Atypical Femur Fractures
- What Have We Learnt So Far?

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IOF CSA BoneCast Webinar
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Disclosures

- Departmental research funding from Amgen, Eli-Lilly and Alexion
- Departmental honoraria from Amgen
Overview

- Osteoporosis – scope and role of bone mineralization
- Effects of anti-resorptive drugs on bone mineralization
- Ethnic differences in AFF and bone microstructure
- Bone mineralization in patients with AFF
  - Bone biopsy data
  - High-resolution peripheral quantitative computed tomography (HR-pQCT) data
- Treatment of AFF
- RCT data
Changing Public Health Impact of Osteoporotic Fractures

- ~22,000 hip fractures in Australia per year
- Post-hip fracture mortality is 25% - 65,000 deaths in USA per year
- >50% permanently incapacitated
- In USA, a survivors’ risk of becoming destitute is doubled
- Numbers of women with a fracture exceeds the combined number of women with incident breast cancer, AMI, or stroke across all ethnic groups each year
- Socioeconomic consequences lead to an estimated burden on society of $18 billion annually in USA – will double by 2050
Regional distribution of hip fractures in women age 65 years and older

1990

- Africa: 0.2%
- Oceania: 0.8%
- Middle East: 2.3%
- Latin America: 7.1%
- Russia: 8.8%
- N. America: 20.9%
- Europe: 28.6%
- Asia: 31.2%

2050

- Africa: 0.6%
- Oceania: 0.7%
- Russia: 4.4%
- Middle East: 5.7%
- N. America: 11.9%
- Latin America: 12.5%
- Europe: 13.0%
- Asia: 51.1%

Under-treatment of Patients at High Risk for Osteoporotic Fractures

- USA - 50% decline in bisphosphonate use from 2008 to 2012
- Media reports and FDA announcements about safety concerns suggests that fear of adverse effects (AFF) is an important factor
- Need more accurate targeting of bisphosphonate therapy to high-risk individuals, appropriate cessation of use after treatment for some years, and/or switching to alternative therapies
- Under-diagnosis in patients with fractures and low treatment rates
- Halving of osteoporosis medication use from 2001-2011 in hip fracture patients, from 40% to 21%
- Those at highest risk (oldest age, males) are not being treated
Bone Hierarchy: From the cell to the whole bone

Adapted from Jepsen K 1994
Biomechanical Properties of Bone

Turner CH. Osteoporos Int 2002; 13(2): 97-104
The higher the remodelling rate, the younger and less mineralised the bone (darker)

Boivin & Meunier. *Calcif Tissue Int* 2002; 70:503-11
Is There an Optimal Reduction in Bone Turnover for an Anti-resorptive Drug?

Insufficient turnover
- Accumulation of microdamage
- Increased brittleness due to excessive mineralization

Excessive turnover
- Increase in stress risers (weak zones)
- Increase in perforations
- Loss of connectivity

Adapted from Weinstein RS. *J Bone Miner Res* 2000; 15: 621
Do osteocytic EphrinB2-dependent processes control bone mineralization and brittleness in Efnb2 KO mice and in patients with AFF?
Mouse model of bone fragility (*Dmp1Cre.Efnb2f/f* mice): Normal BMD, but brittle bone

3 point bending test 12-week-old female control (*Dmp1Cre, w/w, ●*) and *Dmp1Cre.Efnb2f/f* (f/f ○) femora (F-G)

Mean ± SEM; individual data points. **, p<0.01 vs w/w

EphrinB2 knockdown osteocytes deposit more mineral *in vitro*

**C, D:** *Efnb2* knockdown in the Ocy454 osteocyte cell line; **C:** Confirmation of *Efnb2* knockdown (kd) by qPCR;

**D:** Elevated mineral (Alizarin Red stain) in *Efnb2* kd cells. Mean ± SEM; 3 experiments. *, p<0.01; ***, p<0.001.

Summary

- Osteocytic EphrinB2-dependent processes control bone mineralization and brittleness in the *Efnb2* KO mice

- Stimulation of autophagy with increased autophagosome numbers is may control mineral release

- Brittle bone in the *Efnb2* KO mice may be a good model for AFF
Atypical Femur Fracture

Often spontaneous, with prodrome of pain and heralded by an audible crack!
Radiographic Features seen in 2014 ASBMR Definition of AFF

- Short-oblique configuration
- Diffuse cortical thickening
- Medial spike
- No comminution
- Focal lateral cortical thickening ("beaking")
Incidence of AFF According to Duration of Bisphosphonate Use (Unadjusted and Age-adjusted)

Rate per 100,000/year

Dell R et al., J Bone Miner Res 2012; 27:2544-50
Atypical Femur Fractures

- Low absolute risk, ranging from 3.2 to 210 cases per 100,000 person-years
- Risk may rise to as high as 113 per 100,000 person-years with long-term (7-8 years) use, but benefits far outweigh risks
- Anywhere from 80-5,000 fragility fractures are prevented for every AFF possibly induced by treatment, however, patients are concerned
- Need to develop ways to diagnose AFFs before they occur
- Over the longer term, we need to identify those patients who may be at increased risk of AFFs, even before starting osteoporosis medications
Incidence Rate of Atypical Femur Fractures (AFFs) and Hip Fractures, According to Categories of Risk Factors

- 196,129 women
- 277 AFF
Hazard Ratios for Atypical Femur Fracture in a Cohort of Women with Bisphosphonate Use

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
</tr>
<tr>
<td>50–64</td>
<td>0.97 (0.55–1.71)</td>
</tr>
<tr>
<td>65–74</td>
<td>2.36 (1.42–3.92)</td>
</tr>
<tr>
<td>75–84</td>
<td>2.48 (1.48–4.15)</td>
</tr>
<tr>
<td>≥85</td>
<td>Reference</td>
</tr>
<tr>
<td>Race or ethnic group</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>5.18 (4.12–7.01)</td>
</tr>
<tr>
<td>White</td>
<td>Reference</td>
</tr>
<tr>
<td>Other</td>
<td>0.92 (0.65–1.29)</td>
</tr>
<tr>
<td>Duration of bisphosphonate use (yr)</td>
<td></td>
</tr>
<tr>
<td>0 to &lt;0.25</td>
<td>Reference</td>
</tr>
<tr>
<td>0.25 to &lt;3</td>
<td>7.56 (2.67–21.47)</td>
</tr>
<tr>
<td>3 to &lt;5</td>
<td>31.76 (12.07–94.48)</td>
</tr>
<tr>
<td>5 to &lt;8</td>
<td>80.90 (29.22–224.00)</td>
</tr>
<tr>
<td>≥8</td>
<td>179.51 (64.64–498.52)</td>
</tr>
<tr>
<td>Time since last bisphosphonate use (yr)</td>
<td></td>
</tr>
<tr>
<td>≤0.25: current user</td>
<td>Reference</td>
</tr>
<tr>
<td>&gt;0.25–1.25</td>
<td>0.38 (0.27–0.52)</td>
</tr>
<tr>
<td>&gt;1.25–4</td>
<td>0.12 (0.07–0.20)</td>
</tr>
<tr>
<td>&gt;4</td>
<td>0.08 (0.05–0.15)</td>
</tr>
<tr>
<td>Not yet used</td>
<td>0.01 (0.00–0.06)</td>
</tr>
<tr>
<td>Ever smoked</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.40 (0.22–0.76)</td>
</tr>
<tr>
<td>No</td>
<td>Reference</td>
</tr>
<tr>
<td>Height (per 5-cm decrement)</td>
<td>1.39 (1.28–1.52)</td>
</tr>
<tr>
<td>Weight (per 5-kg increment)</td>
<td>0.94 (0.91–0.98)</td>
</tr>
<tr>
<td>Any previous fracture</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.27 (0.87–1.84)</td>
</tr>
<tr>
<td>No</td>
<td>Reference</td>
</tr>
<tr>
<td>Body-mass index (per 1-unit change)†</td>
<td>1.00 (0.98–1.02)</td>
</tr>
<tr>
<td>Glucocorticoid use (yr)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>Reference</td>
</tr>
<tr>
<td>&gt;0 to &lt;1</td>
<td>1.16 (0.90–1.49)</td>
</tr>
<tr>
<td>≥1</td>
<td>2.57 (1.72–3.83)</td>
</tr>
</tbody>
</table>

* Any variable with a P value of more than 0.2 in the univariate model was included in the multivariate model. For continuous variables (height and weight), entry to the multivariate model was determined by P value for continuous univariate analysis.
† Height and weight but not body-mass index were included in the multivariate model.
Hip and Clinical Fractures Prevented as Compared with AFFs Associated with Bisphosphonate Use
Rapid Decline in AFF Risk Following Bisphosphonate Cessation - Denmark

Table, Patterns of BP Use and Risk of AFF in Denmark

- 34% of AFF cases had no BP exposure
- Rate of classic hip fracture was 43.8/10,000
- Rheumatoid arthritis or hypertension were AFF risk factors

<table>
<thead>
<tr>
<th>Duration of BP use (yr)</th>
<th>AFF (N)</th>
<th>Rate 10,000 FY</th>
<th>Adjusted PR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No use</td>
<td>65</td>
<td>0.075</td>
<td>(ref)</td>
</tr>
<tr>
<td>&gt;0.5</td>
<td>8</td>
<td>0.45</td>
<td>6.26 (2.89, 13.58)</td>
</tr>
<tr>
<td>&gt;1-3</td>
<td>18</td>
<td>0.97</td>
<td>10.67 (6.00, 18.98)</td>
</tr>
<tr>
<td>&gt;3-5</td>
<td>21</td>
<td>1.77</td>
<td>27.74 (10.23, 30.77)</td>
</tr>
<tr>
<td>&gt;5-7</td>
<td>31</td>
<td>1.71</td>
<td>35.02 (23.25, 57.63)</td>
</tr>
<tr>
<td>&gt;7</td>
<td>46</td>
<td>4.01</td>
<td>37.50 (28.25, 60.47)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time since last use (yr)</th>
<th>AFF (N)</th>
<th>Rate 10,000 FY</th>
<th>Adjusted PR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current use</td>
<td>35.7</td>
<td>0.17</td>
<td>(ref)</td>
</tr>
<tr>
<td>&gt;0.5</td>
<td>27</td>
<td>2.16</td>
<td>1.05 (0.68, 1.63)</td>
</tr>
<tr>
<td>&gt;1-3</td>
<td>&lt;5</td>
<td>0.48</td>
<td>0.27 (0.09, 0.85)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>&lt;5</td>
<td>0.28</td>
<td>0.20 (0.05, 0.83)</td>
</tr>
</tbody>
</table>
Using DXA AFF Software to Diagnose Early AFF
Recommended after 3 Yrs of BP Therapy – ISCD Guidelines

DXA Image  X-ray
Asian Race Predisposes to AFF

- Kaiser Permanente database: hip fractures, whites, 85%; blacks, 3%; Hispanics, 6%; and Asians, 5%
- In contrast, the race distribution of AFFs was whites, 45%; blacks, 0%; Hispanics, 5.3%; and Asians, 50%
- RR increased by 6 to 7-fold compared with Caucasians
- Other risk factors for AFF are remarkably similar to risk factors for typical osteoporotic fractures, including rheumatoid arthritis and >6-month use of glucocorticoids

Lo JC et al., Bone, 85:142-7, 2016
Associations of Asian Ethnicity with AFFs

Clinical Risk Factors

Younger age

Asian ethnicity

Higher BMI

Glucocorticoid use

Rheumatoid arthritis

Other drugs
  SNRIs/SSRIs
  PPIs

Femoral geometry

Asian Ethnicity

- North American studies:
  - Asian race formed up to half of their AFF cohorts
  - In female BP users, Asian race had 6.6 fold greater hazard of AFF compared to White race

- Singapore and Swedish study
  - Subtrochanteric in Singaporean cohort
  - Diaphyseal in Swedish cohort

- Femoral geometry?
- Bone micro-architecture?
- Genetic factors?

Shane et al. JBMR 2014;29(1): 1-23

Dell et al. JBMR 2012;27(12):2544-50
Schilcher et al. JBMR 2015;30(11):2127-32
Femoral Geometry and AFF

- Geometrical features in patients with AFF that distinguished them from controls:
  - excessive femoral offset
  - proximal femur neck angle in varus
  - greater proximal cortical thickness

- If this approach could be validated in larger cohorts and incorporated into a baseline DXA scan, it may serve to identify a subset of patients at risk of AFF

- Asian race – greater femoral lateral curvature and shorter hip axis length may mean geometric features contribute
Femoral Geometric Measures using DXA

A = Femoral offset;
B = Distance between femoral head rotation center and pelvic center;
C = Femoral head diameter;
D = Neck-shaft angle

A: Canal width (lesser trochanter + 20 mm)
B: Canal width (lesser trochanter - 50 mm)
C: Canal width (lesser trochanter - 100 mm)
D: Lateral cortical width (lesser trochanter)
E: Medial cortical width (lesser trochanter)
F: Lateral cortical width (lesser trochanter - 50 mm)
G: Medial cortical width (lesser trochanter - 50 mm)
H: Femoral neck width
Bone Microarchitectural Changes in Asians and Patients with AFF

- Bone biopsy studies
- *In vivo* bone biopsy using high-resolution pQCT (62 µm)

**High-resolution Peripheral quantitative computed tomography (HR-pQCT)**

- Quantification of cortical and trabecular volumetric BMD
- Quantification of trabecular and cortical bone microarchitecture
- Skeletal muscle
- Knee cartilage
Trabecular and Cortical Bone

**Trabecular Bone**
- Trabecular bone volume
- Trabecular number
- Trabecular thickness
- Trabecular separation
- Trabecular connectivity

**Cortical Bone**
- Thickness
- Porosity
Lower Cortical Porosity and Higher Tissue Mineral Density in Chinese American Versus White Women

Boutroy S et al., JBMR 2013, 29: 551-561. DOI: (10.1002/jbmr.2057)
Lower Cortical Porosity and Higher Tissue Mineral Density in Chinese American Versus White Women – Tibial Cortical Porosity

Boutroy S et al., JBMR 2013, 29: 551-561. DOI: (10.1002/jbmr.2057)
Lower Cortical Porosity and Higher Tissue Mineral Density in Chinese American Versus White Women – Summary

- Greater cortical volumetric BMD is due to both reduced cortical porosity and greater tissue mineral density.
- Consistent with the lower bone remodeling observed in Chinese American compared with white women.
- These findings suggest that the thicker and more preserved cortical bone structure in Chinese American women may contribute to greater bone strength compared with white women.
- It may also predispose to AFF.
## AFF Incidence by Asian Ethnic Groups

<table>
<thead>
<tr>
<th>Ethnic Broad Group</th>
<th>N 29,050</th>
<th>AFF cases 23</th>
<th>AFF incidence rate*</th>
<th>Age-adjusted IRR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Asian</td>
<td>1,288</td>
<td>0</td>
<td>0.0</td>
<td>-</td>
</tr>
<tr>
<td>Chinese Asian</td>
<td>5,165</td>
<td>3</td>
<td>7.0</td>
<td>0.6 (0.2, 2.1)</td>
</tr>
<tr>
<td>North East Asian</td>
<td>275</td>
<td>0</td>
<td>0.0</td>
<td>-</td>
</tr>
<tr>
<td>South East Asian</td>
<td>11,065</td>
<td>15</td>
<td>16.6</td>
<td>3.4 (1.4, 8.1)</td>
</tr>
<tr>
<td>Southern Asian</td>
<td>11,162</td>
<td>5</td>
<td>5.5</td>
<td>0.4 (0.1, 1.1)</td>
</tr>
<tr>
<td>Asian, no specified</td>
<td>95</td>
<td>0</td>
<td>0.0</td>
<td>-</td>
</tr>
</tbody>
</table>

* per 100,000 person-years

Nguyen HH et al., Bone 2020, 135:115319.
Altered Cortical Composition and Reduced Fracture Resistance in AFF

- Bisphosphonate treatment can potentially impair toughening and predispose to AFF through several mechanisms:
  - by decreasing osteonal density, which could alter extrinsic toughening by reducing crack deflection
  - by reducing compositional heterogeneity, which potentially reduces the intrinsic plasticity
  - by increasing nonenzymatic collagen cross-linking, leading to loss of post-yield (intrinsic) toughness
- Examined compositional and mechanical properties of biopsies from long-term bisphosphonate-treated patients with AFFs
- Compared these properties to those from patients with differing fracture morphologies and bisphosphonate treatment histories
Increased Cortical Thickness and Cortical Ratio in AFF in Bone Biopsies

Lloyd AA et al., PNAS 2017 114:8722-8727
Elevated Mineral Content and Collagen Maturity Assessed by Vibrational Spectroscopic Imaging in AFF in Bone Biopsies

Parameter means for compositional (mineral-to-matrix ratio, MM; collagen maturity, XLR; and crystallinity, XST) and nanomechanical (reduced modulus E; hardness H) properties
Long-Term Bisphosphonate Treatment Shows Lower Crack Initiation Toughness and Overall Toughness, with Less Crack Deviation in Bone Biopsies

Reconstructed microbeam µCT crack paths and SEM images of propagated cracks in cortical tissue, with notches and crack paths highlighted in red, from an (A) atypical fracture patient (+BIS Atypical), (B) a typical fracture patient with (+BIS Typical)
### In vivo Bone Microarchitecture Using HR-pQCT

<table>
<thead>
<tr>
<th></th>
<th>AFF</th>
<th>Healthy PostMW</th>
<th>Treated No incident Fx</th>
<th>Treated Incident Fx</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No.</strong></td>
<td>36</td>
<td>34</td>
<td>43</td>
<td>36</td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>74.0 (60 - 89)</td>
<td>72.0 (51 - 84)</td>
<td>70.7 (55 - 85)</td>
<td>74.1 (55 - 90)</td>
</tr>
<tr>
<td><strong>Therapy (yrs)</strong></td>
<td>7.7 (2 - 22)</td>
<td>NA</td>
<td>5.3 (1 - 15)</td>
<td>6.5 (1 - 30)</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>152.0 (137 - 168)</td>
<td>162.2 (157 - 167)</td>
<td>156.4 (149 - 168)</td>
<td>154.6 (136 - 165)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>70.6 (47 - 105)</td>
<td>73.2 (58 - 90)</td>
<td>58.0 (36 - 78)</td>
<td>60.5 (39 - 90)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>30.2 (23 – 40)</td>
<td>27.8 (23 – 34)</td>
<td>23.8 (15 – 33)</td>
<td>25.3 (18 – 41)</td>
</tr>
<tr>
<td><strong>Prevalent Fx (%)</strong></td>
<td><strong>82.6</strong></td>
<td>NA</td>
<td><strong>91.3</strong></td>
<td><strong>82.1</strong></td>
</tr>
</tbody>
</table>
Porosity Matrix Mineralization Density (MMD)

Mean attenuation of photons produced by Voxels with attenuation < 80% of fully mineralized bone (1200mgHA/cc)

Voxels attenuating within 80-100% of fully mineralized bone (1200mgHA/cc)

Photon attenuation = 100% of 1200 mgHA

Matrix Mineralisation Density

Photon attenuation = 80% of 1200 mgHA

‘High’ porosity and ‘high’ MMD above trait mean for 340 premenopausal health women age 20-45 yrs

Zebaze et al 2013
Postmenopausal treated
- No incident fx

Premenopausal healthy

Postmenopausal treated + incident fx

Mineralization Score (%) vs. Porosity (%)
All P < 0.05

Porosity

MMD

Trabecular density

Premeno controls
Healthy PostMW
AFFs
Treated with BP
- incident Fx +
both

Premeno controls
Healthy PostMW
AFFs
Treated with BP
- incident Fx +
both

Both P < 0.05

All P < 0.05
Summary

Patients with AFFs have:

a) Microstructural deterioration
b) High MMD
c) The MMD is disproportionately high relative to level of porosity

Limitations

• Cross sectional, small sample
• No pre-treatment measurements
• No pentosidinex cross-links available
Long-term Approaches to Address AFF – Genetic Causes

- Asian race
- A pilot study using an exome array in 13 patients with AFF and 268 controls identified a greater number of rare variants in the cases compared with the controls.
  - Analyses were restricted to the variants with minor allele frequencies less than 3%, which limited the ability to make meaningful inferences about individual variants.
- WES in 3 sisters who developed AFFs while taking bisphosphonates and 3 unrelated AFF cases showed a p.Asp188Tyr mutation in the GGPS1 (geranylgeranyl pyrophosphate synthase) gene, which is critical to osteoclast function, and is also inhibited by BPs.

Nguyen H et al., JBMR Plus, 2018
Molecular mechanism of action of nitrogen-containing bisphosphonates

Statins block HMG-CoA, which leads to the inhibition of FPP synthase. As a result, FPP synthase is inhibited, blocking the prenylation of small signalling proteins essential for cell function and survival.

- Mevalonate
- Geranyl diphosphate
- Farnesyl diphosphate (FPP)
- Geranylgeranyl diphosphate (GGPP)

N-BPs inhibit FPP synthase, thus blocking the prenylation of small signalling proteins essential for cell function and survival.

Signalling proteins include Ras, Rac, Rho, and Rab.

Diagram shows the inhibition of enzymes FPP synthase and GGPP synthase by nitrogen-containing bisphosphonates (N-BPs), leading to the prenylation block of signalling proteins.
Figure 2: Genes implicated in atypical femoral fractures and their relationship to bone remodelling and bone matrix.
Welcome to the TrAFFIC Study website.

The TrAFFIC study is investigating risk factors and identifying causes of atypical femoral fractures to find ways to prevent it.

Atypical femoral fractures are rare and atypical thigh-bone fractures that have been associated with anti-osteoporosis medications that inhibit bone breakdown. The causes of these fractures are not yet known. If we can understand what factors lead to the development of these fractures, we can try to prevent them. Nevertheless, the benefits of anti-osteoporosis medications to reduce broken bones due to osteoporosis far outweigh the small risk of an atypical femur fracture.

The TrAFFIC study is a multi-center international study that has been approved by Human Research Ethics Committees at each study site. We are investigating clinical and genetic factors that may be involved in the development of these atypical femoral fractures.

If you are a patient who has had an atypical femoral fracture or a clinician who would like to participate in the TrAFFIC Study, please contact us for more information.

You can read more about the TrAFFIC Study here or contact the lead researcher: Professor Peter R Ebeling via +61 3 8572 2570; peter.ebeling@monash.edu

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Melbourne, AU

Monash Health

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Western Health

Researcher: Dr Vivian Grill

Royal Melbourne Hospital

Researcher: Dr Christopher Yates

Sydney, AU

Toronto, CA

Rotterdam, NL

Singapore

Oxford, UK

Gardena, USA
Genetic Analyses

- Whole exome sequencing (WES) and functional studies
- WES performed in a large Belgian family of 3 sisters and one nephew with AFFs and long-term bisphosphonate use – GPPS1 gene negative
- DNA obtained from two families in Singapore with AFFs and long-term bisphosphonate use
- To date WES performed on 250 unrelated individuals with AFF
- The aim is to obtain DNA from 400 individuals with AFF for WES
- Functional studies will be performed in fibroblast cell cultures established from AFF patients (Oxford site – Prof Raj Thakker)
- Validation cohort identified in Toronto – 350 AFF cases
Treatment of AFF

- Withholding bisphosphonates will reduce risk after 12 months
- AFF may be less commonly associated with denosumab
- Teriparatide does not improve healing ofAFF, based on data from TAFF RCT
  - Incomplete AFF did not progress to complete AFF in either treatment group following bisphosphonate cessation
  - Cheung A, ASBMR 2020 abstract #1062
- Contralateral AFF may not be prevented by teriparatide therapy
Conclusion

- Genetic and ethnic factors are likely to predispose to AFF
- The osteocyte transmembrane protein, EphrinB2, regulates bone mineralization and its expression may be downregulated in AFF
- Bone microarchitectural changes may also increase risk in Asians
- Unfavorable changes in cortical bone micro-architecture (increased matrix mineral density compared with porosity) may increase risk
- Homogenous bone mineralization after long-term bisphosphonate therapy may prevent microcrack deviation in cortical bone predisposing to AFF
- Treatment should be bisphosphonate cessation
Acknowledgements

Prof. Natalie Sims, SVIMR
Dr. Roger Zebaze
Q&A
Thank you

On behalf of IOF, we thank you for your participation in this webinar