View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Digital Commons@Becker

Washington University School of Medicine
Digital Commons@Becker

Open Access Publications

2014

Association of atypical femoral fractures with bisphosphonate use by patients with varus hip geometry

Jennifer E. Hagen
University of Maryland - Baltimore

Anna N. Miller
Wake Forest Baptist Health

Susan M. Ott
University of Washington - Seattle Campus

Michael Gardner
Washington University School of Medicine in St. Louis

Saam Morshed
University of California - San Francisco

See next page for additional authors

Follow this and additional works at: http://digitalcommons.wustl.edu/open_access_pubs

Recommended Citation

Hagen, Jennifer E.; Miller, Anna N.; Ott, Susan M.; Gardner, Michael; Morshed, Saam; Jeray, Kyle; Alton, Timothy B.; Ren, Dennis; Abblitt, W. Parker; and Krieg, James C., ,"Association of atypical femoral fractures with bisphosphonate use by patients with varus hip geometry." The journal of bone and joint surgery.96,22. 1905-1909. (2014).
http://digitalcommons.wustl.edu/open_access_pubs/3511

This Open Access Publication is brought to you for free and open access by Digital Commons@Becker. It has been accepted for inclusion in Open Access Publications by an authorized administrator of Digital Commons@Becker. For more information, please contact engeszer@wustl.edu.

Authors
Jennifer E. Hagen, Anna N. Miller, Susan M. Ott, Michael Gardner, Saam Morshed, Kyle Jeray, Timothy B. Alton, Dennis Ren, W. Parker Abblitt, and James C. Krieg

This open access publication is available at Digital Commons@Becker: http://digitalcommons.wustl.edu/open_access_pubs/3511

Copyright © 2014 by The Journal of Bone and Joint Surgery, Incorporated

Association of Atypical Femoral Fractures with Bisphosphonate Use by Patients with Varus Hip Geometry

Jennifer E. Hagen, MD, Anna N. Miller, MD, Susan M. Ott, MD, Michael Gardner, MD, Saam Morshed, MD, Kyle Jeray, MD, Timothy B. Alton, MD, Dennis Ren, BS, W. Parker Abblitt, MD, and James C. Krieg, MD

Background: There is increasing evidence associating "atypical" femoral fractures with prolonged exposure to bisphosphonate therapy. The cause of these fractures is unknown and likely multifactorial. This study evaluated the hypothesis that patients with primary osteoporosis who sustain atypical femoral fracture(s) while on chronic bisphosphonate therapy have a more varus proximal femoral geometry than patients who use bisphosphonates for primary osteoporosis but do not sustain a femoral fracture.

Methods: The femoral neck-shaft angle was measured on the radiographs of 111 patients with atypical femoral shaft fracture(s) and thirty-three asymptomatic patients; both groups were on chronic bisphosphonate therapy. Patients with characteristic lateral cortical thickening, stress lines, and thigh pain were included in the fracture group.

Results: The mean neck-shaft angle of the patients who sustained atypical femoral fracture(s) while taking bisphosphonates (case group) differed significantly from that of the patients on bisphosphonate therapy without a fracture (129.5° versus 133.8°; $p < 0.001$). Fifty-three (48%) of the patients in the case group had a neck-shaft angle that was lower than the lowest angle in the control group (128°). Side-to-side comparison in patients with a unilateral pathologic involvement and an asymptomatic contralateral lower limb did not demonstrate any significant difference between the neck-shaft angles in the two limbs.

Conclusions: Patients on chronic bisphosphonate therapy who presented with atypical femoral fracture(s) had more varus proximal femoral geometry than those who took bisphosphonates without sustaining a fracture. Although no causative effect can be determined, a finding of varus geometry may help to better identify patients at risk for fracture after long-term bisphosphonate use.

Level of Evidence: Prognostic Level III. See Instructions for Authors for a complete description of levels of evidence.

Peer Review: This article was reviewed by the Editor-in-Chief and one Deputy Editor, and it underwent blinded review by two or more outside experts. The Deputy Editor reviewed each revision of the article, and it underwent a final review by the Editor-in-Chief prior to publication. Final corrections and clarifications occurred during one or more exchanges between the author(s) and copyeditors.

An estimated 10 million Americans have osteoporosis, and more than 1.5 million fractures per year are attributed to this disease[1]. Since their introduction in 1995, bisphosphonates have become the standard of care for treatment of osteoporosis, and more than 4 million women in the United States were taking bisphosphonates in 2008[2]. In 2005, reports began to appear of "atypical" femoral fractures in patients on bisphosphonate therapy for a prolonged period of time. Many studies have evaluated the association between the use of bisphosphonates and the occurrence of an atypical fracture[3-7], and a recent meta-analysis suggested an increased risk for atypical femoral fractures in patients taking a bisphosphonate[3]. In a study of 716 femoral shaft fractures in patients on bisphosphonate therapy, Park-Wyllie et al. found that patients on bisphosphonate therapy for longer than five years had a 2.74 times increased risk of diaphyseal femoral fracture as compared with a control group[4].

Disclosure: One or more of the authors received payments or services, either directly or indirectly (i.e., via his or her institution), from a third party in support of an aspect of this work. In addition, one or more of the authors, or his or her institution, has had a financial relationship, in the thirty-six months prior to submission of this work, with an entity in the biomedical arena that could be perceived to influence or have the potential to influence what is written in this work. Also, one or more of the authors has had another relationship, or has engaged in another activity, that could be perceived to influence or have the potential to influence what is written in this work. The complete **Disclosures of Potential Conflicts of Interest** submitted by authors are always provided with the online version of the article.

TABLE I Patient Characteristics

	Case	Control
No. of patients	111	33
No. of hips available for measurement	193	62
Mean age (range) *(yr)*	68.7 (46-91)	66.8 (39-85)
Mean bisphosphonate exposure (range) *(yr)*	7.4 (1-20)*	5 (1-14)
Fracture characteristics *(no. of patients)*		
Complete	88	—
Stress reaction/beaking	23	—
Bilateral	42 (38%)	—
Bilateral complete	22	—
Complete and contralateral stress	15	—
Bilateral stress	5	—

*Not quantified for thirteen patients.

Schilcher et al. found the odds ratio of atypical fracture in patients on bisphosphonate therapy to be 33.3 after adjusting for comorbid conditions[8]. The risk increased with prolonged use and was ten times higher than normal after just two years[8].

We believe that other risk factors must also be present to explain why (1) only a small percentage (0.02% to 0.2%) of patients taking bisphosphonates on a chronic basis develop these fractures and (2) atypical femoral fractures sometimes occur in patients who are not on long-term therapy[5]. It is possible that patients who develop atypical femoral fractures have an anatomic biomechanical predisposition. We hypothesized that patients on chronic bisphosphonate therapy who sustain atypical femoral fracture(s) or display radiographic characteristics consistent with a stress fracture or "lateral cortical beaking"[7] are more likely to have varus proximal femoral anatomy than exposure-matched controls.

Materials and Methods

We performed a multicenter retrospective case-control study of patients from six institutions. Institutional review board approval was obtained at each individual site. A series of 111 patients who had been treated for a complete or incomplete atypical femoral fracture were identified. Each patient had radiographic characteristics of the atypical femoral fracture associated with chronic bisphosphonate use. To be included in the study group, those without a complete fracture had to have thigh or hip pain in addition to radiographic evidence of either lateral cortical beaking or a transverse stress line based on ASBMR (American Society for Bone and Mineral Research) criteria[6]. These 111 patients constituted the case group. All radiographs were reviewed and approved for inclusion by senior authors (J.C.K., A.N.M., S.M.O, S.M., K.J., and M.G.) at each institution. Exclusion criteria included bisphosphonate therapy for diseases other than primary osteoporosis, previous hip arthroplasty, and radiographs not being available.

A control group of thirty-three patients was identified. These patients had a documented duration of bisphosphonate use for primary osteoporosis; no history of fracture; no history of prodromal thigh or hip pain; and hip, pelvic, or femoral radiographs already in the medical record (Table I).

One hundred and forty-four patients were included in the analysis, and radiographs of 255 hips were available for measurement. All patients are female. The radiographs were compiled and reviewed at three sites where the senior authors (J.C.K., A.N.M., and M.G.) practiced. One reviewer was a trauma trained attending surgeon. The other two were a senior resident and a medical student, who could consult with trauma trained attending surgeons for guidance. The reviewers were aware of the hypothesis of the study. A sample of radiographs was sent to all four reviewers, and the interobserver difference between the neck-shaft angle measurements was <1° (standard deviation [SD], 1.6°). Intraobserver reliability was not calculated.

Measurements were made on anteroposterior radiographs of both hips, when radiographs of both were available. The neck-shaft angle was defined as the angle formed by the intersection of a line down the center of the femoral neck and a line through the center of the femoral shaft[9]. We did not arbitrarily assign a cutoff neck-shaft angle to define varus geometry; rather, it was recorded as a continuous variable. Measurements of each hip were recorded as independent data, and measurements in the case group were divided into those on the "pathologic" side(s) and those on the asymptomatic side. The measurements from the pathologic side(s) were compared with the control group as well as the asymptomatic sides of the patients with a unilateral pathologic involvement. The asymptomatic sides of these patients were measured to determine if there was a side-to-side variation in anatomy that correlated with unilateral pathologic involvement.

For patients for whom only post-fracture radiographs were available, the center of the femoral shaft was measured proximal to the level of the fracture to eliminate improper measurement due to any post-fixation malalignment. When rotation of the limb precluded visualization of the neck-shaft junction, the hip was excluded from measurement.

Statistical Analysis

An independent two-sample t test for continuous variables was used to compare the results between the control and study populations and within the study population. All statistical assessments were two-sided and were evaluated at the 0.05 level of significance.

Source of Funding

One senior author (M.G.) received research coordinator support from Synthes.

Results

The mean neck-shaft angle in the case group (129.5°) was significantly lower ($p < 0.001$) than that in the controls (133.8°). The mean neck-shaft angle on the pathologic sides(s) in the case group (129.9°) was also significantly lower ($p < 0.001$) than the mean angle in the control group.

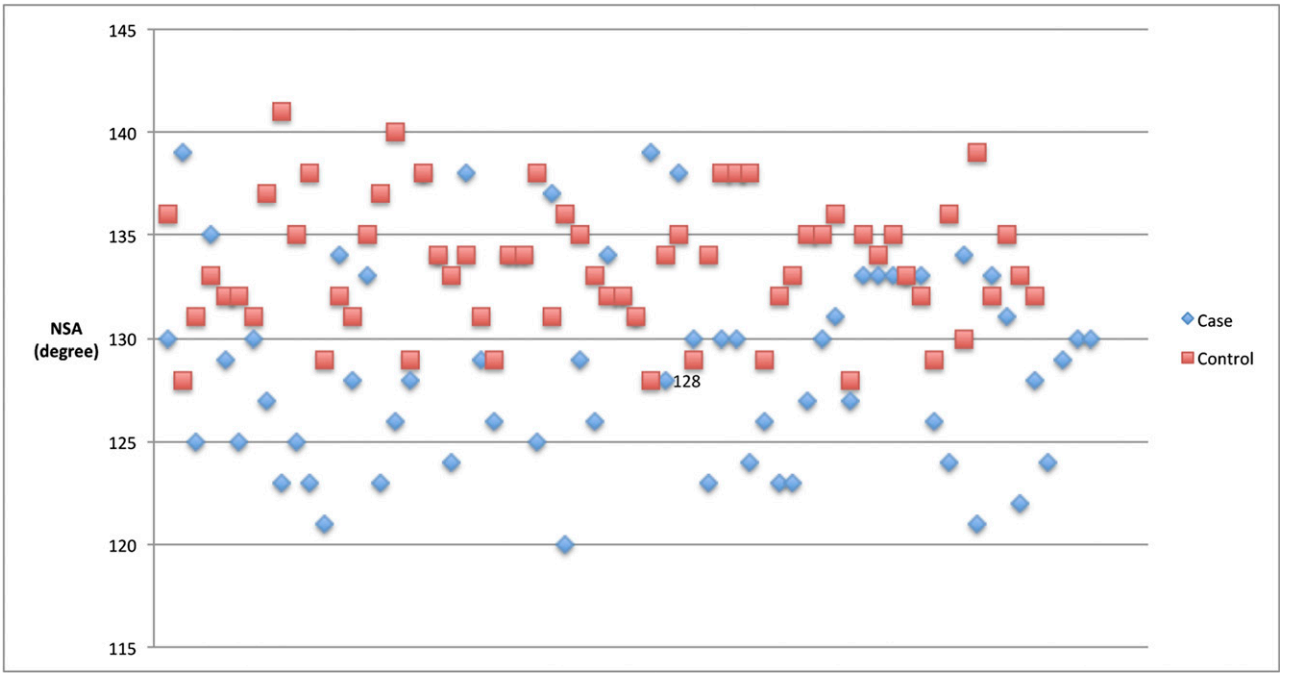

Fig. 1
Plot of neck-shaft angles (NSA) in each group.

Side-to-side comparison of patients with a unilateral pathologic involvement did not demonstrate any significant difference in the neck-shaft angle between the pathologic side (129.8°) and the asymptomatic, contralateral lower limb (128.2°).

The lowest recorded neck-shaft angle was 128° in the control group and118° in the case group. Fifty-three (48%) of the patients in the case group had a neck-shaft angle of <128° on the pathologic side (Fig. 1).

Discussion

Atypical femoral fractures represent a challenge for patients with osteoporosis and osteopenia. Many have speculated about the etiology, and it is likely multifactorial, although no underlying mechanism has been demonstrated. This study was designed to determine if patients with atypical fractures have a more varus proximal femoral geometry than an age and exposure-matched control group. The mean neck-shaft angle of the patients with a fracture was significantly lower than that of the controls, and no control patient had a neck-shaft angle <128°. Overall, we found an association between proximal femoral geometry and the presence of atypical femoral fractures in this population.

In the recently updated ASBMR task force consensus statement, it was concluded that atypical femoral fractures may represent stress fractures that progress over time[7]. These stress fractures are unique in that the transverse component of the fracture begins in the lateral cortex, whereas exercise-induced stress fractures typically initiate in the medial cortex. Very little is known about femoral geometry in this patient population. Proximal femoral strength is decreased with a varus mechanical axis[10,11]. Biomechanical studies have shown that trochanteric and femoral shaft fractures are more common in patients with low neck-shaft angles[12,13]. Koh et al. reviewed the radiographs of forty-eight patients with atypical fractures and found that the fractures clustered in the lateral cortex at the region of maximal tensile loading[14]. Sasaski et al. measured the variations in the anatomic axes of the femora of patients with "low-energy" femoral shaft fractures[15]. These patients were taking medications for osteoporosis but not specifically bisphosphonates. The patients with fractures had a significant increase in the lateral and anterior bow of the femur, and this geometry was thought to result in an imbalance in strains seen in the femur. We believe that this imbalance also occurs with an alteration in the mechanical axis of the lower extremity produced by a varus femoral neck.

A large number of patients in our case group had a neck-shaft angle of <128° on the pathologic side. The study was not powered to calculate the sensitivity and specificity of a neck-shaft angle of <128° predicting the risk of fracture, but studying this risk in a larger cohort would be useful.

A large proportion (38%) of the patients in our study had bilateral pathological involvement. This is consistent with the findings from the study performed by Lo and colleagues, in which 40% of the population had bilateral complete fracture, and an additional 21% had contralateral stress-reaction changes[16]. They found a higher proportion of fractures in women of Asian descent, a factor not controlled for in our study. Nakamura et al. found that women of Japanese descent had lower neck-shaft angles than white American women, and Japanese-descent women could be an at-risk subset of the population[17]. This stresses the importance of obtaining imaging of both femora in patients with a history of atypical femoral fracture and thigh pain.

Our study is limited by all of the factors that routinely affect retrospective reviews. We did not control for patient factors, including body mass index, smoking status, activity level, and bone mineral density. Also, we studied only a small sample of the more than 4 million women on bisphosphonate therapy in the United States.

The reliability of hip measurements has been studied with a variety of modalities in patients with various pathological conditions. In general, the reliability of the neck-shaft angle has been shown to be good. A recent study of patients with cerebral palsy showed an overall intraobserver and interobserver reliability of neck-shaft-angle measurements on hip radiographs of 0.929 and 0.912, respectively[18]. Marmor et al. found that neck-shaft-angle measurements varied <5° with <35° of limb rotation, and the measurements were always greater than the true value[19]. Thus, it is unlikely that our measurements overestimated the actual varus in our patients; if anything, they underestimated it. Many of the measurements in the group with a complete fracture were performed on injury radiographs, for which rotation is the most difficult to control, and it is likely the true neck-shaft angle in this group was in even more varus than we reported.

Bias could have been introduced into the measurements as the majority of those in the case group were done on injury radiographs or radiographs showing the stress reaction; therefore, the reviewers were not blinded to the presence of the pathological condition. It was impossible to avoid this as many of the patients had not sought treatment at our facilities prior to their injury or did not have any reason to have pelvic radiographs prior to the development of symptoms. However, there was not a significant difference between the measurements on the pathologic and nonpathologic sides of our study group, thus providing a marker for internal validity of our measurement techniques.

Another limitation of this study is that the average bisphosphonate exposure times of the study and control patients were not identical. Thirteen patients in the case group did not have numerical documentation of their duration of bisphosphonate use; charts indicated it was "long term." Despite this, the mean exposure times for both groups were greater than those previously documented to incur risk[4,8]. The link between atypical femoral fracture and bisphosphonates is an association; it has not been definitively shown to be causation. The exact duration of exposure that is needed for an increased fracture risk is unknown. Schilcher et al. found the odds ratio of fracture to be ten times higher after just two years of exposure[8]. As our study was a retrospective analysis and we documented fracture or stress reaction in all of the patients in the case group, we can assume that it was an at-risk population. It is possible that the control group was evaluated early in the time course of their disease. We have no current method for monitoring their progression to fracture. A prospective and longitudinal study could better control for this factor by documenting the duration of patients' exposure to bisphosphonates at the time of enrollment and more thoroughly tracking their actual use. The ability to monitor for progression to fracture would help determine the relative risk of fracture.

In conclusion, we found an association between varus proximal femoral geometry and a propensity to sustain atypical femoral fractures in patients on long-term bisphosphonate therapy. We agree with the ASBMR task force's conclusion that more needs to be done to evaluate the impact of femoral geometry on this patient population[16]. The neck-shaft angle is only one variable, but it appears to have a high correlation with atypical femoral fractures, and follow-up measurements are easy, low cost, and noninvasive. The strength of this study was insufficient for us to conclusively advise a change in management of these patients at this time, but we have made a strong argument to use this as a pilot study to prompt further investigation. At a minimum, patients should be counseled to be aware of symptoms that accompany these injuries. Larger studies should be done in a longitudinal fashion to determine the true risk of progression to fracture. While this is likely only one piece of the picture, we think that our findings add a useful clinical marker that could help identify an at-risk subset of this population. ■

NOTE: The authors acknowledge Justin Langan for his contribution to the data-collection portion of this project.

Jennifer E. Hagen, MD
University of Maryland,
22 South Greene Street,
Baltimore, MD 21202.
E-mail address: Jeh29@case.edu

Anna N. Miller, MD
Wake Forest Baptist Health,
131 Miller Street,
Winston-Salem, NC 27103

Susan M. Ott, MD
University of Washington,
4245 Roosevelt Way N.E.,
Box 35470,
Seattle, WA 98105

Michael Gardner, MD
Washington University,
4921 Parkview Place,
St. Louis, MO 63110

Saam Morshed, MD
University of California San Francisco,
2550 23rd Street,
San Francisco, CA 94110

Kyle Jeray, MD
Steadman Hawkins Clinic,
200 Patewood Drive,
Suite C100,
Greenville, SC 29615

Timothy B. Alton, MD
University of Washington,
1959 N.E. Pacific Street,
#356500,
Seattle, WA 98195

Dennis Ren, BS
Tulane School of Medicine,
1430 Tulane Avenue,
New Orleans, LA 70112

W. Parker Abblitt, MD
Wake Forest School of Medicine,
Medical Center Boulevard,
Winston Salem,
NC 27157

James C. Krieg, MD
The Rothman Institute,
Jefferson University,
925 Chestnut Street,
Philadelphia, PA 19107

References

1. Keen RW. Burden of osteoporosis and fractures. Curr Osteoporos Rep. 2003 Sep;1(2):66-70.

2. Siris ES, Pasquale MK, Wang Y, Watts NB. Estimating bisphosphonate use and fracture reduction among US women aged 45 years and older, 2001-2008. J Bone Miner Res. 2011 Jan;26(1):3-11.

3. Gedmintas L, Solomon DH, Kim SC. Bisphosphonates and risk of subtrochanteric, femoral shaft, and atypical femur fracture: a systematic review and meta-analysis. J Bone Miner Res. 2013 Aug;28(8):1729-37. Epub 2013 Feb 13.

4. Park-Wyllie LY, Mamdani MM, Juurlink DN, Hawker GA, Gunraj N, Austin PC, Whelan DB, Weiler PJ, Laupacis A. Bisphosphonate use and the risk of subtrochanteric or femoral shaft fractures in older women. JAMA. 2011 Feb 23;305(8):783-9.

5. Wells G, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, Coyle D, Tugwell P. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev. 2008;(1):CD004523. Epub 2008 Jan 23.

6. Shane E, Burr D, Ebeling PR, Abrahamsen B, Adler RA, Brown TD, Cheung AM, Cosman F, Curtis JR, Dell R, Dempster D, Einhorn TA, Genant HK, Geusens P, Klaushofer K, Koval K, Lane JM, McKiernan F, McKinney R, Ng A, Nieves J, O'Keefe R, Papapoulos S, Sen HT, van der Meulen MC, Weinstein RS, Whyte M; American Society for Bone and Mineral Research. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2010 Nov;25(11):2267-94.

7. Shane E, Burr D, Abrahamsen B, Adler RA, Brown TD, Cheung AM, Cosman F, Curtis JR, Dell R, Dempster DW, Ebeling PR, Einhorn TA, Genant HK, Geusens P, Klaushofer K, Lane JM, McKiernan F, McKinney R, Ng A, Nieves J, O'Keefe R, Papapoulos S, Howe TS, van der Meulen MC, Weinstein RS, Whyte MP. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2014 Jan;29(1):1-23. Epub 2013 Oct 1.

8. Schilcher J, Michaëlsson K, Aspenberg P. Bisphosphonate use and atypical fractures of the femoral shaft. N Engl J Med. 2011 May 5;364(18):1728-37.

9. Kay RM, Jaki KA, Skaggs DL. The effect of femoral rotation on the projected femoral neck-shaft angle. J Pediatr Orthop. 2000 Nov-Dec;20(6):736-9.

10. Antapur P, Prakash D. Proximal femoral geometry: a radiological assessment. J Arthroplasty. 2006 Sep;21(6):897-8.

11. Gong H, Zhang M, Fan Y, Kwok WL, Leung PC. Relationships between femoral strength evaluated by nonlinear finite element analysis and BMD, material distribution and geometric morphology. Ann Biomed Eng. 2012 Jul;40(7):1575-85. Epub 2012 Jan 19.

12. El-Kaissi S, Pasco JA, Henry MJ, Panahi S, Nicholson JG, Nicholson GC, Kotowicz MA. Femoral neck geometry and hip fracture risk: the Geelong osteoporosis study. Osteoporos Int. 2005 Oct;16(10):1299-303. Epub 2005 Aug 5.

13. Thevenot J, Pulkkinen P, Kuhn V, Eckstein F, Jämsä T. Structural asymmetry between the hips and its relation to experimental fracture type. Calcif Tissue Int. 2010 Sep;87(3):203-10. Epub 2010 Jun 17.

14. Koh JS, Goh SK, Png MA, Ng AC, Howe TS. Distribution of atypical fractures and cortical stress lesions in the femur: implications on pathophysiology. Singapore Med J. 2011 Feb;52(2):77-80.

15. Sasaki S, Miyakoshi N, Hongo M, Kasukawa Y, Shimada Y. Low-energy diaphyseal femoral fractures associated with bisphosphonate use and severe curved femur: a case series. J Bone Miner Metab. 2012 Sep;30(5):561-7. Epub 2012 May 19.

16. Lo JC, Huang SY, Lee GA, Khandelwal S, Provus J, Ettinger B, Gonzalez JR, Hui RL, Grimsrud CD. Clinical correlates of atypical femoral fracture. Bone. 2012 Jul;51(1):181-4. Epub 2012 Mar 4.

17. Nakamura T, Turner CH, Yoshikawa T, Slemenda CW, Peacock M, Burr DB, Mizuno Y, Orimo H, Ouchi Y, Johnston CC Jr. Do variations in hip geometry explain differences in hip fracture risk between Japanese and white Americans? J Bone Miner Res. 1994 Jul;9(7):1071-6.

18. Chung CY, Lee KM, Park MS, Lee SH, Choi IH, Cho TJ. Validity and reliability of measuring femoral anteversion and neck-shaft angle in patients with cerebral palsy. J Bone Joint Surg Am. 2010 May;92(5):1195-205.

19. Marmor M, Nystuen C, Ehemer N, McClellan RT, Matityahu A. Accuracy of in situ neck-shaft angle and shortening measurements of the anatomically reduced, varus malreduced and shortened proximal femur: can we believe what we see on the postoperative films? Injury. 2012 Jun;43(6):846-9. Epub 2011 Oct 30.