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RESEARCH

ANALYSIS OF BILATERAL FEMORAL GEOMETRIC PARAMETERS IN 16 PATIENTS WITH ATYPICAL FEMORAL FRACTURES

Abstract

Introduction: This study aimed to investigate the associationbetween femoralgeometry and clinical features and to analyse the effect of bisphosphonate use on atypical femur fracture healing.

Materials and Method: Patients admitted with femoral shaft fractures were examined,and thosewhofulfilled the diagnostic criteria for atypical fractures according to the 2014-revised edition of the American Society for Bone and Mineral Research(ASBMR) were included in this study. Fracture localisation, inner and outer cortical thickness, lateral bowing and femur neck-shaft angle of both fractured and contralateral sides were measured. We analysed the correlations between demographics, clinical factors and radiographic features.

Results: Our study group comprised 14 females and 2 males. The mean age was 76.3 (range, 67–91) years. The mean follow-up period was 45.9 (range, 12–84) months. All the fractures were located on the femoral shaft. The mean duration of fracture union was 8 (range, 4–11) months. The outer cortical thickness of the fractured side was significantly greaterthan that of the contralateral side. No significant difference was observed between the inner corticalthickness of the fractured and contralateral sides. The lateral bowing of the fractured femoral shaft was significantly greater than that of the contralateral femur. A significant positive correlation was observed between the duration of bisphosphonate use and both fracture healing time and lateral bowing of the femoral shaft.

Conclusion: Long-term bisphosphonate usealtersthe femoralgeometry not only on the fractured side but also on the contralateral side and increases the fracture risk.

Keywords: Femoral fractures; Osteoporosis; Alendronate; Diphosphonates

ARAŞTIRMA

ATİPİK FEMUR KIRIĞI OLAN 16 HASTANIN HER İKİ TARAF FEMURLARININ GEOMETRİK PARAMETRELERİNİN DEĞERLENDİRİLMESİ

Öz

Giriş: Bu çalışmada femur geometrisi ile klinik özellikler arasındaki ilişkiyi araştırmak ve bifosfonat kullanımınına tipik femur kırığı iyileşmesi üzerindeki etkisini analiz etmek amaçlanmıştır.

Gereç ve Yöntem: Femoral şaft kırığı ile başvuran hastalar analiz edildi ve Amerikan Kemik ve Mineral Araştırmaları Derneği (ASBMR)'nin 2014'te revise edilmiş baskısına gore atipik kırıklar için tanı kriterlerini karşılayan hastalar çalışmaya dahil edildi. Kırık lokalizasyonu, iç ve dış korteksin kalınlığı, lateral eğilme ve hem kırık hem de karşı tarafların femur boyun-cisim açıları ölçüldü. Demografik, klinik faktörler ve radyografik özellikler arasındaki korelasyonlar analiz edildi.

Bulgular: Çalışma grubumuz 14 kadın ve 2 erkekten oluşmaktadır. Ortalama yaş 76.3 (dağılım, 67–91) idi. Ortalama takip süresi 45.9 (dağılım, 12-84) aydı. Tüm kırıklar femur şaftı üzerinde idi. Ortalama kaynama süresi 8 (4-11) ay idi. Kırık tarafın dış korteksin kalınlığı kontralateral taraftan anlamlı derecede yüksekti. Kırık tarafın iç korteksinin kalınlığı kontralateral taraftan anlamlı derecede farklı değildi. Kırık femur şaftının lateral eğimi, kontralateral femurdan anlamlı derecede yüksekti. Bisfosfonat kullanım süresi ile hem kırık kaynama süresi hem de femur şaftının lateral eğilmesi arasında anlamlı bir pozitif korelasyon gözlendi.

Sonuç: Uzun vadeli BFS kullanımı femur geometrisini sadece kırık tarafında değil kontralateral tarafta da değiştirir ve kırılma riskini arttırır.

Anahtar sözcükler: Femur kırıkları; Osteoporoz; Alendronat; Bifosfonat

INTRODUCTION

Osteoporosis is a skeletal disorder characterised by low bone density resulting inmicrostructure disorders that can increase fracture susceptibility (1). Osteoporosis has a higher prevalence among older adults. Notably, treatment of osteoporosis-related fractures can be expensive (2). Bisphosphonates (BPs) are widely used as therapy to efficiently treat and prevent fractures in patients with osteoporosis. Furthermore, they are often used as the first line of treatment for osteoporosisaccording to the current evidence-based guidelines (3). Moreover, BPsare used in the treatment of Paget's disease, metastatic bone disease and multiple myeloma.

Several large clinical trials have revealed the reliability and tolerability of BPs (4). However, post-marketing reports and epidemiological studies have reported some rare and potentially graveadverse effects associated with the long-term BPuse, such as dyspepsia, nausea, muscular pain, osteonecrosis of the jaw and atrial fibrillation (5). Becauseof theadverse effectsof BPs,despite the primary use of BPs to prevent osteoporosis-related fractures, a paradoxicalassociationbetween BPs and atypical femoral fractures (AFFs) was first demonstrated in 2008 (6). Several reports have suggested a possible association between BP use and AFFs (7-12).

The American Society for Bone and Mineral Research (ASBMR) defined the diagnostic criteria for AFFs in 2010 (13), and this has recently garnered interest. In 2014, the updated diagnostic criteria were published. AFF is diagnosed based on subtrochanteric or femoral shaft location and the presence of at least the following four or five major criteria: minimal trauma, fracture originating at the lateral cortex and being substantially transverse, complete fractures extending through both cortices, localised periosteal or endosteal cortical thickening and minimal comminution. Diagnosis excludes minor criteria; however, it includesincreased cortical thickness of the femoral diaphysis, bilaterality, a prodrome of thigh or groin pain and delayed fracture healing (14).

Few studies have investigated the association between AFFs and femoral geometry. Jang et al. reported the association between bowing and cortical thickness (15). A study by Starr et al. concluded that a decrease in the femoral neck-shaft angle and an increase in lateral bowing increased the risk of AFF because of the tensile stress applied to the lateral femoral cortex (16).

Therefore, our study included both clinical features and radiological measurements, including femoralgeometry. This study aimed to investigate

Figure 1. BP-related fracture of the femur shaft.

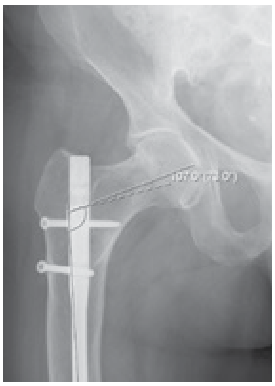

Figure 2. Measurement of femur neck-shaft angle.

Figure 3. Method of lateral bowing measurement.

Figure 4. Lateral cortical thickness.

Table 1. Demographic features of the patients.

Variable		Min.-Max	Median	Mean±sd
Age		67.0-91.0	74.0	76.3±7.4
Gender	Female		14	87.5%
	Male		2	12.5%
Fracture location (Femur)	Shaft		16	100.0%
Operation type	IMN		12	75.0%
	Plate		4	25.0%
Type of Bisphosphonate	Alendronate		12	75.0%
	Risedronate		4	25.0%
Duration of Bisphosphonate use (Year)		4.0-12.0	7.0	7.1±2.3
Supplement	Ca		16	100.0%
	D-Vit		16	100.0%
Fracture healing time(months)		4.0-11.0	8.0	7.9±1.8

the association between femoralgeometry and clinical features, alongwiththe effect of BPs on fracture healing.

MATERIALS AND METHOD

Patients admitted to a Level 1 Trauma Centre between January 2012 and January 2018 with femoral shaft fractures were analysed, and those who fulfilled the diagnostic criteria for atypical fractures according to the 2014-revised edition of the ASBMR were included in this study. Exclusion criteria were femoral fractures following high-energy trauma, patients who had previously undergone femoral surgery, patients whose BPuse duration was <4 years and thosewith inadequate radiographs that did not permit measurements. In total, 16 patients were included in this study. The patients' medical records and radiographs (pelvis anteroposterior andbilateral femur anteroposterior views) were examined retrospectively. Demographic data were collected, including patients' age, gender, BP use duration, type of surgery performed and type of BP used.

Image analysis

Calculations were independently performed by two orthopaedic surgeons according to the ASBMR. Fracture localisation, inner and outer cortical thickness, lateral bowing and femoral neck-shaft angle of both the fractured and contralateral sides were measured (Figures 1-4).

The femoral neck-shaft angle was calculated and classifiedinto three groups: normal (between 125°–140°), coxa valga (>140°) and coxa vara (<125°). The femoral bowing angle was described as the angulation between the proximal and distal quarters of the femoral diaphysis. We analysed the associations between demographics, clinical factors and radiographic features.

Table 2. Measurements by the two orthopaedic surgeons.

	1st Orthopaedic surgeon		2nd Orthopaedic surgeon		p^w	r (%95 Confidence Interval)	p^{IC}
	mean±sd	median	mean±sd	median			
Cortical thickness							
Fractured side(outer)	6.7±1.3	7.0	6.7± 1.3	6.9	0.083	0.998 0.995 - 0.999	**0.000**
Fractured side (inner)	5.7±1.3	5.7	5.7±1.3	5.7	0.285	0.997 0.993 - 0.999	**0.000**
Contralateral side (outer)	5.7±0.8	6.0	5.7±0.8	6.0	0.083	0.996 0.987 - 0.999	**0.000**
Contralateral side (inner)	5.9±1.7	5.3	5.8±1.7	5.3	0.083	0.998 0.995 - 0.999	**0.000**
Femur neck-shaft angle							
Fractured side	123.7±8.0	121.5	123.7±8.0	121.8	1.000	0.995 0.985 - 0.998	**0.000**
Contralateral side	127.8±5.6	127.0	127.8±5.2	127.3	0.873	0.995 0.985 - 0.998	**0.000**
Lateral bowing							
Fractured side	6.7±3.2	6.5	6.7±3.2	6.4	0.282	0.999 0.996 - 1.000	**0.000**
Contralateral side	6.0±2.7	6.0	6.0±2.7	6.1	0.475	0.999 0.998 - 1.000	**0.000**
Nail diameter	11.8±1.2	12.0	11.8±1.2	12.0	1.000	1.000 1.000 - 1.000	**0.000**
Medulla diameter	15.1±3.0	14.5	15.1±2.8	14.4	0.822	0.993 0.975 - 0.998	**0.000**

p^w Wilcoxon test / p^{IC} Intraclass Correlation

Statistical analysis

The mean, standard deviation, median lowest, highest, frequency and ratio values of the descriptive statistics were used. The distribution of the variables was measured using the Kolmogorov–Smirnov test. The Wilcoxon test was used to analyse dependent quantitative data. Correlation was analysed using the intra-class correlation analysis. The statistical analysis was performed using the SPSS 22.0 programme.

Ethical approval

The study was approved by the Ethics Committee of the University of Kyrenia (Northern Cyprus) (RY-2018-28).

RESULTS

Our study group comprised 14 females and 2 males. The mean age was 76.3 (range, 67–91) years. The mean follow-up period was 45.9 (range, 12–84) months. All the fractures were located on the femoral shaft. Twelve of these fractures were treated using anintramedullary nail (IMN), and the other fourwere treated using plate fixation.

In one of the IMN surgeries, the distal one-third ofthe femoral shaft was fractured; however, the surgerywas completed by pushing the nail forwards and distal to the iatrogenic fracture line withoutadditionalintervention.

Twelve and four patients were using alendronate and risedronate, respectively. The BP useduration ranged from a minimum of 4 to a maximum of 12 years. All patients used calcium and vitamin D supplementation.

The mean duration of fracture union was 8 (range, 4–11) months (Table 1). The coxa vara was present in nine patients, whereasseven patients had a normal femoral neck-shaft angle. On the contralateral side, eight coxa vara and eight normal hips were detected.

Furthermore, no significant difference was observed between the measurements conducted by the two orthopaedic surgeons, and a significant correlation was observed (Table 2).

The outer cortical thickness of the fractured side was significantly higher than that of the contralateral side ($p<0.05$) (Figure 5). No significant difference was observed between the inner corticalthickness of the fractured and contralateral sides ($p>0.05$). The lateral bowing of the fractured femoral shaft was significantly greaterthan that of the contralateral femur ($p<0.05$) (Table3). A significant ($p<0.05$) positive correlation was observed between fracture healing time and BP useduration (Table 4). Furthermore,a significant ($p<0.05$) positive correlation was observed between the lateral bowing of the fracture side shaft and BPuse duration.

DISCUSSION

Osteoporosis remains a health concern for the growing elderlypopulation.Long-term BPtherapy for treating patients with osteoporosis is associated with AFFs. An increasing number of reports have identified complete AFFsduring pre-and post-operative periods in patients using BPs (7-12). However, whetherBPs are the only cause of AFFs is yet unclear because some reports have identified AFFsthat are unrelated to BP use (17). AFFs have been frequently reported since 2005 (18), accounting for approximately 1% of all femoral fractures (19).

A study by Napoli et al. identified that women with thinner medial cortices were at a higher risk of subtrochanteric/diaphyseal femoral fracture. Moreover, they indicated that medial or total cortical thickness strongly correlated with fracture risk compared with the lateral cortical thickness (20). In our study, the outer corticalthickness of the fractured side was significantly greater than that of the contralateral side. However, no significant difference was observed between the inner cortical thickness of the fractured and contralateral sides.

Table 3. Comparison of the measurements between fractured and contralateral sides.

	Fractured side		2nd Orthopaedic surgeon		p^w
	mean±sd	median	mean±sd	median	
Cortical thickness-outer cortex	6.7±1.3	7.0	5.7±0.8	6.0	**0.011**
Cortical thickness-inner cortex	5.7±1.3	5.7	5.9±1.7	5.3	0.469
Femur neck-shaft angle	123.7±8.0	121.5	127.8±5.6	127.0	0.098
Lateral bowing of the femur	6.7±3.2	6.5	6.0±2.7	6.0	**0.028**

p^w Wilcoxon test

Our study observed coxa vara in 56% of fractured femurs and 50% of contralateral femurs on analysis ofBP-related anatomical changes. However, increased femoral lateral bowing was observed in all patients, and the degree of lateral bowing was positively correlated with BP use duration. Thecomputed tomography (CT)-based nonlinear finite element analysis results in the literature revealed that decreased femoral neck-shaft angle and increased lateral bowing can increase the tensile stress over the subtrochanteric area and femoral shaft, respectively (21). We believe that the increased stress results inthe thickening of the lateral femoral cortex and that the continuous load results in fatigue fractures. Furthermore, increased fragility may be associated with histological changes caused by long-term BP use.

Lloyd et al. examined bone tissue from women with AFFs and revealedthat long-term BP treatment degrades the fracture-resistance and strengthening mechanisms that are inherent to a healthy bone (22). The likely anatomical and histological changes inthe femur in a patient with long-term BP use should be considered perioperatively because of the iatrogenic fracture risk, particularly following IMN. Notably, we experienced an iatrogenic distal femoral fracture in one of our study patients treated with IMN.

We observedan increase in the outer corticalthickness and a decrease in the femoral neck-shaft angle in the bowing side. Coxa vara was detected in approximately half of the patients on both the fractured and contralateral sides. When the femoral neck-shaft angles were compared, no statistically significant difference was found between the fractured and contralateral sides. This finding may suggest that a decrease in the femoral neck-shaft angle in the contralateral femur may increase the fracture risk.

Narusel et al. investigated the effect of alendronate in a rat model and identified that alendronate did not prevent long bone fragility in an inactive rat model;they concluded that BP use may provide therapeutic benefit to individuals with osteoporosis whose daily activity is not limited (23). Most patients receiving BP therapy are elderly and have limited mobilisation. Therefore, Narusel et al. reported that long-term BP use in these patients may have a negative effect on long bone fragility (23). Notably, our study group consisted of inactive patients who were typically mobilised within their home.

However, when these fractures occur,prophylactic surgical treatment of the contralateralextremity is controversial. A recent study advocated that prophylactic surgical treatment is cost-effective in patients with more than one risk factor. The risk factors were determined to be Asian ethnicity, prodromal pain, coxa vara, femoral bowing, periosteal beaking and transverse radiolucent line (24). Furthermore, IMN, which is the gold standard forfemoral shaft fractures, is performed for AFFs. IMN is advantageous because it decreasesthe load on the lateral cortex compared with the plate fixation. Therefore, IMN is recommended by most authors. However, only 4 of 16 patients inour study groupunderwentplate fixation. Therefore, we could not adequately compare the results of plate fixation and IMN because ofthe inequality between the two groups.

The limitations of our study are its retrospective design, the small number of patients and the lack of bone densitometry and inactivity scores.

In conclusion, our study predicted that long-term BP use not only changes the femoralgeometry on the fractured side but also on the contralateral side and increases the fracture risk. Furthermore, we predicted that the delay in fracture union may be associated with BPuse duration and that the fracture union is affected by changes in the femoral geometry.

The increased intraoperative fracture risk and delayed union of AFFs in the elderly, inactive and non-expressive patients with long-term BPusemust be considered to facilitate successful diagnosis and treatment.

Conflict of interest

All authors declare that there is no conflict of interest regarding this work.

Table 4. Correlation between measurements and demographic features.

Measurement parameter		Age	Duration of Bisphosphonate Use	Fracture Healing Time	Medulla-Nail thickness difference
Fracture healing time	**r**	0.491	0.549	-	0.084
	p	0.054	0.028	-	0.796
Medulla-Nail thickness difference	**r**	−0.342	−0.012	0.084	-
	p	0.277	0.969	0.796	-
Cortical thickness					
Fractured side-outer cortex	**r**	−0.084	−0.102	0.295	0.222
	p	0.756	0.707	0.268	0.488
Contralateral side-outer cortex	**r**	0.146	0.076	0.537	−0.374
	p	0.602	0.788	0.039	0.257
Fractured side-inner cortex	**r**	0.269	0.047	0.376	−0.251
	p	0.333	0.868	0.167	0.457
Contralateral side-inner cortex	**r**	0.116	−0.095	0.412	−0.544
	p	0.668	0.726	0.113	0.068
Femur neck-shaft angle					
Fractured side	**r**	−0.249	−0.273	−0.309	−0.207
	p	0.351	0.306	0.245	0.519
Contralateral side	**r**	0.028	0.188	−0.125	−0.274
	p	0.917	0.486	0.644	0.389
Lateral bowing of the femoral shaft					
Fractured side	**r**	0.467	0.509	0.377	0.309
	p	0.068	0.044	0.150	0.329
Contralateral side	**r**	0.393	0.386	0.299	0.405
	p	0.132	0.140	0.261	0.191

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