Case Report

Unusual Subtrochanteric Femoral Insufficiency Fractures Associated with the Prolonged Use of Alendronate and Risedronate: A Report of Two Cases

Chayanin Angthong MD*,
Wirana Angthong MD**

** Department of Orthopaedic Surgery, Faculty of Medicine, Thammasat University, Pathumthani, Thailand*
*** Department of Radiology, Faculty of Medicine, Srinakharinwirot University, Nakhon Nayok, Thailand*

Objective: *Previous studies reported that prolonged alendronate use was related to insufficiency fractures. Fewer reports presented this phenomenon in patients with risedronate use. The present study reported on two patients, both of whom had long-term use of alendronate and risedronate then sustained subtrochanteric femoral insufficiency fractures with minimal trauma.*

Case summary: *One of the patients was treated with alendronate therapy in concern of her risk factors for osteoporosis (her previous a hysterectomy with bilateral oophorectomy) with unsubstantiated evidence of her pretreatment, bone-mineral-density measurements (BMD), for a 10-year prior episode of left prodromal thigh pain and an insufficiency fracture at 8 days post experiencing the pain. The other patient had a history of the hysterectomy and right salpingo-oophorectomy, a low-energy metatarsal fracture with resulting osteopenia verified with BMD measurements. She was treated with alendronate for 42 months before switching to risedronate for 6 months per patient's request but no history of prodromal thigh pain. Subsequently, she sustained an insufficiency fracture, while standing and turning her body. Both patients had the significant long-term uses of bisphosphonate and exhibited the typical radiographic characteristics of insufficiency fracture. From the present report, risedronate is another prospective medication that might be related to insufficiency fractures.*

Conclusion: *The present study concluded that cautious consideration is essential for long-term alendronate and risedronate use for any individual patient. The index of suspicion for the subtrochanteric femoral insufficiency fracture should be higher in the patients presenting with prodromal thigh pain. Further studies are necessary to identify the class effect of other bisphosphonate drugs, the definitive mechanisms between all generations of bisphosphonate treatments and their complications, including the individual risk factors of the insufficiency fracture.*

Keywords*: Subtrochanteric femoral insufficiency fracture, Alendronate, Risedronate, Osteoporosis*

J Med Assoc Thai 2011; 94 (Suppl. 7): S214-S220
Full text. e-Journal: *http://www.jmat.mat.or.th*

Alendronate has been proven in decreasing the amount of bone turnover. This agent acts as a potent inhibitor of bone resorption. Alendronate is also the medication used in the prevention of osteoporotic fractures according to the approval of USA Food and Drug Administration in 1995[1]. However, later studies revealed patients sustaining low-energy fractures after prolonged alendronate therapy[1-4]. Neviaser and colleagues (2008) reported the association between low-energy fractures of the femoral shaft; exhibiting a simple, transverse pattern, with hypertrophy of the diaphyseal cortex with alendronate use[4]. They proposed that impaired microdamage repair and the retardation of the reparative process by the reduction of osteoclast activity, could be caused by prolonged alendronate use. Fewer reports presented this phenomenon in patients with treatment with bisphosphonates other than alendronate[5,6].

Although there were an increasing number of reports around the world about the association of the bisphosphonate therapy and atypical femoral fractures, to date of our knowledge, the present report might be a part of early reports about this association in Thailand, especially for the relationship with risedronate which was rarely reported. The aim of the present study was to report on two patients who had taken alendronate

Correspondence to:
Angthong C, Department of Orthopaedic Surgery, Faculty of Medicine, Thammasat University, Paholyothin Road, Klong Luang, Pathumthani 12120, Thailand.
Phone: 0-2926-9775, Fax: 0-2926-9793
E-mail: chatthara@yahoo.com, chayaninboom@gmail.com

and risedronate for long durations and sustained subtrochanteric fractures with minimal trauma. The present study obtained permission from both patients for this academic report.

Case summary

Case 1

A 75-year-old female patient underwent a hysterectomy with bilateral oophorectomy 30 years ago due to benign uterine tumors. A year after surgery, she was put on estrogen replacement (Primarin 0.625 mg/day) for 4 years for treatment of climacteric symptoms. Ten years ago, she was treated with alendronate treatment (Fosamax 70 mg/week) secondary to concerns of risk factors for osteoporosis (previously bilateral oophorectomy) with unidentified evidence of her bone mineral density (BMD). She was also supplemented with oral calcium carbonate 2 g/day. However, her BMD was not consecutively followed-up. Other medical history included Alzheimer's disease and cataracts. She had no history of long-term steroid use. Her pre-injury ambulatory function was noted as indoor-independence with a walker.

After 10 years of the continuation of alendronate treatment and oral calcium supplementation, she visited our institution complaining of left thigh pain with no history of trauma. Her left thigh pain was increased during sitting and motion of left lower extremity. She could not bear her weight on her left lower extremity due to thigh pain. The duration of these symptoms was recorded as one week. At our institution, the plain radiographs were obtained and revealed lateral, cortical hypertrophies in the subtrochanteric and diaphyseal regions of both left and right femurs. This included transverse radiolucent lines at the lateral cortex of the left proximal femoral shaft (Fig. 1). The bone scintigraphy using Tc99m methylene disphosphonate (MDP) was investigated and demonstrated increased activity at the proximal shaft region of left femur corresponding with the position of the lateral cortical thickening as evidenced on the plain radiograph (Fig. 2). Her diagnosis was an impending left subtrochanteric femoral fracture. She was advised to avoid ambulation and use a wheelchair for mobility and made aware of the fracture. Further investigation was planned to define the primary cause of this lesion. A day after the hospital visit, she sustained a left subtrochanteric femoral fracture while transferring herself from her bed to her wheelchair (Fig. 3). Her left subtrochanteric fracture was classified as a Russell-Taylor type IA with extension to the femoral shaft and

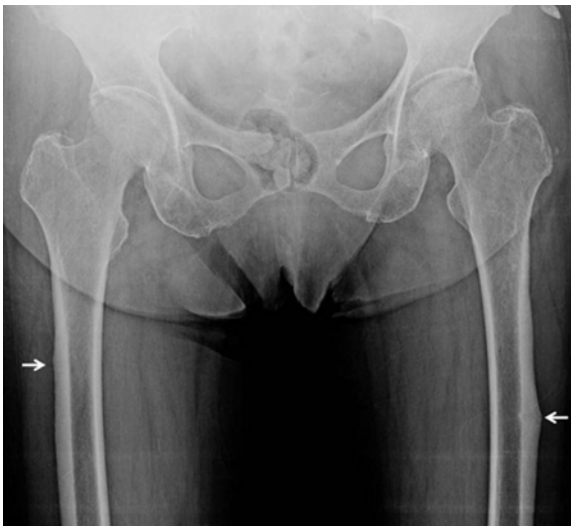

Fig. 1 Anteroposterior radiograph of both left and right femur showing hypertrophy on the lateral cortex of both sides of femoral shaft (arrow). The lateral cortical reaction of the left proximal femoral shaft is also shown

showed the fracture configuration consisting of lateral, cortical hypertrophy of the subtrochanteric region and the proximal shaft of the left femur, a transverse fracture, and a medial cortical spike. Other tests, including serum tumor markers, showed as no evidence of metastatic causes before definitive fixation. Eventually, this patient was treated with open reduction and internal fixation with a locking plate (Fig. 4). She recovered uneventfully. In addition, alendronate treatment was discontinued.

Case 2

A 58-year-old female patient underwent a hysterectomy with right salpingo-oophorectomy 8 years ago for endometriosis of the uterus and right ovary. She was put on estrogen replacement (Primarin 0.625 mg/day) for 1 month for treatment of climacteric symptoms. She had no history of long-term steroid use. Four years later she sustained a right, fifth metatarsal, basal fracture after falling from standing height. Her pre-injury status was in community ambulation. She was treated conservatively using a short leg cast for 6 weeks. Her bone mineral density (BMD) was also measured at that time and showing -2.0, -1.7 and -2.0 T-scores of the lumbar spine, proximal femur, and distal radius, respectively. She was then placed on alendronate (Fosamax 70 mg/week) for 42 months before switching to risedronate (Actonel 35 mg/week) per the patient's request. She was also

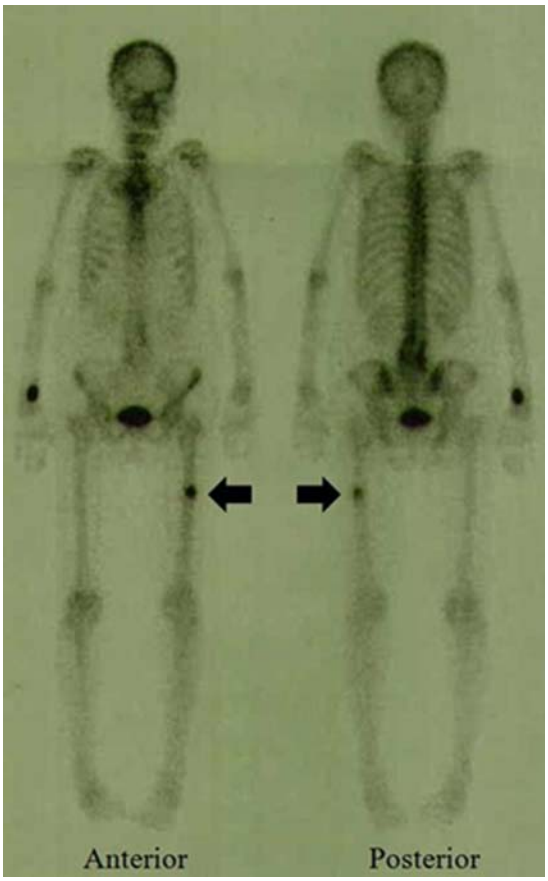

Fig. 2 Tc99m-MDP anterior and posterior whole body bone scan demonstrates increased uptake in the left femur (arrow) corresponding to the position of the lateral cortical reactions evidenced on the plain radiograph

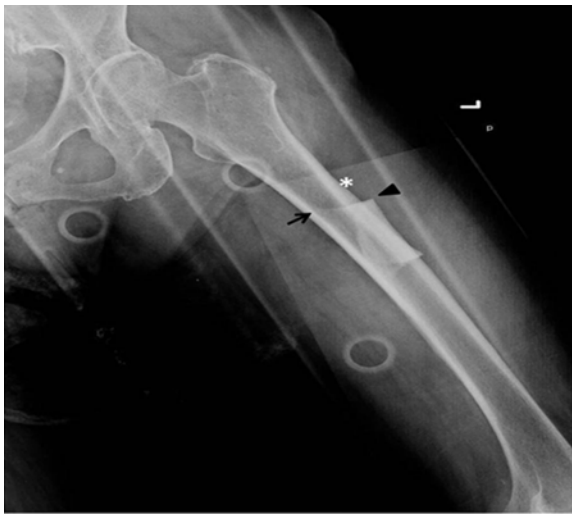

Fig. 3 Anteroposterior radiograph of the left femur revealing the appearance of (1) lateral cortical hypertrophy (*), (2) transverse fracture (black arrow head) and (3) medial cortical sharp spike (black arrow)

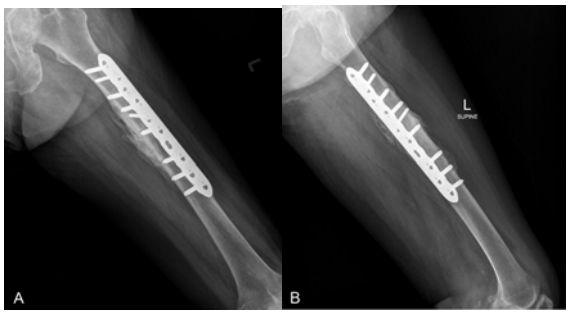

Fig. 4 (A,B) Plain radiographs of the left femur showing the 16-month postoperative alignment and configuration, including exuberant callus at fracture site

supplemented with regular doses of oral calcium carbonate 1 g/day and calcitriol 0.50 micrograms/day. Her BMD measurements were followed-up one year ago. The results were shown as -1.2, -1.4 and -2.2 for T-scores of the lumbar spine, proximal femur and distal radius, respectively. Although her BMD values were improved at her lumbar spine and proximal femur, her risedronate was continued.

She had been receiving bisphosphonate therapy for 4 years until sustaining a subtrochanteric fracture of the left femur while standing and turning her torso. She could not bear her weight on the left lower extremity due to pain in her left thigh. However, she did not report the prodromal thigh pain prior to this event. The plain radiographs revealed a left subtrochanteric femoral fracture which was classified as a Russell-Taylor type IA and showed a fracture configuration consisting of lateral, cortical hypertrophy of the subtrochanteric region and the proximal shafts of both femurs, and a medial cortical spike of the left proximal femur (Fig. 5). In addition, the bone scintigraphy using Tc99m methylene disphosphonate (MDP) demonstrated an increased activity at the proximal shaft region of both femurs corresponding to the positions of lateral cortical thickening of both proximal femurs (Fig. 6). Other investigations, including serum tumor markers, showed no evidence of metastatic causes prior to definitive fixation. This patient was treated with closed reduction and internal fixation using a cephalomedullary nail (Fig. 7). Eventually, bisphosphanate treatment was discontinued.

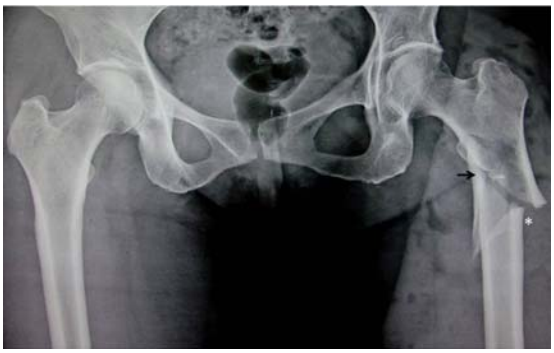

Fig. 5 Anteroposterior radiograph of the left femur showing the appearance of (1) lateral cortical hypertrophy (*) and (2) medial cortical sharp spike (black arrow)

Discussion

In the aging global population, osteoporosis has become a worldwide problem largely due to the age-association, exponentially increasing prevalence, medical costs, rates of morbidity and mortality[7]. Osteoporosis is the most common metabolic bone disease in humans. This disease is characterized by decreased bone mass, declining micro architectural structure, weakened bone strength, and an increased risk of fractures[8]. Realizing the burden of the consequences of osteoporosis, numerous measurements were studied to aid in the early recognition, prevention and treatment of the disease. Currently, many measures to detect osteoporosis at the earlier stages are widely in use[9]. Rates of early osteoporosis recognition are increasing along with the rate of the protocols used in prevention and treatment, for example, pharmacological interventions.

Alendronate is a drug in the bisphosphonate family. It is used frequently to decrease the risk of fractures in the elderly[4]. This medication is also the first-line therapy for the prevention of osteoporotic fractures. Alendronate is a potent inhibitor of osteoclast mediated bone resorption. Its action is to suppress osteoclastic activity and induce apoptosis of the osteoclasts. As alendronate has an important role in the management of osteoporosis, this medication also appears to be safe. Despite this, many researchers are concerned about the potential complications of long-term alendronate treatment, with concern to its widespread use. Later, many studies reported on the fractures that occurred in patients being treated with alendronate[1-4,10]. Odvina et al (2005), proposed that severely suppressed bone turn over (SSBT) occurred after prolonged alendronate treatment[10]. This SSBT

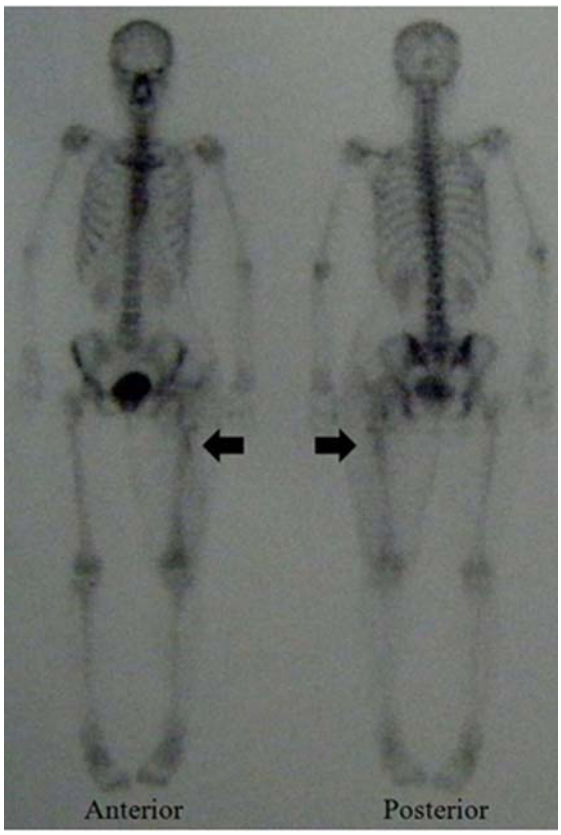

Fig. 6 Tc99m-MDP anterior and posterior whole body bone scan demonstrates increased uptake in the left femur (arrow) corresponding to the position of the lateral cortical reactions evidenced on the plain radiograph

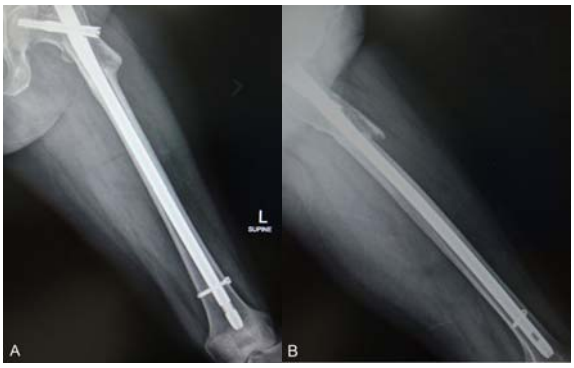

Fig. 7 (A,B) Plain radiographs of the left femur showing the 10-month postoperative alignment and configuration, including satisfactory healing of the fracture

was proven using bone histomorphometry analysis and was correlated with citing the poor healing tendencies

of nonspinal fractures. In animal models, this explanation might be related with the decreases in the strength of the bone secondary to the microdamage accumulation and the deficiency of the effective remodeling within the bone[11-13]. These changes might contribute to fractures from low-energy trauma in high tensile areas such as the subtrochanteric area and the shaft of the femur. These studies emphasized the caution of this potential complication during bisphosphonate therapy, specifically, alendronate. However, there were still controversial evidences about increasing microdamages from suppressed bone turnover in human trial. Stepan et al proposed that elevated microdamage gathering may arise in low BMD patients with alendronate treatment[14]. Chapurlat et al reported the oppositional results that low microcrack frequency were found in the iliac bone of postmenopausal osteoporotic women with long term bisphosphonate treatment[15]. Some researchers presented other mechanism possibly explained the association of bisphosphonates and atypical fracture from some evidences such as nitrogen-containing bisphosphonates might inhibit angiogenesis *in vivo*[16-18]. This might provide the adverse effects to the bone healing.

Citing risedronate treatment, Kwek and colleagues (2008), reported on a patient in their case series who receive risedronate for 6 years after 4 years of alendronate therapy[3]. Bush et al (2009), reported on the case of an 85-year-old woman who sustained a subtrochanteric femoral shaft, insufficiency fracture after receiving risedronate therapy (Actonel 35 mg/ week) for six years for the treatment of her osteoporosis[6]. They also reported about a case of an insufficiency femoral shaft fracture, 1.5 years after using intravenous zoledronic acid (Zometa), from the likelihood of osteoclast over-suppression as found in the curettage specimens from the fracture site[5]. Bamrungsong and Pongchaiyakul presented a report of bilateral atypical femoral fractures in a woman with alendronate therapy for nine years and changed to ibandronate treatment for one year[19]. In the present report, the authors second patient was on risedronate for 6 months after a 42-month period of alendronate therapy. These examples might suggest a relation with the influences of long-term use of bisphosphonates other than alendronate, such as risedronate, ibandronate and zoledronic acid, relating to subtrochanteric femoral insufficiency fractures. However, the class effects of these subtypes of bisphosphonate are necessary to have further study about their association with insufficiency femoral fracture. In addition to the issue about pharmacological effects of bisphosphonates, although risk factors of other kinds of osteoporotic fracture were determined[20-23], risk factors of the insufficiency fracture are not well defined. The further studies including enormous numbers of patients are needed to clarify this point.

The subtrochanteric region and the shaft of the femur appear to be the common sites of fractures in patients with prolonged bisphosphonate intake or the possible, now termed, "insufficiency or atypical fracture". Lateral cortical hypertrophy of the subtrochanteric region, including the femoral shaft region, seems to appear in many patients who were observed for this, typical fracture[3,4]. Goh et al (2007), discussed that the characteristics of these typical fractures correlate with high stress reactions at the subtrochanteric region that has exposure to maximal, bending stress[2] High stress reactions were produced from increased mineralization of the bone and inhibition of bone remodeling. Thus, this region is increased in fracture susceptibility secondary to increased fragility and microdamage accumulation[3]. In addition, the propagation of a stress fracture could initially exhibit prodromal thigh pain in patients who could sustain subsequent fractures from minimal or low energy trauma. The SSBT also supports previous explanations for the relationship between the characteristics of this typical fracture with long-term bisphosphonate treatment.

The present study demonstrates the unusual subtrochanteric femoral shaft fractures in two patients who had prolonged treatment of bisphosphonate (alendronate, risedronate) therapy and oral calcium supplementation, including calcitriol intake. To date of the authors' knowledge, the present study might be a part of early reports which showed that risedronate, another upcoming medication in the bisphosphonate class, might be related to insufficiency fractures.

Conclusion

In conclusion, the emphasis is that prolonged bisphosphonate treatment should be considered in equilibrium between the significant benefits of these medications in patients with osteoporosis against the possibly increased risk of the insufficiency fractures in any individual patient, especially in patients exhibiting prodromal thigh pain. Moreover, there was no certain data to determine that only alendronate, risedronate, ibandronate and zoledronic acid related with higher

risks of these insufficiency fractures. Further studies are necessary to define the class effect of other bisphosphonate drugs, the definitive mechanisms between all generations of bisphosphonate treatments and their complications, including the individual risk factors of the insufficiency fracture.

Potential conflicts of interest

None.

References

1. Armamento-Villareal R, Napoli N, Panwar V, Novack D. Suppressed bone turnover during alendronate therapy for high-turnover osteoporosis. N Engl J Med 2006; 355: 2048-50.
2. Goh SK, Yang KY, Koh JS, Wong MK, Chua SY, Chua DT, et al. Subtrochanteric insufficiency fractures in patients on alendronate therapy: a caution. J Bone Joint Surg Br 2007; 89: 349-53.
3. Kwek EB, Goh SK, Koh JS, Png MA, Howe TS. An emerging pattern of subtrochanteric stress fractures: a long-term complication of alendronate therapy? Injury 2008; 39: 224-31.
4. Neviaser AS, Lane JM, Lenart BA, Edobor-Osula F, Lorich DG. Low-energy femoral shaft fractures associated with alendronate use. J Orthop Trauma 2008; 22: 346-50.
5. Bush LA, Chew FS. Subtrochanteric femoral insufficiency fracture following bisphosphonate therapy for osseous metastases. Radiology Case Reports 2008; 3: 232. DOI: 10.2484/rcr.v3i4.232.
6. Bush LA, Chew FS. Subtrochanteric femoral insufficiency fracture in woman on bisphosphonate therapy for glucocorticoid-induced osteoporosis. Radiology Case Reports 2009; 4:261. DOI: 10.2484/rcr.v4i1.261.
7. Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY. Severely suppressed bone turnover: a potential complication of alendronate therapy. J Clin Endocrinol Metab 2005; 90: 1294-301.
8. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. No. 843 of Technical Reports Series. Geneva: WHO; 1994.
9. Johnell O. The socioeconomic burden of fractures: today and in the 21st century. Am J Med 1997; 103(2A): 20S-25S.
10. Pongchaiyakul C, Songpattanasilp T, Taechakraichana N. Burden of osteoporosis in Thailand. J Med Assoc Thai 2008; 91: 261-7.
11. Li J, Mashiba T, Burr DB. Bisphosphonate treatment suppresses not only stochastic remodeling but also the targeted repair of microdamage. Calcif Tissue Int 2001; 69: 281-6.
12. Mashiba T, Hirano T, Turner CH, Forwood MR, Johnston CC, Burr DB. Suppressed bone turnover by bisphosphonates increases microdamage accumulation and reduces some biomechanical properties in dog rib. J Bone Miner Res 2000; 15: 613-20.
13. Mashiba T, Turner CH, Hirano T, Forwood MR, Johnston CC, Burr DB. Effects of suppressed bone turnover by bisphosphonates on microdamage accumulation and biomechanical properties in clinically relevant skeletal sites in beagles. Bone 2001; 28: 524-31.
14. Stepan JJ, Burr DB, Pavo I, Sipos A, Michalska D, Li J, et al. Low bone mineral density is associated with bone microdamage accumulation in postmenopausal women with osteoporosis. Bone 2007; 41: 378-85.
15. Chapurlat RD, Arlot M, Burt-Pichat B, Chavassieux P, Roux JP, Portero-Muzy N, et al. Microcrack frequency and bone remodeling in postmenopausal osteoporotic women on long-term bisphospho-nates: a bone biopsy study. J Bone Miner Res 2007; 22: 1502-9.
16. Fournier P, Boissier S, Filleur S, Guglielmi J, Cabon F, Colombel M, et al. Bisphosphonates inhibit angiogenesis *in vitro* and testosterone-stimulated vascular regrowth in the ventral prostate in castrated rats. Cancer Res 2002; 62: 6538-44.
17. Wood J, Bonjean K, Ruetz S, Bellahcene A, Devy L, Foidart JM, et al. Novel antiangiogenic effects of the bisphosphonate compound zoledronic acid. J Pharmacol Exp Ther 2002; 302: 1055-61.
18. Stresing V, Fournier PG, Bellahcene A, Benzaid I, Monkkonen H, Colombel M, et al. Nitrogen-containing bisphosphonates can inhibit angiogenesis *in vivo* without the involvement of farnesyl pyrophosphate synthase. Bone 2011; 48: 259-66.
19. Bamrungsong T, Pongchaiyakul C. Bilateral atypical femoral fractures after long-term alendronate therapy: a case report. J Med Assoc Thai 2010; 93: 620-4.
20. Angthong C, Suntharapa T, Harnroongroj T. Major risk factors for the second contralateral hip fracture in the elderly. Acta Orthop Traumatol Turc 2009; 43: 193-8.
21. Cummings SR, Nevitt MC, Browner WS, Stone K,

Fox KM, Ensrud KE, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med 1995; 332: 767-73.
22. Chapurlat RD, Bauer DC, Nevitt M, Stone K, Cummings SR. Incidence and risk factors for a second hip fracture in elderly women. The Study of Osteoporotic Fractures. Osteoporos Int 2003; 14: 130-6.
23. Frost M, Abrahamsen B, Masud T, Brixen K. Risk factors for fracture in elderly men: a population-based prospective study. Osteoporos Int 2011 Mar 16. [Epub ahead of print]. DOI: 10.1007/s00198-011-1575-4.

กระดูกต้นขาหักจากความบกพร่องภายในที่ผิดปกติภายหลังการรักษาด้วยยา alendronate และ risedronate ระยะยาว: รายงานผู้ป่วย 2 ราย

ชญานิน อ่างทอง, วิรณา อ่างทอง

วัตถุประสงค์*: การศึกษาก่อนหน้านี้ได้รายงานผู้ป่วยที่เกิดกระดูกต้นขาหักจากการกระแทกที่ไม่รุนแรง ซึ่งสัมพันธ์กับการรักษาด้วยยา alendronate ระยะยาว อย่างไรก็ตาม มีจำนวนน้อยที่รายงานถึงปรากฏการณ์ดังกล่าวในผู้ป่วยที่ใช้ยา risedronate การศึกษานี้ได้นำเสนอผู้ป่วย 2 รายที่เกิดกระดูกต้นขาหักจากความบกพร่องภายในที่ผิดปกติภายหลังการรักษาทั้งจากยา alendronate และ risedronate ระยะยาว*

รายงานผู้ป่วย*: ผู้ป่วยรายแรกได้รับยา alendronate เป็นเวลา 10 ปี เนื่องจากปัจจัยเสี่ยงของกระดูกพรุนจากการผ่าตัดรังไข่และมดลูกจากปัญหาทางนรีเวชก่อนหน้านี้ ผู้ป่วยเกิดกระดูกต้นขาหักจากการกระแทกที่ไม่รุนแรงหลังจากเริ่มมีอาการปวดต้นขานำมาก่อนเป็นเวลา 8 วัน ผู้ป่วยรายที่ 2 ได้รับยา alendronate เป็นเวลา 42 เดือนและ risedronate เป็นเวลา 6 เดือน (เปลี่ยนยาเนื่องจากความต้องการของผู้ป่วย) การได้รับยาดังกล่าวเนื่องจากปัจจัยเสี่ยงของกระดูกพรุนจากการผ่าตัดรังไข่ข้างขวาและมดลูก จากปัญหาทางนรีเวชและกระดูกเท้าหัก จากการกระแทกที่ไม่รุนแรงก่อนหน้านี้ ร่วมกับผลการตรวจความหนาแน่นของกระดูกที่ลดลง (osteopenia) ผู้ป่วยเกิดกระดูกต้นขาหักจากการหมุนลำตัวขณะเท้าอยู่กับที่โดยไม่มีอาการปวดต้นขานำมาก่อน ผู้ป่วยทั้ง 2 รายได้รับการรักษาด้วยการยึดตรึงกระดูกตามความเหมาะสมต่อไป*

สรุป*: การศึกษานี้สรุปว่าการให้ยา alendronate และ risedronate ระยะยาวของผู้ป่วยแต่ละรายนั้นควรได้รับการพิจารณาอย่างละเอียดถี่ถ้วนและรอบคอบ อาการปวดต้นขานำมาก่อนนั้นเป็นอาการที่เตือนล่วงหน้าให้สงสัยถึงภาวะกระดูกต้นขาหักจากความบกพร่องภายในที่ผิดปกติจากการได้รับยาข้างต้นในระยะยาว ดังนั้นจึงจำเป็นที่จะต้องมีการศึกษาในแง่ของผลข้างเคียงที่มีต่อกระดูกจากยาตัวอื่นๆในกลุ่ม bisphosphonate รวมทั้งปัจจัยเสี่ยงและกลไกที่ชัดเจนของการเกิดผลข้างเคียงดังกล่าวจากยาทุกตัวในกลุ่มนี้ต่อไป*