AOTRAUMA ASIA PACIFIC

AOTrauma Asia Pacific Multi-Center Study Grant 2016 Application Form

1. Project title

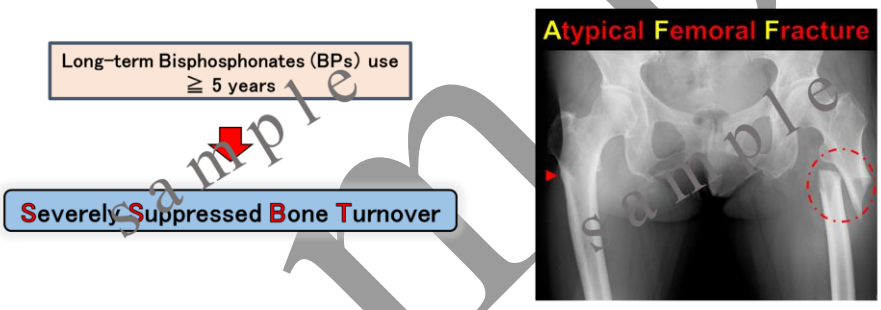
Validation of novel classification for atypical femoral fractures

2. Rationale

1. Severely suppressed bone turnover (SSBT) after long-term bisphosphonates (BPs) use has been considered to be a major factor of low-energy diaphyseal femoral fractures, commonly called atypical femoral fractures (AFFs). However, the correlation between AFFs and long-term BPs use has not been clearly identified.

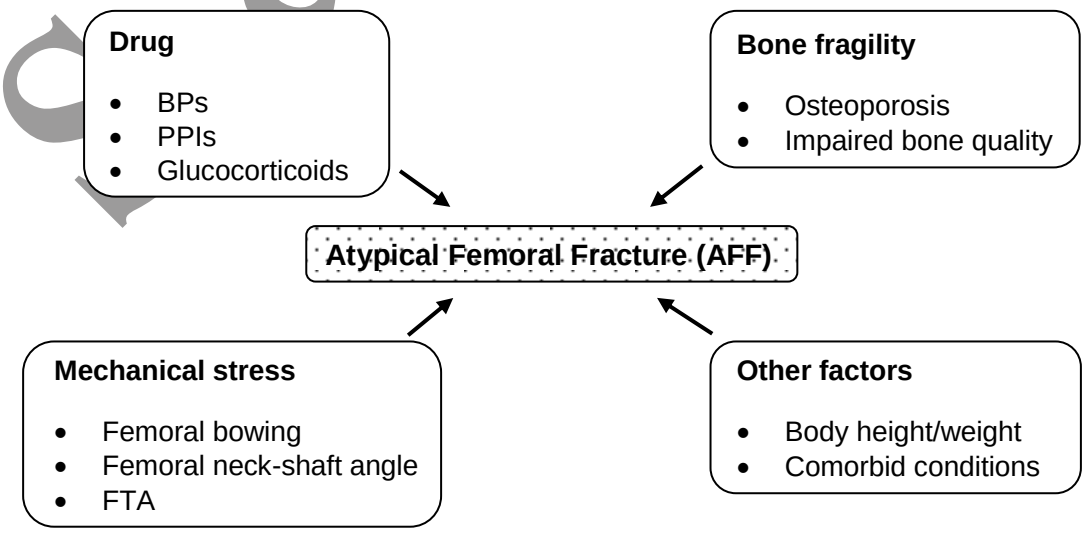
Odvina CV. J Clin Endocrinol Metab. 2005;90:1294–301.

Dell RM. J Bone Miner Res. 2012;27:2544–50.



2. Recently, AFFs have already been reported as a multifactorial disease since osteoporosis, loading stress (stress fractures), comorbid conditions, and pharmaceutical agents are known to be involved in their pathogenesis.

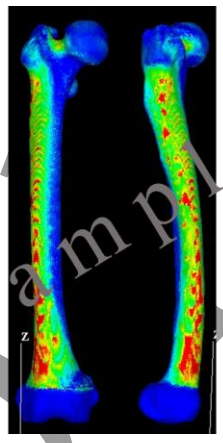
Shane E. J Bone Miner Res. 2014;29:1–24.



3. Authors previously studied stress fractures of the bowed femoral shaft (SBFs) not associated with BPs use, and indicated that significant tensile stress due to bowing deformity can induce AFFs through mechanical analysis by the CT-based finite element method (CT/FEM).

Oh Y. J Orthop Sci. 2014;19(4):579-86.

Oh Y. Injury. 2014;45:1764–71.



4. Varus hip geometry (small neck-shaft angle) may be another cause of subtrochanteric AFFs caused by SSBT.

Hagen JE. J Bone Joint Surg Am. 2014;96:1905-9.

5. Incidence of AFFs are very low (1 AFF in the 200 femur fractures). It is difficult to accumulate enough data in single-center study.

Schilcher J. N Engl J Med. 2011;364:1728–37.

3. Objective and success criteria

Validation of subtype classification for AFFs.

Recommendation for the new concept of diagnostic criteria and treatment according to a subtype of AFFs.

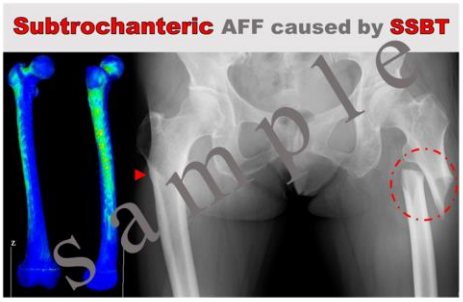
4. Hypothesis

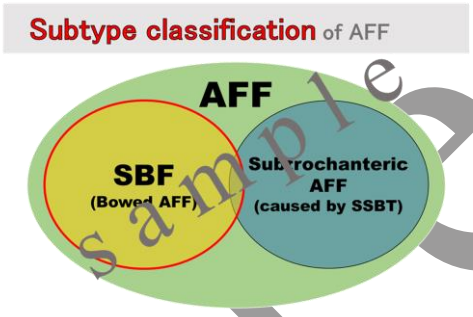
In patients with SBFs (bowed AFFs), we have detected marked short stature and severe osteoporosis. We consider that femoral shaft bowing deformity may be affected by short stature and bone fragility.

Meanwhile, in patients with subtrochanteric AFFs after long-term BPs use, we have detected stress concentration localized in the subtrochanteric region through mechanical analysis by CT/FEM. We consider that subtrochanteric

AFFs are caused not only by SSBT but also by stress distribution focused in the subtrochanteric region due to small neck-shaft angle.

On ground of these findings, we advocate that AFFs could be classified into two types; “SBFs (bowed AFFs)” and “subtrochanteric AFFs caused by SSBT”.





Through the subtype classification of AFFs, we can advocate a new concept of diagnostic criteria and treatment according to a subtype of AFFs.

As for the result of the present study, it is expected to be the reference materials of scientific researches and treatment guidelines.

5. Method

5.1 Material

Design: multi-center prospective clinical study

Setting: 1 university hospital and 11 affiliated hospitals in Japan

Patients: patients with AFFs (30-40 patients per year)

Inclusion criteria

Meet the criteria of the AFFs’ case definition revised by the ASBMR Task Force 2013

Females over 65 years

Ambulate independently (before the injury)

Cognitive ability to understand the purpose of this study

Consent with a signature

Exclusion criteria

Past history of lower extremity operation (except AFFs)

Past history of bilateral femur internal fixation (patients with AFFs)

Mental disorder

5.2 Methodology

Age

Physical build (body height/weight)

Comorbid conditions

Drug use career (BPs, PPIs, glucocorticoids)

Plain X-ray: Hip AP, Femur 2R (AP and lateral), Standing AP of the lower extremity

CT scan: DICOM data is used for mechanical analysis by CT/FEM and the MECHANICAL FINDER (Research Center of Computational Mechanics, Inc., Tokyo, Japan) analysis software

Dual energy X-ray absorptiometry (femoral neck, lumbar spine)

Bone metabolic markers (DPD/Cr, TRACP-5b, BAP, Intact P1NP, ucOC)

Bone biopsy

5.3 Data analysis/statistics

Physical build (body height/weight)

Drug use career

Morphological assessment of lower extremity (femoral bowing, neck-shaft angle, femorotibial angle)

Bone metabolism (bone resorption, bone formation, bone quality)

Histopathological analysis

Mechanical analysis by CT/FEM

Statistics: Mann-Whitney U test, Kruskal-Wallis test

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6. Literature

1. **Oh Y**, et al. Potential pathogenic mechanism for stress fractures of the bowed femoral shaft in the elderly: Mechanical analysis by the CT-based finite element method. Injury. 2014;45:1764–71.

2. **Oh Y**, et al. Stress fracture of the bowed femoral shaft is another cause of atypical femoral fracture in elderly Japanese: a case series. J Orthop Sci. 2014;19(4):579-86.

3. Odvina CV, et al. Severely suppressed bone turnover: a potential complication of alendronate therapy. J Clin Endocrinol Metab. 2005;90:1294–301.

4. Park-Wyllie LY, et al. Bisphosphonate use and the risk of subtrochanteric or femoral shaft fractures in older women. JAMA. 2011;305:783–9.

5. Dell RM, et al. Incidence of atypical no traumatic diaphyseal fractures of the femur. J Bone Miner Res. 2012;27:2544–50.

6. Shane E, et al. 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;29:1–24.

7. Schilcher J, et al. Bisphosphonate use and atypical fractures of the femoral shaft. N Engl J Med. 2011;364:1728–37.

8. Hagen JE, et al. Association of Atypical Femoral Fractures with Bisphosphonate Use by Patients with Varus Hip Geometry. J Bone Joint Surg Am. 2014;96:1905-9.

9. Borrelli J, et al. Atypical Femur Fractures. J Orthop Trauma. 2014;28:S36-42.

10. Martelli S, et al. Femoral shaft strains during daily activities: Implications for atypical femoral fractures. Clinical Biomechanics. 2014;29:869-76.

11. Saita Y, et al. The fracture sites of atypical femoral fractures are associated with the weight-bearing lower limb alignment. Bone. 2014;66:105-10.

12. Maratt J, et al. Variation in the femoral bow: a novel high-throughput analysis of 3922 femurs on cross-sectional imaging. J Orthop Trauma. 2014;28:6-9.

13. Adler RA. Duration of anti-resorptive therapy for osteoporosis. Endocrine. 2016;51:222-4.

14. Schilcher J, et al. Atypical Fractures are Mainly Subtrochanteric in Singapore and Diaphyseal in Sweden: A Cross-Sectional Study. J Bone Miner Res. 2015;30:2127-32.

15. Adler RA, et al. Managing Osteoporosis in Patients on Long-Term BisphosphonateTreatment:ReportofaTaskForceofthe American Society for Bone and Mineral Research. J Bone Miner Res. 2016;31:16-35.

7. Time table (milestones, pilot study, main study)

Study planning finished: by 31st July 2015

Start inclusion period: 1st August 2015

Pilot study finished: by 31st March 2016

End inclusion period: 31st January 2018

Data complete: 28th February 2018

Final Report: 31st March 2018

< Pilot study >

Unpublished data (oral presentation in 3rd AOTAP Scientific Congress 2016)

Study period: August 2015 to March 2016

Patients: SBF (bowed AFF; __ patients), Subtrochanteric AFF (__ patients), Control (__ patients data from authors' previous study)

Data of subjects

	Age (years)	Lateral bowing angle (°)	Anterior radius of curvature (mm)	Neck-shaft angle (°)	Bone density (g/cm^2)
SBF (bowed AFF) (n = __)	__ ± __	__ ± __	__ ± __	__ ± __	__ ± __
Subtrochanteric AFF (n = __)	__ ± __	__ ± __	__ ± __	__ ± __	__ ± __
Control (n = __)	__ ± __	__ ± __	__ ± __	__ ± __	__ ± __
	p = __	p < __	p < __	p < __	p < __

**Statistics: Kruskal-Wallis test*

Histopathological analysis of the incomplete fracture site

Fig. A Fig. B

A B

A. SBFs (bowed AFFs)

_____ were seen in the fracture face.

B. Subtrochanteric AFFs caused by SSBT

_____ were seen in the fracture face.

_____ filled the incomplete fracture face.

Summary of pilot study

Subtype characteristics of AFF

	Bowing deformity	Neck-shaft angle	Osteoporosis	Bone turnover
SBF (Bowed AFF)	++	↑	++ (High risk of femoral neck fracture)	low
Subtrochanteric AFF	-	↓	-	very low (SSBT)

< Main study >

The examples for analyses will be increased to verify our suggestion.

Desired number of cases are 30-40 patients of each SBFs (bowed AFFs) and subtrochanteric AFFs.

< Advanced study >

Investigation for risk of developing femoral neck fractures in patients with AFFs through assessment of bone metabolism and mechanical analysis.

We consider that SBFs (bowed AFFs) are associated with bone fragility (severe osteoporosis and impaired bone quality) and at high risk of femoral neck fractures.

8. Applicant(s)

8.1. Project leader

➢ (Surname, First name, Academic degree, Institution, Contact number and email address, Past research experience)

Surname: Oh

First name: Yoto

Academic degree: M.D., Ph.D.

Institution: Assistant Professor, Department of Orthopaedic and Spinal Surgery, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University

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Email: oh.orth@tmd.ac.jp

Past research experience:

Lilly research grant program 2016 (Japan osteoporosis foundation): Clarification of pathogenic factors leading to atypical femoral fractures

AOTrauma Asia Pacific Research Grants 2013 (Ref: AOTAP13-13): Stress fractures of bowing femoral shaft in elderly Asians must be distinguished from atypical femoral fractures by SSBT: Mechanical analysis by CT-based finite element method

Potential pathogenic mechanism for stress fractures of the bowed femoral shaft in the elderly: Mechanical analysis by the CT-based finite element method. **Oh Y**, Wakabayashi Y, Kurosa Y, Fujita K, Okawa A. **Injury**. 2014 November;45(11):1764-71

Stress fracture of the bowed femoral shaft is another cause of atypical femoral fracture in elderly Japanese: A case series. **Oh Y**, Wakabayashi Y, Kurosa Y, Ishizuki M, Okawa A. **J Orthop Sci**. 2014 Jul;19(4):579-86

Stress fractures of bowing femoral shaft in the elderly - another cause of atypical femoral fractures. **Oh Y**, Wakabayashi Y, Kurosa Y, Ishizuki M, Okawa A. **Bone Joint J** 2013 vol.95-B no.SUPP 16 9

8.2. Co-applicant

- (Surname, First name, Academic degree, Institution, Contact number and email address, Past research experience)

1. Fujita Koji, M.D., Ph.D.

Institution: Assistant Professor, Department of Orthopaedic and Spinal Surgery, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University

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Tel: +81-3-5803-5279 Fax: +81-3-5803-5281

Email: _____@_____

Past research experience:

Isolation and characterization of human osteoblasts from needle biopsies without in vitro culture. Fujita K, Roforth MM, Atkinson EJ, Peterson JM, Drake MT, McCready LK, Farr JN, Monroe DG, Khosla S. **Osteoporos Int**. 2014;25(3):887-95

Mutual enhancement of differentiation of osteoblasts and osteocytes occurs through direct cell-cell contact. Fujita K, Xing Q, Khosla S, Monroe DG. **J Cell Biochem**. 2014;115(11):2039-44

Vitamin E decreases bone mass by stimulating osteoclast fusion. Fujita K, Iwasaki M, Ochi H, Fukuda T, Ma C, Miyamoto T, Takitani K, Negishi-Koga T, Sunamura S, Kodama T, Takayanagi H, Tamai H, Kato S, Arai H, Shinomiya K, Itoh H, Okawa A, Takeda S. **Nat Med**. 2012;18(4):589-94

2. Okawa Atsushi, M.D., Ph.D.

Institution: **Chairperson**, Department of Orthopaedic and Spinal Surgery, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University

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3. Sawaguchi Takeshi, M.D., **AOTrauma Japan Chairperson**

Institution: Vice director, Toyama Municipal Hospital

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9. Finance (Maximum CHF 25,000)

- All amount requested in Swiss francs

Personnel costs (per diems to surgeons cannot be included):

Study assistant (1 person) for data analysis; CHF 4,000

Material costs (cost of implants and surgical equipment cannot be included):

Statistical software; CHF 1,000

Computer for analysis / data management; CHF 2,000

English language editing; CHF 4,000

Maintenance expense of mechanical analysis software; CHF 6,000

Travel and accommodation costs: CHF 8,000

Total amount requested in Swiss francs for the project:

CHF 25,000

Please submit your application directly to AOTrauma Asia Pacific, Jennifer Hung, at: research@aotap.org. Thank you!