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The cumulative effect of bisphosphonates and statins on stress fractures. Is it a failure of steroid biosynthesis?

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Abstract

Osteoporosis related fractures pose a significant economic and healthcare problem. There is a growing concern about increased numbers of stress or low energy fractures after bisphosphonates therapy. A 65-year-old woman is presented with a stress fracture of the left femur. From our point of view, this fracture was associated with a long-term statin and bisphosphonate therapy. We did not find a similar presentation in medical literature.

INTRODUCTION

Hypercholesterolemia and osteoporosis are highly prevalent conditions for aging patients. The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (or statins) are frequently used for the treatment of hypercholesterolemia. In recent years there has been high interest in the use of statins for osteoporosis due to the possible effect on bone tissue (Hatzigeorgiou & Jackson 2005).

Bisphosphonates are currently used for treatment of osteoporosis. Recent studies have shown an association between long-term use of these drugs and atraumatic or low-energy atypical femoral fractures (Kumar & Colin 2013; Balach *et al.* 2015). Stress fracture was originally described by Breithaupt in 1855. Damage to the bone occurs as the result of the imbalance between osteoblast and osteoclast activity (Astur *et al.* 2015). Bisphosphonates decrease bone resorption via inhibition of the farnesyl diphosphate synthase in mevalonic acid pathway. Statins affect the same pathway only at an earlier stage. Statins inhibit HMG-CoA reductase, preventing synthesis of mevalonate but also of isoprenoids, which affect osteoclast activity (Uzzan *et al.* 2007). Bisphosphonates have similar effect on osteoclasts. Statins and bisphosphonates have a major impact on cholesterol biosynthesis pathway (Figure 1).

In this article we present a case of low-energy (stress) left femoral shaft fracture which, from our point of view, was associated with a long-term statin and bisphosphonate therapy. Based on our review of literature to date there are no reports available on combined effect of statins and bisphosphonates on risk of stress fractures.

CASE REPORT

In September 2013 a 65-year-old Caucasian woman presented to the emergency room with pain in the left proximal to mid femur region. She was stepping out of her bathtub and heard a pop and felt sharp pain in her left thigh with a resultant deformity of the leg and inability to bear weight

CASE REPORT

on her left lower extremity due to pain. Patient did not sustain any other injuries. She had positive swelling in her left proximal third of her thigh with tenderness to palpation over the proximal femur. Her lower extremity was neurovascularly intact. She was initially placed in a traction splint.

Physical examination: Height 160 cm. Weight is 49 kg. Blood pressure 160/70 mmHg. BMI 19.2 kg/m^2. Medical history included history of breast cancer with bilateral mastectomy (November 2010), hysterectomy (2005), hypertension, hypercholesterolemia, gastroesophageal reflux disease (GERD), insomnia, bruisability, memory problem, and degenerative joint disease. Her breast cancer was ER positive, PR and HER-2 negative. She has a significant history for osteoporosis and had been on bisphosphonate therapy for about 5 years and was switched to denosumab (Prolia) over the last year. Patient sustained left nondisplaced ulnar fracture with minimal trauma in 2012. Her medications included Crestor, Letrozole, Celebrex, Prolia, aspirin, Omeprazole, Trazodone, Voltaren Gel, vitamin B complex, calcium and vitamin D, Centrum Silver. No significant abnormalities were noted on her preoperative lab work. X-rays of the chest, pelvis, and femur were performed. Radiographs of the femur revealed a horizontally oriented fracture through the proximal femoral diaphysis with approximately 2 cm of overlapping of the fracture fragments (Figure 2). After reviewing her medical history we suspected bisphosphonates, Prolia, and Crestor as a possible cause of atypical femur fracture due to negative cumulative effect on bone metabolism. The patient's case was discussed in detail with orthopaedic surgeon who evaluated the patient and performed operative repair of femur fracture with closed reduction and intramedullary nailing of the left femoral shaft. Postoperative femur radiographs showed a good alignment of the proximal femoral fracture fragments with an indwelling intramedullary rod (Figure 3). Prolia was stopped after surgery. We recommended avoiding bisphosphonates in the future. We suggested discussing Crestor discontinuation with primary care physician. The femoral fracture healed uneventfully after the surgery. Currently patient is asymptomatic with her left leg and ambulates without any restrictions. She has a full range of motion of the left hip and knee and full strength in the left lower extremity. There is no rotational deformity of the leg.

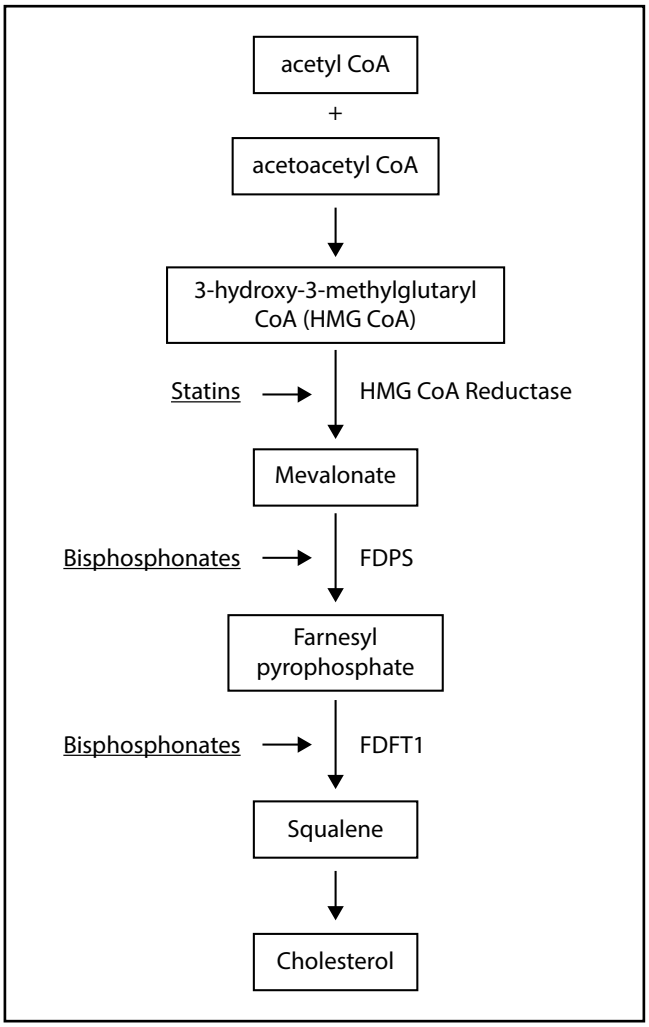

Fig. 1. Effect of statins and bisphosphonates on cholesterol biosynthesis.

DISCUSSION

Healthy bone physiology requires hormones, minerals, and vitamins which control balance between osteoblast and osteoclast activity. Hormones are most powerful agents which are responsible for the normal bones turnover. Certain hormones predominantly stimulate osteoblast activity (testosterone, progesterone, DHEA, growth hormone, thyroid hormone) and other hormones affect osteoclast activity (estrogens, calcitonin).

Several peptides such as calcitonin (Zaidi *et al.* 2002; Carter & Schipani 2006), parathyroid hormone (Carter & Schipani 2006; Hirai *et al.* 2011), calcitonin gene related peptide (CGRP) (Liang *et al.* 2015), and growth hormone (Kaufmann *et al.* 1992; De Boer *et al.* 1994; Holmes *et al.* 1994) play a significant role in bone resorption and formation.

Thyroid hormones stimulate osteoblast activity both directly and indirectly via numerous growth factors and cytokines (Rizzoli *et al.* 1986; Bassett & Williams 2003).

DHEAS levels decrease with age and have a positive association with IGF-I levels and a negative association with IL-6 levels. DHEA deficiency may contribute to age-related bone loss through anabolic (IGF-I) and anti-osteolytic (IL-6) mechanisms. High serum DHEAS is associated with less bone loss at both femoral neck and lumbar spine (Haden *et al.* 2000; Ghebre *et al.* 2011).

Estrogens maintain bone mass by restoring the balance between osteoblastic bone formation and osteoclastic bone resorption (Turner *et al.* 1994). Also, estrogens promote osteogenesis in addition to its inhib-

itory effect on the development of osteoclasts (Matsumoto *et al.* 2010). Long-term replacement therapy with estrogen considerably reduces the risk of hip fractures and vertebral deformations (Notelovitz 1997).

Progesterone increases osteoblast numbers (Prior 1990; Scheven *et al.* 1992; Tremollieres *et al.* 1992) as well as promotes osteoblast maturation and differentiation (Scheven *et al.* 1992). Progesterone appears to play a differing but also physiological role in partnership with estrogens in achieving optimal peak bone mass.

Testosterone level decreases during aging. Testosterone replacement therapy has been shown to increase bone mineral density in many clinical trials (Anderson *et al.* 1996; Katznelson *et al.* 1996; Anderson *et al.* 1997; Kenny *et al.* 2000; Snyder *et al.* 2000; Snyder 2001; Wang *et al.* 2001).

Cortisol negatively affects bone density by altering bone turnover, impairing intestinal absorption and renal reabsorption of calcium. Inverse association between cortisol and bone density (Dennison *et al.* 1999; Raff *et al.* 1999; Cetin *et al.* 2001; Reynolds *et al.* 2005) and a positive association between cortisol and fracture risk (Greendale *et al.* 1999) were shown in several studies.

Vitamin D-3 downregulates collagen gene in osteoblasts (Harrison *et al.* 1989) and activates genes for osteocalcin and osteopontin (Noda *et al.* 1990).

From our point of view this patient had multiple physiologic disturbances. Aging per se is a cause for decline in hormonal production, a low level of bone mineral content, and imbalanced osteoblast/osteoclast activity. Prescription medications such as bisphosphonates and statins may potentially contribute to the disruption of the balance between osteoblasts and osteoclasts via inhibition of the major hormonal pathways and cause low mineral content within the bone.

Our body uses over sixty steroids derived from cholesterol. Several publications show that statins are associated with hormonal perturbations (Ormiston *et al.* 2004; de Keyser *et al.* 2015) and can decrease production of steroid hormones such as androstenediol, total testosterone (–23%, $p<0.001$), free testosterone (–32%, $p<0.001$), androstendione (–20%, $p<0.01$), and dehydroepiandrosterone sulfate (–17%, $p<0.05$) (Smals *et al.* 1991; Azzarito *et al.* 1996; Rabijewski *et al.* 2005; Krysiak *et al.* 2014; Mędraś *et al.* 2014). It was shown that statins induced a profound concentration-dependent inhibition of DNA synthesis, decreased production of progesterone (by up to 49%), and testosterone (by up to 52%) (Izquierdo *et al.* 2004).

As we showed previously estrogens, progesterone, testosterone, cortisol, DHEA, and vitamin D-3 have a significant effect on osteoclast and osteoblast activity. Disruption of homeostasis during aging can be a start-

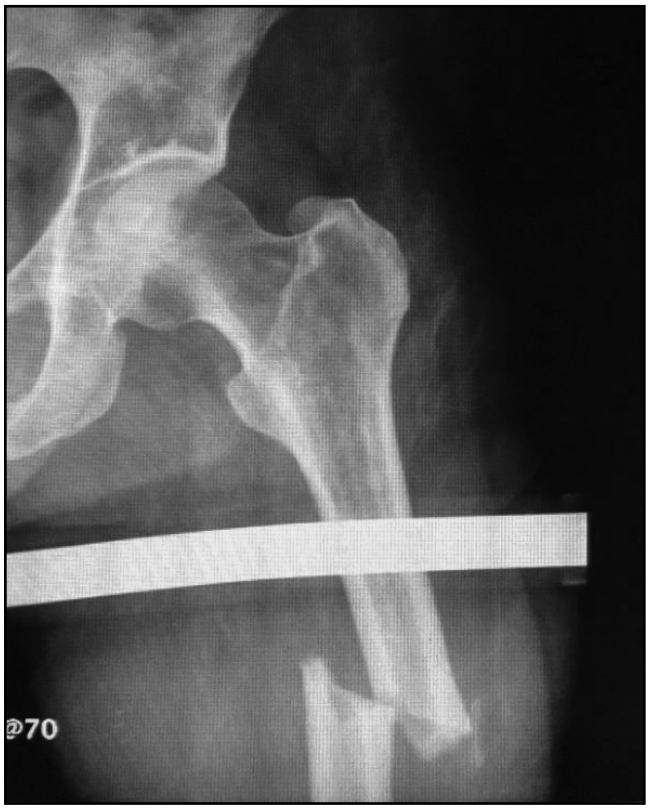

Fig. 2. Radiograph of left femur showed a horizontally oriented fracture through the proximal femoral diaphysis with approximately 2 cm of overlapping of the fracture fragments.

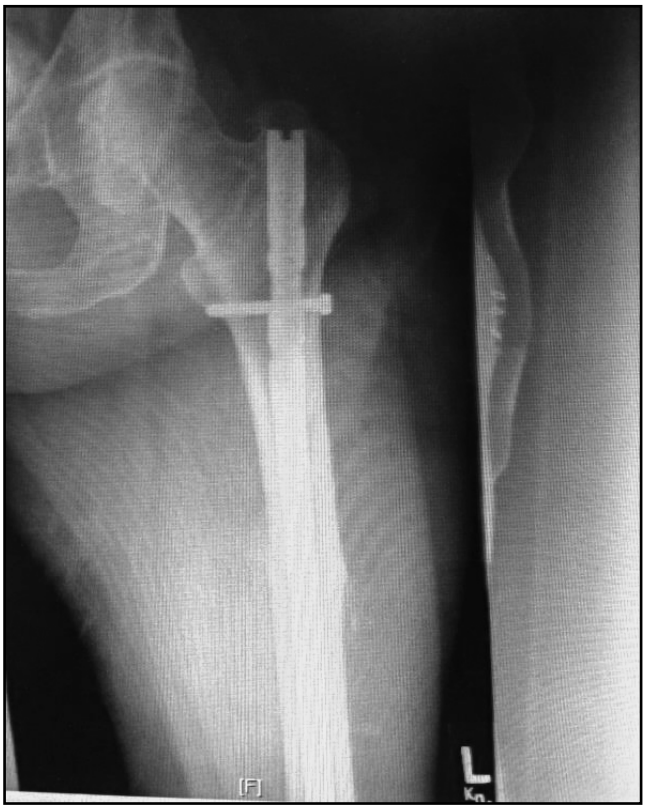

Fig. 3. Postoperative left femur radiograph showed a good alignment of the proximal femoral fracture fragments with an indwelling intramedullary rod.

ing point for osteoporosis which can lead to an increase in frequency of fractures in aging population.

Unfortunately, there is no information available on effect of bisphosphonates on steroidogenesis. It is possible that bisphosphonates have similar effect on steroidal hormone production as statins since they both affect cholesterol biosynthesis pathways. There is very limited information on the effect of bisphosphonates on lipid metabolism (Kondo & Mizuno 2014; Gonnelli *et al.* 2014). In one animal study it was shown that diphosphonate reduced plasma cholesterol in different animals from16 to 33% (Jackson *et al.* 2000).

We speculate that in this case there is a cumulative negative effect of statins and bisphosphonates on steroidogenesis resulting in a stress fracture.

CONCLUSION

We believe that the concurrent use of statins and bisphosphonates should be carefully studied because of a possible negative cumulative effect of these drugs on cholesterol biosynthesis, steroidogenesis, and bone homeostasis, which could lead to an increased risk of low-energy (stress) fractures. Unfortunately, current very limited evidence is not conclusive and further research is necessary.

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