Using GE Lunar DXA to Quantify, Visualize, and Trend Incipient Atypical Femoral Fractures

The management of osteoporosis underwent a paradigm shift in 1995 with the approval of the first bisphosphonate, risedronate. Since then, several other bisphosphonates have been approved, including alendronate, ibandronate, and zoledronate, as well as the first biologic treatment for osteoporosis, denosumab. These drugs reduce fracture risk by decreasing bone resorption.[1] Their use is attributed to a significant reduction in the incidence and mortality of hip fractures since 1995.[2]

The use of bisphosphonates, however, has plummeted since case reports appeared in 2005 linking their long-term use to an increased risk of atypical femoral fractures (AFF), defined as stress fractures that occur in the femur shaft.[1,3]

The pathogenesis of AFF is likely due to the oversuppression of bone remodeling caused by the antiresorptive drug, which leads to an impaired ability to repair skeletal microcracks resulting in increased skeletal fragility.[1] Such fractures may be accompanied by a focal or diffuse periosteal reaction of the lateral cortex surrounding the region where the fracture initiated. An area of cortical thickening called a "beak" or a "flare" indicates an incipient AFF (Figure 1).[1] Table 1 lists current criteria for an AFF.

Atypical femoral fractures are extremely rare, however, with an absolute risk in patients on bisphosphonates of between 3.2 and 50 cases per 100,000 person years.[4] Nonetheless, a study published in 2015 found that the use of oral bisphosphonates fell more than 50% between 2008 and 2012 (P<0.001) after increasing for more than a decade. One reason for the decline appeared to be media reports about AFF and other adverse effects.[4]

Figure 1: Incipient atypical femoral fracture, beak identified by arrow (Courtesy of Fergus McKiernan, MD, Marshfield Clinic, Marshfield, WI)

A June 2016 front page article in *The New York Times* highlighted the growing concern in the medical community over the large numbers of women who are refusing to consider bisphosphonates to prevent fractures or to remain on the drugs more than a few months.[5,6]

In September 2016, the American Society for Bone and Mineral Research (ASBMR) and 34 other bone-related organizations and societies issued a call to action to address what they called a "crisis in the treatment of osteoporosis."[5] They cited a reduction in the use of bisphosphonates following hospitalization for hip fracture from 15% in 2004 to 3% in the last quarter of 2013 as well as evidence that more than 60% of patients in the US prescribed bisphosphonates stop taking them after 1 year (3 years of continuous use is required to reduce the incidence of spine and hip fracture by 50% in those with osteoporosis or a previous vertebral fracture).[7]

There is also emerging evidence that the 30-year downward trend in hip fractures in the US has plateaued in recent years.[8]

Monitoring Patients for AFF

The only external signs of an incipient break are prodromal, such as chronic hip or groin pain.[9] However, recent evidence suggests that the use of hip DXA images combined with conventional assessment of prodromal symptoms can detect pre-fractures earlier than relying on prodromal symptoms alone.[9]

The ASBMR's AFF Task Force's 2014 update on the medical management of AFF suggests that AFF fractures evolve over time beginning with the development of a cortical "bump." The bump likely represents early periosteal thickening and the eventual appearance of a transverse cortical lucency (fracture) in the region of periosteal thickening, the committee wrote, which may or may not progress to a complete fracture.[1] Thus, the task force recommends evaluating such lesions when detected on DXA scans or plain radiographs, along with MRI or, if MRI cannot be performed, CT scan.

However, there is evidence that radiologist compliance with published guidelines for the reporting of AFF is low. One large retrospective analysis of 1,558 X-ray scans found that none of the 16 patients exhibiting evidence of an incipient AFF had been identified.[10] Once identified, 4 of the 16 required surgery.

GE Lunar AFF enCORE™ Software

enCORE version 17 AFF software feature for the Prodigy™ with Pro and Advance software packages and iDXA™ systems provides clinicians with the ability to identify and assess early evidence of AFF without exposing patients to additional radiation through a CT scan or to the cost and inconvenience of an MRI.[11]

Table 1

ASBMR Task Force 2014 Revised Case Definition of AFFs

- The fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare
- At least four of five major features must be present:*
  1. The fracture is associated with minimal or no trauma, as in a fall from a standing height or less.
  2. The fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur.
  3. Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex.
  4. The fracture is noncomminuted or minimally comminuted.
  5. Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site ("beaking" or "flaring").
- Minor features are not required for diagnosis but have sometimes been associated with AFFs. They include:
  - Generalized increase in cortical thickness of the femoral diaphyses
  - Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh
  - Bilateral incomplete or complete femoral diaphysis fractures
  - Delayed fracture healing

* Excludes fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, periprosthetic fractures, and pathological fractures associated with primary or metastatic bone tumors and miscellaneous bone diseases (e.g., Paget's disease, fibrous dysplasia).

It was developed based on the pioneering research of Fergus Eoin McKiernan of the Center for Bone Disease at the Marshfield Clinic in Wisconsin. He published the first report of the use of serial DXA to document AFF, then conducted a small clinical trial with 30 participants to further demonstrate its utility. Importantly, that study showed that the extended femur scan does not impact the results of the BMD exam.[12,13]

Atypical femur fracture measurement and analysis provides an X-ray image of the entire femur for both qualitative visual assessment and quantitative measures to identify areas of focal thickening along the lateral cortex of the femoral shaft (Figure 2). The AFF measurement also provides bone mineral density (BMD) values.

The updated software, which fully integrates with the entire DXA patient database, also provides a "Beaking Index" value. This is a measure of the magnitude of the increase in the cortical width (mm) at the location of the localized periosteal reaction. This analysis can quickly be run on a femur scan for both BMD and AFF assessment, with serial measurement trends tracked graphically over time. This allows the visualization and quantification of any potential AFF sites.

Figures 3-5 depict sample graphs.

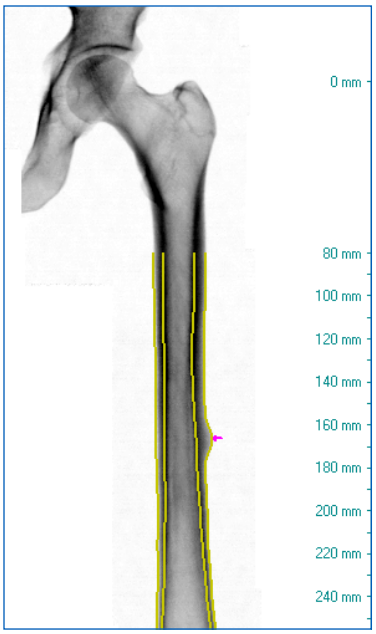
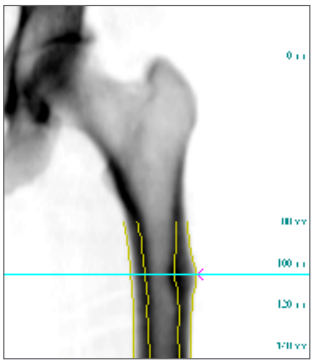


Figure 2: Incipient AFF Image (beak identified by arrow)

Figure 3: Beaking Profile



Beaking profile: Profile along the femoral shaft of the "Beaking Index" in mm. This example depicts the Beaking Index trend over time.

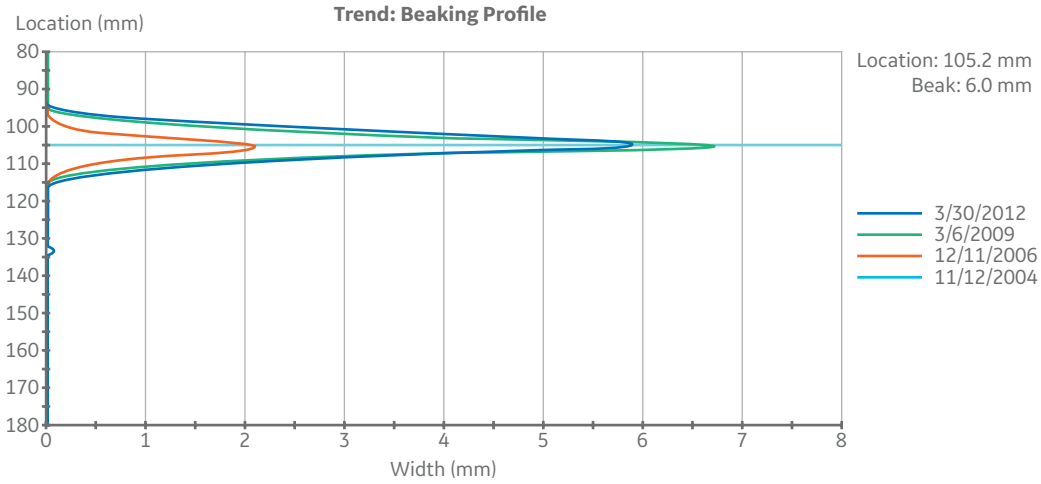
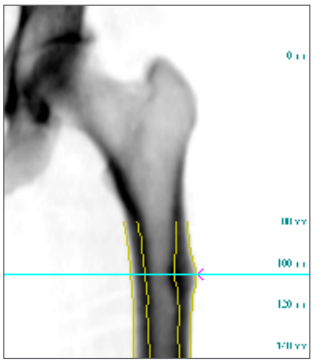


Figure 4: Lateral Cortical Width



Profile along the femoral shaft of the lateral cortical width in mm

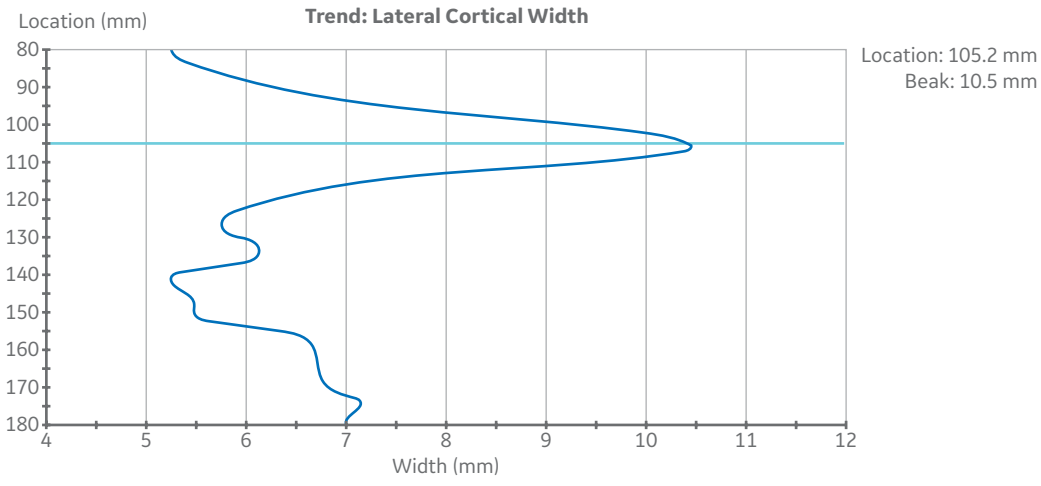
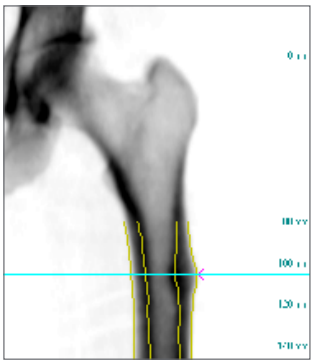
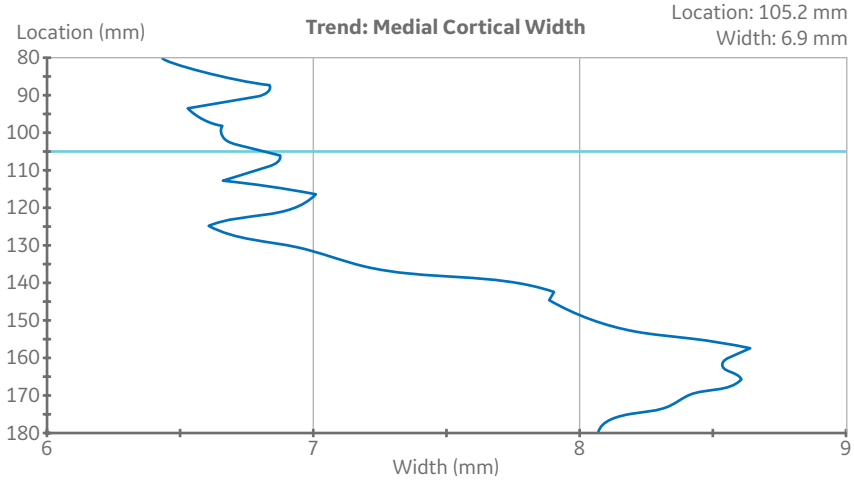


Figure 5: Medial Cortical Width





Profile along the femoral shaft of the medial cortical width in mm. The literature states that beaking is found on the Lateral side, we include the medial profile for research purposes.

The greatest value of the AFF assessment may lie in its negative predictive value. The lack of any beak could possibly provide greater confidence to clinicians and their patients in starting or continuing antiresorptive therapy. Further research is required.

The ability to quantify cortical width, graphically trend incipient AFFs over time, retrospectively reanalyze past femur scans, and measure both the proximal and distal femur in a single scan are exclusive to Prodigy and Lunar iDXA systems. Other manufacturers give you only the ability to find the incipient AFF through visual inspection. As mentioned earlier, if trained radiologists have a hard time finding incipient AFFs using standard X-ray it would seem problematic to rely on the eye of the DXA technologist, regardless of how well trained.

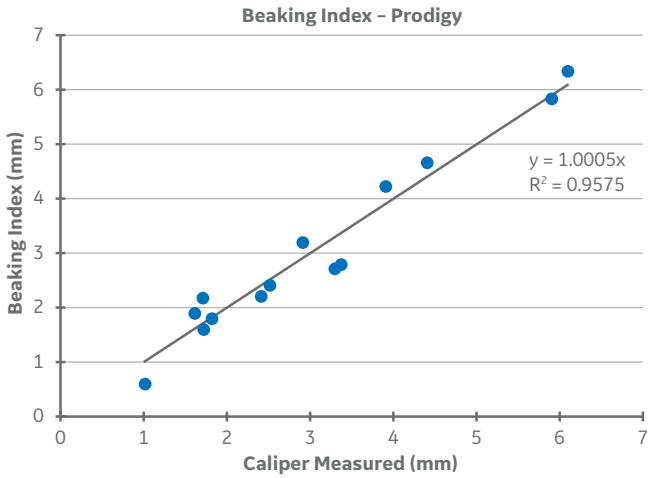
Phantom Study Results

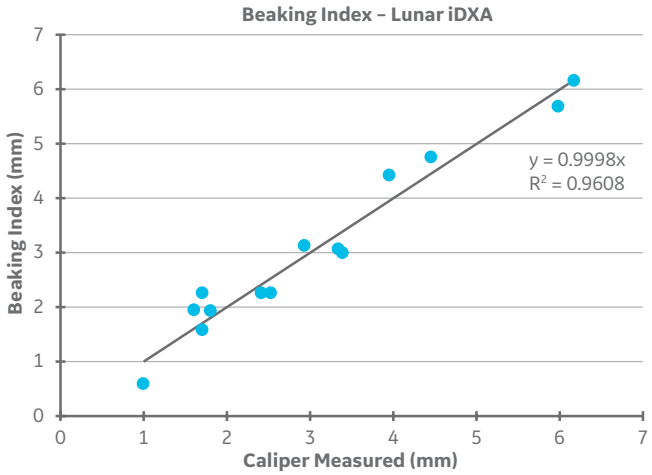
The utility of enCORE v17 to assess incipient AFF was demonstrated in a phantom study.[14] AFF bench testing was performed using a set of 5 anthropomorphic femur phantoms with simulated beaks of different sizes. Simulated beaks were composed of a calcium carbonate-based compound that mimics the expected size and density of AFF beaks in vivo. The projected beaks on all 5 phantoms were measured on Prodigy and iDXA and the beaking index at each beak compared to expected values measured with digital calipers.

Accuracy of Beak Size

A linear regression line was fit to the data points to calculate slope and the Pearson correlation coefficient was calculated (Figure 6). The standard error of the estimate is <0.4 mm and is the projected beak size accuracy error.

Figure 6: Prodigy and iDXA Projected Beak Size Average Measurements





Value	Prodigy		Lunar iDXA	
	SEE*	Slope (r^2)	SEE*	Slope (r^2)
Beak Index	0.36 mm	1.0005 (0.9575)	0.33 mm	0.9998 (0.9608)

*Standard error of the estimate

Reproducibility of Beak Size

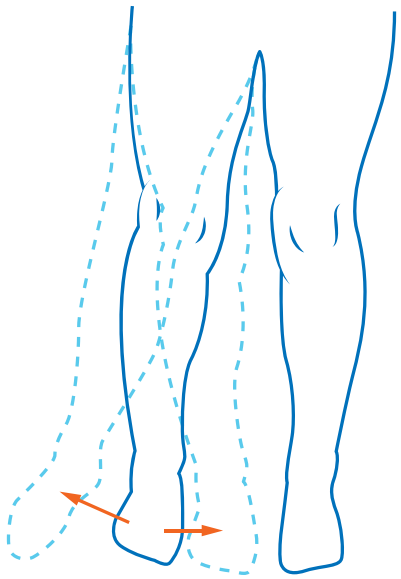
Intra-scanner reproducibility error was determined from measurements taken on 5 scanners measuring 5 simulated beaks (range: 1.7 – 5.9 mm) 5 times each. For Prodigy (iDXA) the intra-scanner reproducibility error was 0.18 mm (0.12 mm).

Inter-scanner reproducibility error for Prodigy (iDXA) was 0.1 mm (0.22 mm). Precision error is the root mean square of the intra- and inter-scanner reproducibility. For Prodigy (iDXA) precision error was 0.20 mm (0.25 mm), which is <0.3 mm.

The accuracy and precision error results from these studies were used to set an expected error margin of 0.5 mm. (Standard deviation = SQRT (0.42 + 0.32)).

Beak Size Dependence on Positioning

Skewing of femur angle relative to the DXA table long axis from -5° to +5° produced beak size variation of ±0.2 mm.



Key Point

The size of a beak is dependent on its orientation in a two-dimensional DXA image. The user must use the foot brace to control leg position and can verify rotation by looking at the prominence of the lesser trochanter on the DXA scan image. The standard deviation of a beak size measurement is expected to be 0.5 mm with consistent patient positioning. Clinical measurement error may vary.

Summary

Large numbers of individuals with osteoporosis and fracture risk have turned away from bone resorptive medications because of fears they will experience the rare event of an AFF. This, in turn, has led experts in the field to identify a “crisis” in the management of osteoporosis and fractures.

The GE Lunar enCORE v17 software available for Prodigy with Pro and Advance software packages and the Lunar iDXA enables clinicians to identify incipient AFF in women on bisphosphonates and track bone changes over time.

Such information could provide important information to clinicians and their patients about starting or continuing on bisphosphonates and other bone resorptive compounds.

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