088)	0.560 (0.089)	<0.0001[a]
At trochanter	0.483 (0.086)	0.452 (0.086)	0.007[a]
Body mass index (kg/m$^{2)}$, mean (SD)	23.3 (3.5)	22.4 (3.1)	0.054[a]
Systolic blood pressure (mmHg), mean (SD)	147.9 (23.7)	156.9 (23.9)	0.005[a]
Blood variables, mean (SD)			
Hemoglobin (g/dl)	12.4 (1.2)	12.2 (1.1)	0.303[a]
Albumin (g/dl)	4.2 (0.2)	4.1 (0.2)	0.011[a]
HbA_{1c} (%)	5.6 (0.8)	5.6 (0.7)	0.958[a]
Total cholesterol (mg/dl)	190.1 (29.0)	196.2 (32.0)	0.159[a]
HDL cholesterol (mg/dl)	51.7 (12.3)	50.4 (11.3)	0.434[a]
Medical history, no (%)			
Stroke	4 (2.1)	3 (3.7)	0.430[b]
Heart disease	28 (14.7)	11 (13.6)	0.853[b]
Hypertension	78 (41.1)	31 (38.3)	0.687[b]
Diabetes mellitus	8 (4.2)	5 (6.2)	0.538[b]
Fracture	6 (3.2)	3 (3.7)	0.536[b]
Current alcohol drinking, n (%)	43 (22.6)	16 (19.8)	0.403[b]
Current smoking, n (%)	2 (1.1)	2 (1.2)	0.669[b]

[a] Student t test

[b] Chi-squared test

and alcohol drinking and smoking status. The reason why the frequency of diabetes mellitus in medical history showed significant differences among these three groups, i.e., highest frequency in the middle tertile, is unclear.

The crude and adjusted hazard ratios of BMD at the femoral neck and at the trochanter for 12-year mortality in the three categories using Cox proportional model are shown in Table 4. In this table, model 1 shows the crude ratio without any adjustments and model 2 shows the results after multiple adjustments for all variables including age, BMI, systolic blood pressure, blood variables (five items), medical history (five items), and alcohol drinking and smoking status, all of which are major potential confounding factors for mortality. Multiple adjustments

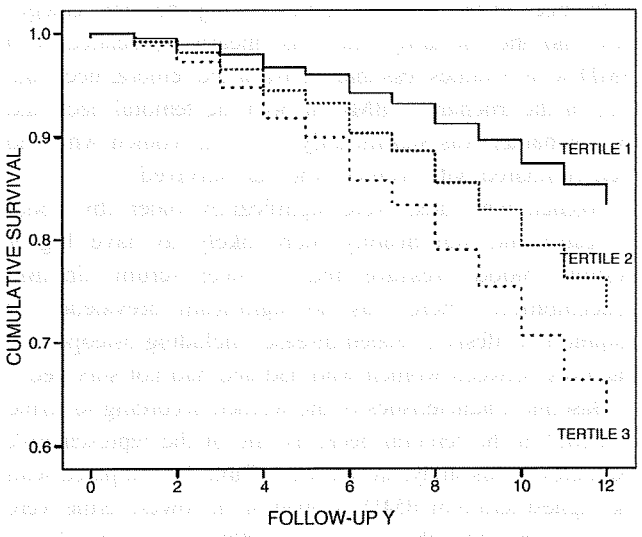

Fig. 1 Cumulative survival rate during 12-year follow-up period according to tertile of BMD at femoral neck in women. Tertiles 1 (*highest*), 2 (*middle*), and 3 (*lowest*) represent 0.624 g/cm^2 or greater, 0.552–0.624 g/cm^2, and 0.552 g/cm^2 or less for BMD at femoral neck, respectively

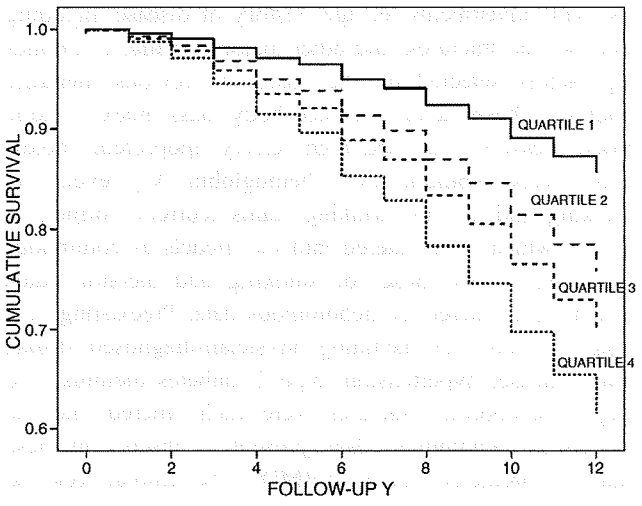

Fig. 2 Cumulative survival rate during 12-years of follow-up period according to the quartile of BMD at the femoral neck in women. Quartiles 1 (*highest*), 2 (*higher*), 3 (*lower*), and 4 (*lowest*) represent 0.652 g/cm^2 or greater, 0.584–0.651 g/cm^2, 0.540–0.583 g/cm^2, and 0.539 g/cm^2 or less for BMD at femoral neck, respectively

Table 2 Cumulative mortality rates during the 12-year follow-up period in the three categories by baseline BMD (g/cm^2) at the femoral neck

BMD		Mortality rate (number)	p value[a]
Diagnostic criteria	Osteoporosis (≦0.533)	41.9 (26/62)	
	Osteopenia (0.534–0.610)	36.0 (36/100)	
	Normal (≧0.611)	17.4 (19/109)	$p<0.001$ ($\chi^2=14.15$)
Tertile	Lowest (≦0.552)	43.3 (39/90)	
	Middle (0.553–0.624)	29.5 (26/88)	
	Highest (≧0.625)	17.2 (16/93)	$p<0.001$ ($\chi^2=14.91$)
Quartile	Lowest (≦0.539)	44.8 (30/67)	
	Lower (0.540–0.583)	35.3 (24/68)	
	Higher (0.584–0.651)	25.0 (17/68)	
	Highest (≧0.652)	14.7 (10/68)	$p<0.001$ ($\chi^2=16.29$)

[a] Chi-squared test

somewhat weakened the BMD relationship; however, BMD at the femoral neck still remained significant in these women. When women with osteoporosis were compared with those without osteoporosis (normal), the adjusted HR was 2.17 (95% confidence interval [CI] 1.07–4.41; p= 0.032), and, when women in the lowest tertile or quartile of BMD at the femoral neck were compared with those in the highest, the adjusted HR was 2.58 (95% CI 1.29–5.15; p= 0.007) in this tertile and 3.13 (95% CI 1.26–7.73; p=0.014) in this quartile. We repeated the analysis using BMD at the trochanter, and the results although similar were weaker. The adjusted HR was 1.89 (95% CI 0.97–3.70; p=0.06) in the tertile and 1.85 (95% CI 0.87–3.91; p=0.109, not significant) in the quartile.

Table 3 Baseline characteristics of 271 elderly women aged 67–89 years in the TMIG-LISA according to tertiles of BMD at the femoral neck

Characteristics	Lowest (≦0.552g/cm^2; (n=90)	Middle (0.553–0.624g/cm^2; n=88)	Highest (≧0.625; n=930)	p value
Age, mean (SD), years	75.1 (5.2)	72.4 (4.3)	71.1 (4.0)	<0.0001[a]
Body mass index, mean (SD), kg/m^2	21.8 (3.2)	23.0 (3.3)	24.2 (3.3)	<0.0001[a]
Systolic blood pressure, mean (SD), mmHg	151.1 (25.1)	148.9 (23.4)	151.7 (23.7)	0.723[a]
Blood variables, mean (SD)				
Hemoglobin, g/dl	12.1 (1.2)	12.4 (1.1)	12.5 (1.2)	0.110[a]
Albumin, g/dl	4.2 (0.3)	4.2 (0.2)	4.2 (0.2)	0.708[a]
HbA_{1c}, % of total hemoglobin	5.5 (0.5)	5.7 (0.7)	5.7 (0.9)	0.094[a]
Total cholesterol, mg/dl	189.8 (28.7)	193.8 (31.0)	193.1 (30.2)	0.637[a]
HDL cholesterol, mg/dl	50.1 (12.0)	52.8 (12.0)	51.1(12.0)	0.320[a]
Medical history, no. (%)				
Stroke	3 (3.3)	4 (4.5)	0 (0.0)	0.134[b]
Heart disease	8 (8.9)	12 (13.6)	19 (20.4)	0.082[b]
Hypertension	33 (36.7)	33 (37.5)	43 (46.2)	0.342[b]
Diabetes mellitus	2 (2.2)	9 (10.2)	2 (2.2)	0.015[b]
Fracture	2 (2.2)	3 (3.4)	4 (4.3)	0.734[b]
Alcohol drinking status, no. (%)				
Current	20 (22.2)	19 (21.6)	20 (21.5)	0.993[b]
Former	4 (4.4)	5 (5.7)	4 (4.3)	
Never	66 (73.3)	64 (72.7)	69 (74.2)	
Smoking status, no. (%)				
Current	1 (1.1)	1 (1.1)	1 (1.1)	0.500[b]
Former	1 (1.1)	0 (0.0)	3 (3.2)	
Never	88 (97.8)	87 (98.9)	89 (95.7)	

[a] Analysis of variance

[b] Chi-squared test

Table 4 Hazard ratios of BMD at the femoral neck and trochanter regions for 12-year mortality after additional adjustment for certain variables

Diagnostic criteria	Femoral Neck		Trochanter	
	Model 1[a]	Model 2[b]	Model 1 [a]	Model 2 [b]
Osteoporosis (≦0.533)	2.80 (1.55–5.06)**	2.17 (1.07–4.41)*		
Osteopenia (0.534–0.610)	2.26 (1.30–3.95) *	2.07 (1.11–3.85) *		
Normal (≧0.611)	1.0 (reference)	1.0 (reference)		
BMD tertile				
Lowest (≦0.552)	2.94 (1.64–5.26)***	2.58 (1.29–5.15)[c, **]	2.14 (1.22–3.74)**	1.89 (0.97–3.70) ns
Middle (0.553–0.624)	1.81 (0.97–3.36) ns	1.71 (0.84–3.48)[c] ns	1.64 (0.91–2.95) ns	1.59 (0.82–3.07) ns
Highest (≧0.625)	1.0 (reference)	1.0 (reference)[c]	1.0 (reference)	1.0 (reference)
BMD quartile				
Lowest (≦0.539)	3.61 (1.77–7.41)***	3.13 (1.26–7.73)[c, *]	2.39 (1.26–4.55)**	1.85 (0.87–3.91) ns
Lower (0.540–0.583)	2.65 (1.27–5.54) **	2.32 (0.96–5.60)[c] ns	1.94 (0.99–3.79) ns	1.35 (0.63–2.90) ns
Higher (0.584–0.651)	1.72 (0.79–3.76) ns	1.78 (0.72–4.44)[c] ns	1.23 (0.60–2.49) ns	0.88 (0.40–1.92) ns
Highest (≧0.652)	1.0 (reference)	1.0 (reference)[c]	1.0 (reference)	1.0 (reference)

ns not significant

*$p<0.05$; **$p<0.01$; ***$p<0.001$

[a] Model 1 shows the crude unadjusted results

[b] Model 2 is adjusted for all the variables including age, BMI, SBP, blood variables (five items), medical history (five items), alcohol drinking status, and smoking status

[c] p value for trend in femoral neck was less than 0.01

Discussion

We observed a strong and independent association between BMD at the femoral neck and total mortality during a 12-year follow-up period in 67–89-year-old women living in a community enrolled in the population-based TMIG-LISA in 1994–1995. Although weak and not significant following multivariate adjustment analysis, BMD at the trochanter region showed a similar association between BMD and total mortality to that of femoral neck BMD. This is the first study to document the clinicoepidemiological prognostic value of BMD at the femoral neck as an independent predictor of total mortality in elderly Japanese women who have a significantly lower prevalence and incidence of hip fracture compared with those in Caucasian women [15, 16].

There have been a few prospective studies concerning the association between low BMD and mortality in elderly women. Browner et al. [11] reported that one SD decrease in BMD at the proximal radius was associated with a 1.19-fold increase in mortality (95% CI 1.04–1.30). The study found a strong inverse association between low BMD at the proximal radius and stroke mortality. However, it is very interesting that this association was not confounded by history of previous diseases such as stroke, hypertension, diabetes mellitus, and smoking habits. Our data also showed no significant associations with previous diseases such as stroke, hypertension, heart diseases, and smoking habits at baseline. This means that the significant association between low BMD and increased risk of mortality is independent of a past history of lifestyle-related diseases.

Ensrud et al. [8] reported that prevalent vertebral deformities in older women with low bone mass were associated with an increased risk of mortality in a prospective cohort study in the USA. The relative risk (RR) adjusted for many factors including age, smoking status, hypertension, heart disease, and any history of fracture since the age of 50 did not alter the crude association between prevalent vertebral deformities with low BMD and risk of mortality (RR=1.49, 95% CI 1.05–2.21). Although the study participants were predominantly white female volunteers with low hip BMD who visited clinical centers as osteoporotic patients, the association between low hip BMD and increased risk of mortality in older women is similar to that in our prospective cohort study, in which the subjects were older Japanese women. Similar results were also found in another prospective cohort study in which mortality was compared in women who had vertebral fractures and in women without fractures [7]. The authors found that women with one or more vertebral fractures had a 1.23-fold greater age-adjusted mortality rate (95% CI 1.10–1.37), and mortality increased as the number of vertebral fractures increased.

A Danish study reported a 43% increase in mortality (RR= 1.4, 95% CI 1.0–2.0) per one SD decrease in bone mineral content in women at menopause [26]. When only cardiovascular death was considered in their study, the relative risk of

dying within 17 years of the menopause was increased 2.3-fold (95% CI 1.0–5.3). Our data showed that lower baseline BMD at the femoral neck is a significant predictor of all-cause mortality among community-dwelling elderly women. These findings are very similar to those recently reported by Nguyen et al. [10]. These authors found that lower baseline BMD at the femoral neck was associated with an increased risk of mortality (HR per SD 1.3: 95% CI 1.0–1.7) after adjusting for age in women aged 60 and over in a 15-year longitudinal study conducted in Australia. They also reported that women with osteoporotic BMD at baseline (i.e., T-scores$\leqq -2.5$) had a significantly reduced survival probability compared with women with either osteopenic (i.e., T-scores -2.4 to -1.1) or normal BMD (i.e., T-scores$\geqq -1.0$) during a 15-year follow-up period.

Although there are a few exceptions, such as the prospective cohort study conducted in the Netherlands which found no significant relationship between low BMD at the femoral neck and all-cause mortality among elderly women [27], many longitudinal and population-based clinicoepidemiological studies, including the present study, have revealed a significant relationship between low BMD at the femoral neck or hip and increased risk of mortality in elderly women. However, the exact mechanism of this relationship is unclear. It is unlikely that low BMD per se could directly influence mortality since fractures contribute only a tiny proportion to total mortality in the older general population.

One of the most plausible explanations for the relationship between low BMD and increased risk of mortality is atherosclerosis. Osteoporosis and atherosclerosis are both highly prevalent conditions [28]. Recent evidence for a shared pathogenesis between these two chronic conditions is emerging from both basic and clinical research, i.e., numerous factors are implicated in the common pathophysiological mechanism of these two conditions [29–33]. In addition, vascular calcification caused by atherosclerosis increases the risk of cardiovascular diseases and mortality independent of the effects of traditional risk factors [34, 35]. As previously mentioned, epidemiological research in three studies has shown that women with low BMD or a vertebral fracture were observed to have increased mortality caused by cardiovascular diseases [7, 26, 36]. Recently, Sambrook et al. [37] reported that, in the frail elderly, high bone turnover is associated with all-cause mortality independent of age, sex, and hip fracture status. These authors estimated that the mechanism of the effect of bone turnover on mortality could also be due to cardiovascular causes.

In another prospective study, women with vertebral fractures had a higher risk of subsequent cancer and pulmonary death, particularly women with severe kyphosis at baseline [7]. A positive association between BMD and the incidence of breast cancer has also been observed, which may indicate that BMD reflects lifetime exposure to estrogen [38, 39].

In the present study, however, it is not possible to analyze the underlying mechanism of excess mortality associated with low BMD at the femoral neck since one of the limitations of this study was that the causes of death were not defined.

This study has other limitations. First, the number and characteristics of the subjects must be considered. Although the subjects analyzed were all eligible women aged 67 years or older living in a rural community, the women were relatively healthy and were able to travel from their homes to the health examination center, get into the vehicle, and lie on the instrument table in the prone position for measurement of BMD at the hip during the baseline survey conducted in 1994–1995. As a result, the final sample size was 57.4% (271/472), and the present findings may not be applicable to frail older people who have low physical functional capacity where BMD at the hip could not be measured in the prone position. Second, BMD has been measured at virtually all available measurement sites (spine, proximal femur, forearm, whole body, calcaneus, and tibia) [40, 41]. In the present study, only the proximal femur, i.e., the femoral neck and trochanter regions, was used as an indicator of all-cause mortality. In general, measurement of BMD at the lumbar spine is widely used as a standard manner. BMD measurement at the femoral neck and the trochanter is also recommended, particularly in elderly women whose BMD at the lumbar spine is commonly contaminated by degenerative and sclerotic changes, such as osteophyte formation and compression fractures. The findings of the present study may not be directly comparable with those in other studies, particularly those which used vertebral deformity as an indicator [7, 8]. It is well known that BMD at the femoral neck is the strongest predictor of femoral neck fracture risk [42, 43]. Fujiwara et al. [44] reported that baseline BMD and loss of BMD at the femoral neck predicted the risk of spine and hip fractures in a Japanese population. However, few studies have been carried out to determine which site of BMD measurement is the most suitable and predictive for all-cause mortality risk in elderly Japanese people. A more comprehensive approach, including the measurement of bone mass at various sites and the use of different BMD determination methods in a large sample of elderly people to evaluate the associations between low BMD at different sites and mortality is necessary. Third, this study did not ascertain the primary and exact cause of death of participants during the follow-up period. Due to strict privacy protection, it is difficult to access personal health information, particularly cause of death, via the municipal government.

Even with these limitations, this study has several strengths, in particular, the use of a population-based sample of the TMIG-LISA cohort and the 12-year follow-up period. In addition, the availability of comprehensive information in the TMIG-LISA database allowed us to adjust for important

factors which might have confounded the relationship between low BMD at the femoral neck and total mortality.

The study participants were all initially ambulatory and healthy elderly women living in the community, which enabled us to extend the results to general community-dwelling elderly persons. Furthermore, in spite of the low prevalence of hip fractures among Japanese women compared with those of Caucasian women, our results indicate that bone health in the proximal femur is a universal and powerful predictor of general health status in elderly people.

Conclusion

In conclusion, our longitudinal study showed that low bone mineral density at the femoral neck is a potential predictor of increased mortality in elderly women in Japan. This finding suggests that preventive strategies should be considered to increase and maintain bone mineral density at the femoral neck even in elderly subjects, not only to prevent hip fractures but also probably to reduce mortality in the aging population.

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Conflicts of interest None.

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Original article

The effect of geometry of the tibial polyethylene insert on the tibiofemoral contact kinematics in Advance Medial Pivot total knee arthroplasty

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Abstract

Background. In modern total knee arthroplasty (TKA), it is important to reproduce both medial pivot motion and posterior femoral rollback to obtain greater postoperative knee flexion. Several studies have reported the factors affecting knee motion and range of motion after TKA. The purpose of this study was to evaluate the effect of the tibial insert geometry on the tibiofemoral contact kinematics, especially focusing on the medial pivot motion and posterior femoral rollback.

Methods. Seven cadaveric knees were replaced with the Advance Medial Pivot TKA, and two different geometries of polyethylene tibial insert, the standard medial pivot design (MP-design) and double high design (DH-design), were biomechanically compared. Four experimental configurations were evaluated in each specimen in this order: (1) the MP-design with posterior cruciate ligament (PCL) retaining, (2) the DH-design with PCL retaining, (3) the MP-design with PCL sacrificing, and (4) the DH-design with PCL sacrificing.

Results. Under the PCL-retaining condition, both designs showed no medial pivot but bicondylar femoral rollback more than 60° of knee flexion. In the MP-design, tibiofemoral contact point (estimated contact point, ECP) of the medial compartment was located on the posterior lip of the ball-in-socket structure while demonstrating greater than 120° of knee flexion. The posterior translation was also the same in both designs. On the other hand, ECP of the MP-design and the DH-design showed only medial pivot pattern under the PCL-sacrificing condition. In the DH-design, ECP of the lateral compartment showed paradoxical anterior translation from 0° to 60° of knee flexion. Total posterior translation was significantly greater in the lateral compartment than that in the medial compartment.

Conclusions. The results of this study suggest that in this type of TKA system the ball-in-socket geometry in the MP-design has an advantage for reproducing medial pivot motion in the PCL-sacrificing condition, and the flexion path structure in the DH-design is considered to be both effective and safe for femoral rollback in the PCL-retaining condition. However, neither design is sufficient to reproduce medial pivot motion and posterior femoral rollback. Therefore, a different design of tibial insert is needed for more physiological kinematics after TKA.

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Introduction

An important aim of total knee arthroplasty (TKA) is to return the arthritic knee to as close to normal function as possible. The physiological motion of the knee joint has both medial pivot motion and femoral rollback.[1–3] This motion pattern is seen not only in the midflexion area but also in a deep flexion range of more than 100°.[4] Therefore, the combination of a medial pivot motion and femoral rollback is thought to be the key motion for high flexion of the knee joint. There are several factors that influence the three-dimensional knee motion after TKA: these include the geometry of the femoral and tibial component, the setting alignment of these implants to the bone, changes in the level of the joint line, soft tissue balance and tension, and retention or sacrifice of the posterior cruciate ligament (PCL).[5–8] Fluoroscopic studies of modern TKA have not yet demonstrated expected knee motion close to normal conditions but rather a nonphysiological motion such as paradoxical sliding forward or paradoxical rolling forward.[8–10] Furthermore, these studies have analyzed the knee motion during normal gait, up/down stairs, and rising from/sitting in a chair. In these activities, the maximum flexion of the knee joint is never greater than 90°; therefore, precisely how the knee joint moves after TKA thus remains unclear, especially in deep flexion.

Recently, an asymmetrical tibial polyethylene insert, a ball-in-socket on the medial side and an arcuate

groove on the lateral side, was introduced to reproduce the medial pivot motion during knee extension-flexion.[11] In this type of TKA system, the typical medial pivot motion was observed by an in vivo kinematic study using fluoroscopy.[12] However, it is not clearly demonstrated whether we should preserve or sacrifice the PCL at surgery. Furthermore, it is unknown whether posterior femoral rollback is reproduced in this type of TKA system. The purpose of the current study was to evaluate the effect of polyethylene tibial insert geometry in the medial pivot TKA on the tibiofemoral contact kinematics in relationship to retaining or sacrificing PCL, especially focusing on the medial pivot motion and posterior femoral rollback in deep knee flexion.

Materials and methods

Seven fresh-frozen cadaveric knee joints were used in this study. Consent for the design of this study was obtained from the Institutinal Review Board and the ethical committee of our institute. X-ray examination was previously performed to select knee joints of almost the same size. None of the knees had any evidence of skeletal deformity, and it was confirmed that the PCL was in an intact condition.

After the skin and subcutaneous tissue were stripped, leaving the capsule, ligaments, and muscles intact, each knee was replaced with the Advance Medial Pivot Prosthesis (Wright Medical Technology, Arlington, TN, USA). The distal femur was cut in 5° of valgus and 3° of external rotation. The proximal tibia was cut at a right angle to the tibial axis in the coronal plane and 3° of posterior slope in the sagittal plane. The PCL was preserved, and the patella was not resurfaced. After bone cutting was completed, a size 2 femoral and tibial component with a 10-mm-thick polyethylene insert was placed. The metal rods were inserted into the intramedullary space of the femur and tibia, and the femoral rod was rigidly fixed to the motion frame. The tibial rod was fixed to the clamp that allows 6-degrees-of-freedom motion. The knee joint was moved from 0° to 150° of flexion by a load cell under the loading condition of 40 N on the quadriceps tendon and 20 N on each medial and lateral hamstring muscle through the semitendinosus and biceps femoris tendon. The load ratio of quadriceps and hamstring was according to previous reports; however, the actual amount of load was less than that of the physiological condition as a result of the strength of the motion frame and load cell.[13,14]

The tibiofemoral contact kinematics was then evaluated using the photostereometric knee motion analysis system (KKN/1B), which was basically developed at our institute (Faculty Engineering, Niigata University). This system consists of eight LEDs (BR 3371X; Stanley Denshi, Tokyo, Japan) with marker devices mounted onto the femoral and tibial bone, two sets of three linear high resolution CCD cameras (TCD141C; Toshiba, Tokyo, Japan) for tracking the LED position, and a PC for data analysis. The spatial resolution was designed to be 0.06 mm when the LEDs were located on the focal plane of the CCD cameras, and overall accuracy of the measuring system was within 0.52 and 0.11 mm at any point on the femoral component. Three-dimensional computer-aided design (CAD) solid models of the femoral component, tibial tray, and polyethylene insert were obtained, and the positional relationship between these models was also measured. Intersurface distance between the femoral component and polyethylene insert was quantitatively assessed, and the area where the value of the intersurface distance was less than or equal to 0.75 mm was defined as the estimated contact area. The center of the estimated contact area was finally defined as the estimated contact point (ECP), and the contact kinematics was evaluated by changing the ECP.[15–17]

In the current study, two different designs of the polyethylene tibial insert were compared: one was the standard medial pivot design (MP-design) and the other was the double high design (DH-design). In the MP-design, a medial socket exactly conformed to the sphere of the femoral component, thus providing the medial ball-in-socket kinematics, and the lateral part was an arcuate groove centered on the medial socket. The basic geometry of the DH design was the same as the MP-design: the main difference between the MP-design and the DH-design was the geometry of the posterior lip. In the MP-design, the geometry of the posterior lip was part of the ball-in-socket and arcuate groove design; on the other hand, the posterior lip of the DH-design was 3 mm lower than that of the MP-design, which resulted in a posterior slope (Fig. 1a–c). The concept of posterior slope was that this slope will act as a "flexion path" when femoral rollback occurs. The medial pivot femoral component was used for both the MP-design and the DH-design. Both medial and lateral condyles of the medial pivot femoral component had a sphere and C-curve design with a single radius in all three planes. Both types of polyethylene inserts were exchanged on the same metal tibial component, so that the difference of the design was directly comparable using the same cadaveric knee joint.

Four experimental configurations were evaluated in each specimen in this order: (1) the MP-design with PCL retaining, (2) the DH-design with PCL retaining, (3) the MP-design with PCL sacrificing, and (4) the DH-design with PCL sacrificing.

At the time of measurement under the PCL-sacrificing condition, the extension gap and the flexion gap were evaluated and a polyethylene insert 2 mm thicker was used.

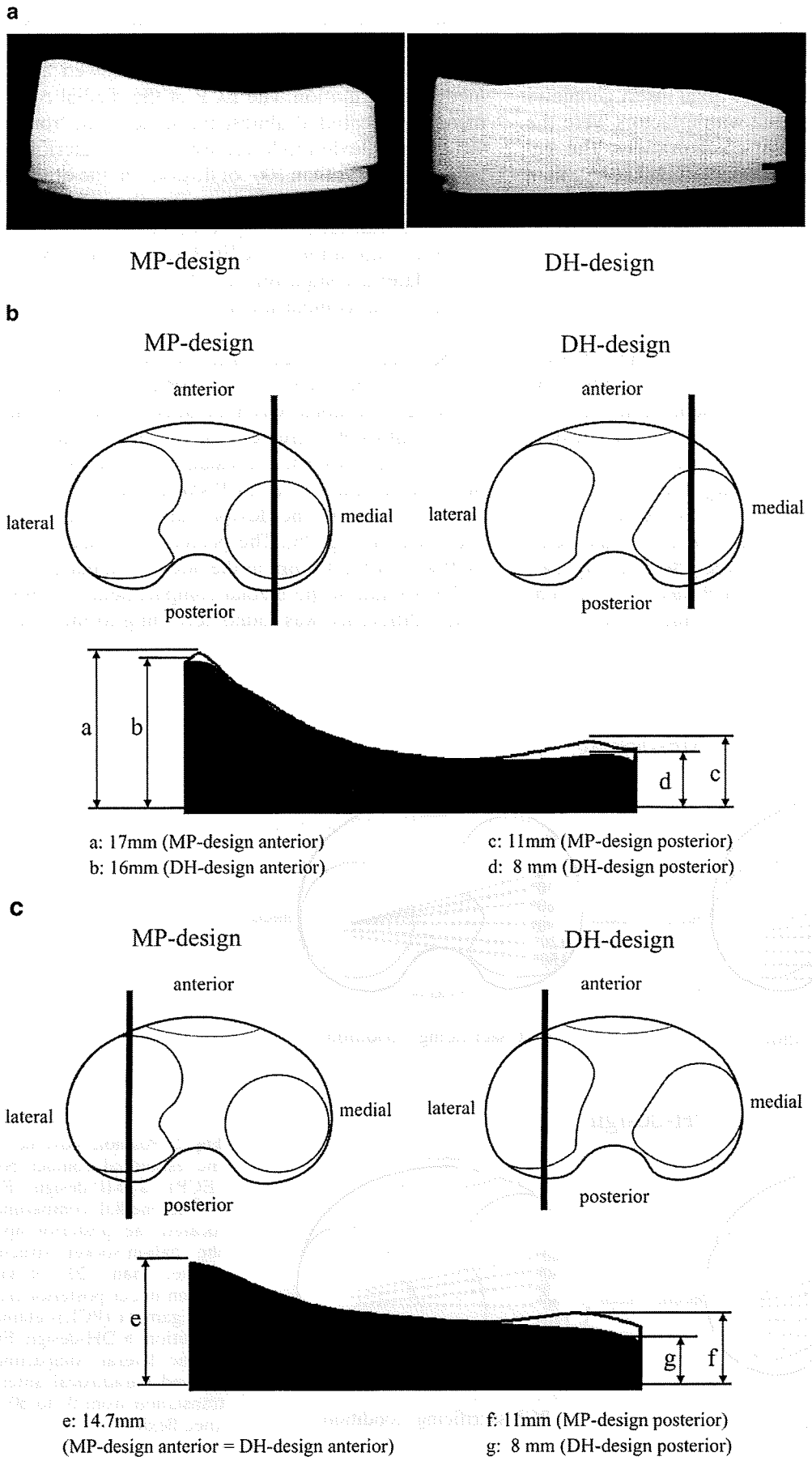

Fig. 1. Geometric characteristics of medial pivot design (DH-design) and double high design (DH-design). **a** Lateral view. **b** Cross-sectional geometry of the medial compartment. **c** Cross-sectional geometry of the lateral compartment

In this study, the anteroposterior motion of the ECP in the medial and lateral condyles was analyzed. Two-way analysis of variance (ANOVA) with within factors was used to analyze the effect of tibial insert geometry on the contact kinematics. The within factors were the aforementioned four different configurations. The significance level was set at a probability value less than 0.05.

Results

The MP-design showed bicondylar posterior translation under the PCL-retaining condition and medial pivot motion under the PCL-sacrificing condition. When the PCL was retained, the ECP of the medial compartment shifted posteriorly mainly more than 60° of knee flexion, and the ECP of the lateral compartment showed continuous posterior translation along knee flexion. The ECP of the medial compartment was located on the posterior lip of the ball-in-socket structure while demonstrating greater than 120° of knee flexion (Fig. 2a). The posterior translation of the ECP was 15.1 ± 3.1 mm (mean ± SD) in the lateral compartment and 11.6 ± 2.9 mm in the medial, and no statistical difference was seen between either compartment (Fig. 3). After the PCL was sacrificed, the MP-design showed a typical medial pivot motion. The ECP of the medial compartment was located at almost the same point from 0° to 90° of knee flexion followed by a slight posterior translation of greater than 100° of flexion. On the other hand, the ECP of the lateral compartment showed continuous posterior translation along knee flexion (Fig. 2a). The posterior translation of the ECP was significantly greater in the lateral compartment (11.1 ± 3.8 mm) than that in the medial compartment (3.3 ± 2.5 mm) ($P = 0.022$) (Fig. 3).

The DH-design had basically the similar tracking pattern of the ECP as the MP-design under PCL-retaining conditions, which included a posterior shift of the medial ECP of greater than 60° of knee flexion and a continuous posterior translation of the lateral ECP. Both medial and lateral ECP shifted posteriorly on the posterior slope of the flexion path more than 120° of knee flexion (Fig. 2b). The posterior translation of the ECP was 14.5 ± 4.2 mm in the lateral compartment and 10.7 ± 3.8 mm in the medial compartment, and no statistical difference was found according to these results

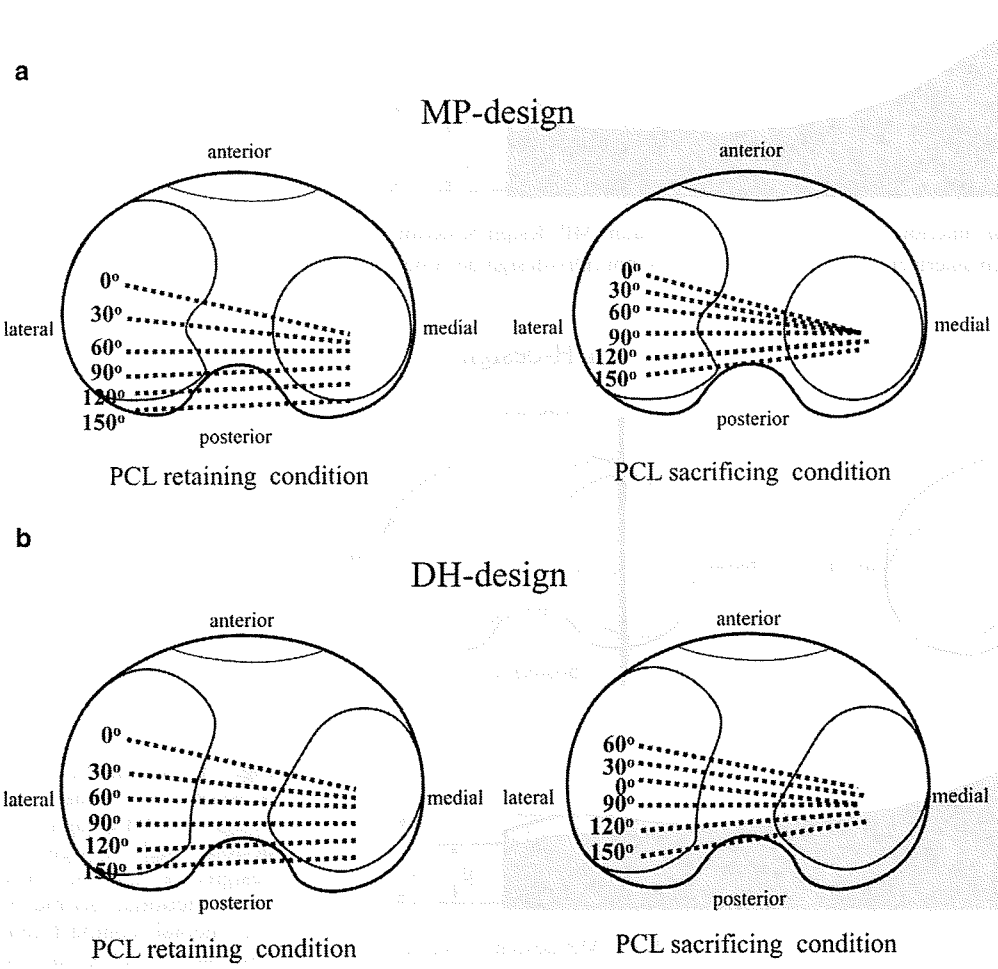

Fig. 2. Position movement of the estimated contact point (ECP). **a** MP-design. ECP of the medial compartment located the posterior lip of the ball-in-socket structure greater than 120° of knee flexion under posterior cruciate ligament (PCL)-retaining condition. **b** DH-design. ECP of the lateral compartment showed paradoxical anterior translation from 0° to 60° of knee flexion

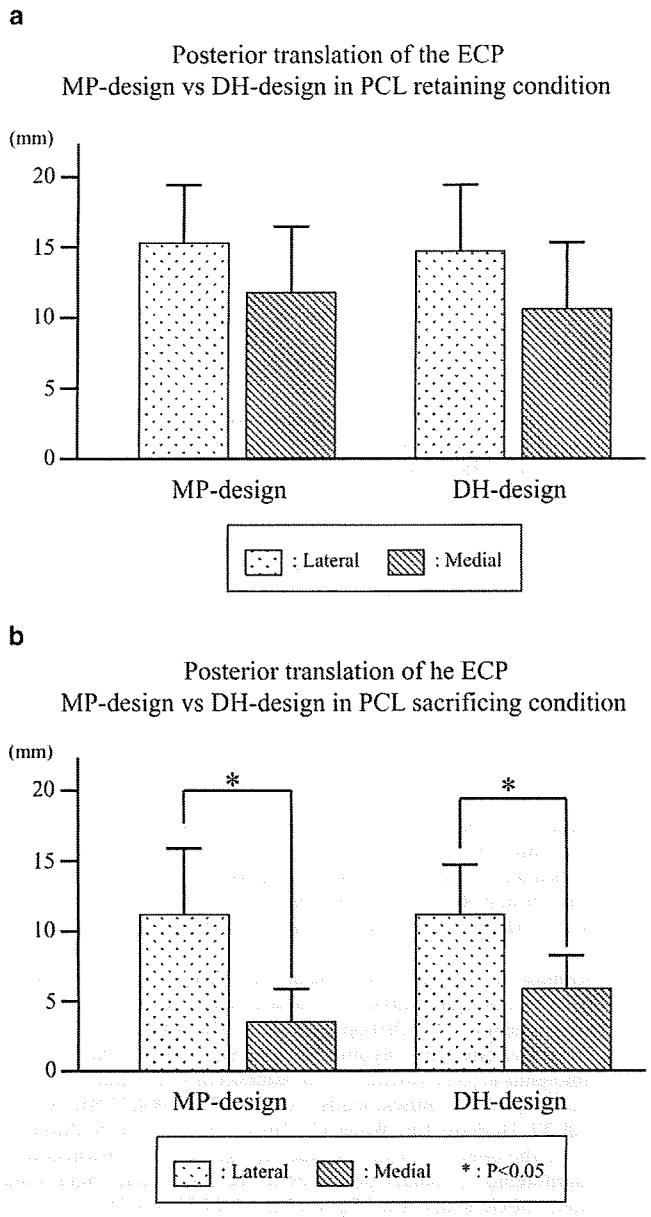

Fig. 3. Posterior translation of the ECP. **a** PCL-retaining condition. **b** PCL-sacrificing condition

(Fig. 3). The DH-design also showed a medial pivot motion after the PCL was sacrificed. The ECP of the medial compartment did not move from 0° to about 120° of knee flexion and then it slightly shifted to the posterior direction. In the lateral compartment, ECP showed paradoxical anterior translation from 0° to 60° of knee flexion followed by continuous posterior translation (Fig. 2b). The posterior translation of the ECP was 11.2 ± 3.6 mm in the lateral compartment and 5.5 ± 2.7 mm in the medial compartment, and then the posterior translation in the lateral ECP was significantly greater than that on the medial compartment ($P = 0.028$) (Fig. 3).

When comparing both designs, posterior translation of the ECP was not statistically different between the MP-design and DH-design under both PCL-retaining and PCL-sacrificing conditions.

Discussion

Currently, very few studies exist on the kinematic analysis of the medial pivot type TKA. Saari et al.[18] evaluated the Samuelson total knee prosthesis and described that the medial spherical condyle stabilized anteroposterior motion. Schmidt et al.[12] studied the Advance Medial Pivot prosthesis using fluoroscopy and showed medial pivot motion during the stance phase of the gait cycle. Moonot et al.[19] analyzed the Medial Rotation Knee with fluoroscopy and demonstrated medial pivot motion in a lunge motion.

In the present study, two different geometries of the polyethylene insert in the Advance Medial Pivot TKA were compared. The medial pivot geometry (MP-design) has a highly conformed "ball-in-socket" design to reproduce the medial pivot motion. On the other hand, the double high tibial insert (DH-design) is designed to achieve both medial pivot motion and posterior femoral rollback in deep knee flexion that will hopefully lead to more physiological kinematics and a better flexion angle. However, our data in the current study demonstrate that the contact kinematics by ECP did not substantially differ between the MP-design and the DH-design, especially in the deep flexion area greater than 120° of knee flexion. When the PCL was retained, both designs showed no medial pivot but did have bicondylar rollback, and, when the PCL was sacrificed, both designs showed no femoral rollback but typical medial pivot motion.

The first reason for this result is that medial ball-in-socket geometry is a highly conformed design and has an advantage in reproducing medial pivot motion, but it is insufficient for femoral rollback even if the posterior slope was made. The second reason is that femoral rollback is essentially controlled by the PCL, and this effect is stronger than that of the geometric conformity of the tibial insert as the MP-design and the DH-design under the PCL-retaining condition. Most et al.[20] analyzed femoral rollback after cruciate-retaining and stabilizing TKA and described that the cam-spine engagement structure played an important role in restoring posterior femoral rollback in the PCL-substituting TKA. However, the cam-post mechanism is not thought to reproduce medial pivot motion. Therefore, this study suggests that if we would reproduce both medial pivot motion and femoral rollback after TKA, a new concept and design of the tibial insert geometry will be needed.

In the MP-design, the ECP of the medial compartment located on the posterior edge of the ball-in-socket structure greater than 120° of flexion from bicondylar femoral rollback under the PCL-retained condition. Li et al.[21] evaluated the in vivo tibiofemoral contact kinematics of a cruciate-retaining TKA and showed that the current component design did not allow the femoral condyle to roll off the polyethylene edge at high degrees of flexion because of the geometry at the posterior lip. Abnormal contact conditions between the polyethylene insert and metal tray in the MP-design may present some risk of polyethylene wear or limitations of knee flexion. On the other hand, the lateral ECP of the DH-design showed paradoxical anterior translation from 0° to 60° knee flexion under the PCL-sacrificing condition, possibly because of the lesser conformity of the medial ball-in-socket structure by decreasing the height of the anterior and posterior lip. Recently, short- to mid-term clinical results of the Advance Medial Pivot prosthesis were reported. However, none of the authors clearly described the treatment for the PCL.[11,12,22] From the results of the present biomechanical study, it is recommended that the PCL should be sacrificed when the MP-design is used and retained when the DH-design is used.

There are several limitations because this is an in vitro cadaveric study. The first limitation is the number of specimens. Only seven cadaveric knees were evaluated in this study because it was difficult to obtain enough cadavers. Moreover, we selected knee joints of the same size for sequential evaluations, eliminating interspecimen variations. The second limitation is the loading condition. The load ratio of quadriceps and hamstring was close to physiological conditions; however, the actual amount of load was smaller than that of physiological condition as a result of the strength of the motion frame and load cell. In the near future, an in vivo kinematic study comparing the MP-design and the DH-design is needed.

The results of this study indicate that the ball-in-socket geometry in the MP-design has an advantage in reproducing medial pivot motion in the PCL-sacrificing condition and that the flexion path structure in the DH-design is effective for femoral rollback in the PCL-retaining condition. However, neither design is sufficient to reproduce medial pivot motion and posterior femoral rollback. Thus, a different design of tibial insert with a new concept is needed for more physiological kinematics after TKA.

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ORIGINAL ARTICLE

Relationship between radiological knee osteoarthritis and biochemical markers of cartilage and bone degradation (urine CTX-II and NTX-I): the Matsudai Knee Osteoarthritis Survey

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Abstract Biochemical markers of cartilage and bone degradation are becoming increasingly important in the evaluation of knee osteoarthritis (OA). To clarify the correlation between radiological knee OA and urine CTX-II (C-terminal crosslinking telopeptide of collagen type II) or urine NTX-I (N-terminal crosslinking telopeptide of type I collagen), we conducted a cross-sectional study in the cohorts of the epidemiological knee survey at the Matsudai district in Niigata Prefecture, Japan. Urine specimens were collected from 296 subjects, and CTX-II and NTX-I were measured using ELISA. Standing knee AP X-rays were obtained and graded according to the Kellgren–Lawrence classification. The subjects were then divided by gender, age (40- to 59-year-old group and 60- to 79-year-old group), and the X-ray grade (Grade 0, 1, Grade 2, and Grade 3, 4). In non-OA (Grade 0, 1) subjects, the 60- to 79-year-old group had significantly higher CTX-II values than the younger group only in females. The subjects of both genders aged over 60 years of age with OA Grade 3, 4 had significantly higher CTX-II values than the Grade 0, 1 group or the Grade 2 group. For NTX-I, there were no significant differences between each OA grade although the Grade 3, 4 group females from 60 to 79 years of age had higher values than the Grade 2 group. In addition, in the 60- to 79-year-old subjects of both genders, a positive correlation was observed between the urine CTX-II and urine NTX-I. For the subjects ranging from 60 to 79 years of age in both genders, the urine CTX-II values indicate the progression of OA. In addition, the weak but positive correlation between urine CTX-II and urine NTX-I in the subjects ranging from 60 to 79 years of age in both genders suggests that bone resorption and cartilage degradation appear to develop in parallel.

Keywords Knee osteoarthritis · Urine CTX-II · Urine NTX-I

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Introduction

In the last several years, the average age of people in Japan has been increasing rapidly, and knee osteoarthritis (OA) is becoming a very frequently occurring disease. Currently, diagnosis of knee OA is based on symptoms, history, physical findings, laboratory findings of the blood and synovial fluid, image assessments (e.g., X-ray, MRI).

An evaluation of the function and pain in knee OA is performed based on the functional scores (e.g., the Knee Society Score, the Japanese Orthopaedic Association Knee OA score), and QOL assessments (e.g., SF-36, WOMAC