

# Depot medroxyprogesterone acetate (DMPA)-associated early-onset osteoporotic fracture

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## Summary

Depot medroxyprogesterone acetate (DMPA) is a highly effective injectable contraceptive, but is associated with reduced bone mineral density (BMD) and increased fracture risk in some studies because it inhibits the hypothalamic–pituitary–ovarian axis. Herein, we present the diagnostic challenging case of a premenopausal woman with an unusual hip fracture and prolonged use of intramuscular DMPA injection. Whole-exome sequencing revealed a rare heterozygous variant of the *ALPL* gene, which could cause adult-onset hypophosphatasia (HPP). However, it was classified as a variant of unknown significance. Our case highlights the fracture risk from long-term use of DMPA, which is widely used as progestogen-only contraceptive method in low- and middle-income countries. Clinicians should inform women on the potential adverse effect of prolonged use of DMPA for contraception on bone health and advise them to adopt healthy lifestyle habits, with adequate calcium and vitamin D intake.

## Learning points

- Evidence shows that intramuscular depot medroxyprogesterone acetate (DMPA) negatively affects BMD by inhibiting the hypothalamic–pituitary–ovarian axis.
- However, the risk of bone fragility fracture from DMPA remains uncertain because of paucity of data on fracture incidence.
- Herein, we present a case of a premenopausal woman with an unusual hip fracture and a history of prolonged use of intramuscular DMPA contraception.
- Our case also highlights that the patient's clinical presentation is essential for interpreting genetic sequencing results.

Keywords: bone; osteoporosis; DMPA; puberty; calcium; vitamin D

## Background

Depot medroxyprogesterone acetate (DMPA) is a progesterone-only contraceptive that is administered by 3-month interval intramuscular injection. Its use has been associated with slower accrual of bone mineral density

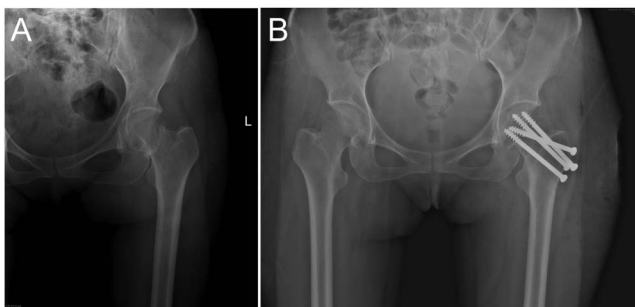
(BMD) and increased fracture risk in some studies from its effects in suppressing the hypothalamic–pituitary–ovarian axis (1). However, DMPA is a highly effective and a cheap method of contraception. Moreover, previous evidence

suggests that recovery of BMD occurs after discontinuation of DMPA (2). Therefore, DMPA has been endorsed as a long-term contraceptive method and routine DXA for BMD monitoring is not recommended (3, 4). Herein, we present a diagnostically challenging case of a premenopausal woman with an unusual hip fracture and prolonged use of DMPA for 7 years for contraception.

## Case presentation

A previously healthy 37-year-old Thai woman was diagnosed with osteoporosis (a BMD Z-score of  $-2.6$  at femoral neck) after having developed a proximal left femur fracture 6 months earlier. She came to see us for further treatments of early-onset osteoporosis. The proximal left femur fracture was associated with a slip and fall (minor trauma) when leisurely sitting at home. She had multiple cannulated screws for proximal left femur fracture from another hospital (done 48 h after the accident), as shown in Fig. 1. A dual-energy X-ray absorptiometry (DEXA) scan revealed T-score  $-2.7$  and Z-score  $-2.6$  consistent with osteoporosis at right neck of femur. No BMD at the spine was done at that time. Work-up at that time was notable for vitamin D insufficiency (17 ng/mL; normal  $\geq 30$  ng/mL) and slightly elevated plasma intact parathyroid hormone (iPTH) level (70.5 pg/mL; normal 15–65 pg/mL).

She had no prior fracture or family history of osteoporosis or fractures. Her birth and childhood history were unremarkable. The patient denied teeth problems, eating disorders or psychiatric conditions. She had no history of smoking and was not on any medications such as steroids. A 3-month intramuscular DMPA injection was continuously used for more than 7 years as a hormonal contraceptive. Her menarche was at the age of 13 years and menstruation ceased since DMPA administration. She had never been pregnant and had no underlying disease. She eats a variety of foods but having a sedentary lifestyle.



**Figure 1**

(A) Pre-operative X-ray image of left femoral neck fracture (B) multiple cannulated screw fixation of left femoral neck fracture was done 48 h after the accident.

She also reported not taking concomitant medications known to affect bone health. Post-operation, she was treated with oral vitamin D2 60,000 units per week for 6 months.

Upon presentation to our hospital, which is a specialty hospital for endocrine disorders in Bangkok (6 months after fracture), the patient's height was 168 cm and weight was 44.1 kg, and a BMI of 16.8 kg/m<sup>2</sup>. There was no clinical evidence of craniofacial abnormality and no thyroid abnormalities.

## Investigation

Initial work-up for secondary osteoporosis at our hospital showed normal vitamin D level, normal plasma iPTH level, normal levels of plasma alkaline phosphatase (ALP) and normal other hormones-related secondary osteoporosis, as shown in Table 1. A skeletal survey revealed no metabolic bone disease findings and no vertebral fracture was found. An HIV test showed negative result. Repeated DEXA done at our hospital (6 months after hip fracture) showed significant osteopenia, with a T-score of  $-2.2$  at the lumbosacral (LS) spine and  $-2.5$  at the right femoral neck and a

**Table 1** Laboratory investigations in this patient at the time of initial presentation at our hospital (6 months after fracture).

Laboratory data	Normal values	At initial presentation
Serum glucose		
mmol/L	<5.6	4.8
mg/dL	<100	86
Serum creatinine		
μmol/mL	35.4–88.4	53.1
mg/dL	0.4–1.0	0.6
Serum ALP (U/L)	35–104	76
Serum calcium		
mmol/L	2.2–2.5	2.4
mg/dL	8.6–10.0	9.4
Serum phosphate		
mmol/L	0.8–1.5	1.4
mg/dL	2.5–4.5	4.3
Serum intact PTH		
pmol/L	1.6–6.9	2.3
pg/mL	15–65	22
Serum 25-OH vitamin D		
nmol/L	>75	118
ng/mL	>30	47
Serum TSH (μIU/mL)	0.27–4.30	2.01
Serum prolactin		
μg/L	5–23	11
ng/mL	5–23	11
Serum LH (mIU/mL)	1.7–8.6	3.6
Serum FSH (mIU/mL)	3.5–12.5	8.1
Serum estradiol		
pmol/L	45.5–855.4	55.1
pg/mL	12.4–233.0	15.0

ALP, alkaline phosphatase.

Z-score of  $-1.6$  at the LS spine and  $-2.1$  at the right femoral neck.

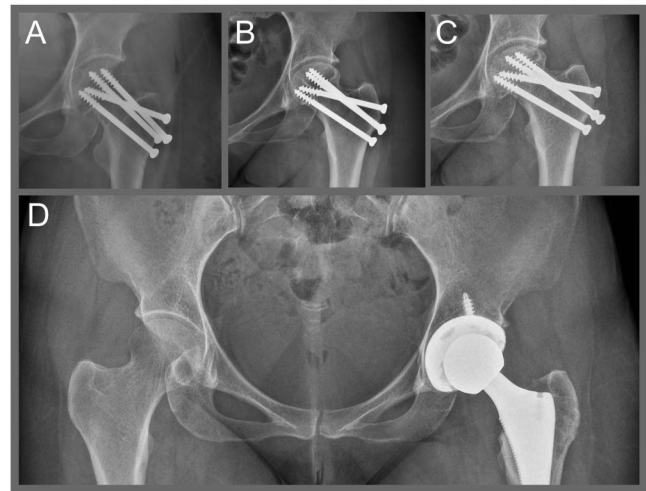
Whole-exome sequencing to investigate monogenic bone disorders was done and the patient was started on a weekly oral alendronate 70 mg per day with oral calcium and vitamin D2 supplement. She was advised to stop intramuscular DMPA injection and switched to other contraceptive methods. Whole-exome sequencing revealed a rare heterozygous variant c.1069C>T (p.Arg357Trp) of the *ALPL* gene, which could cause adult-onset hypophosphatasia (HPP), but it was classified as a variant of uncertain significance (VUS) by the American College of Medical Genetics and Genomics (ACMG) guidelines (5). However, based on the very low allele frequency (0.000097) from gnomAD, the possibility of pathogenicity of this variant could not be excluded. However, additional testing revealed normal plasma pyridoxal 5'-phosphate (an ALP substrate), and her history of prolonged use of DMPA did not support the diagnosis of HPP. Repeat laboratory (1 year after the fracture) results indicated a normal ALP level of 51 U/L (normal 35–104 U/L). Extended family members were tested to determine whether the variant was shared by other unaffected individuals. It was thereby found that the patient had inherited this variant from her mother and her brother also carries this variant without a history of fracture. As a result, the possibility of HPP was disregarded.

## Treatment

Oral alendronate, but not oral calcium and vitamin D2 supplement, was discontinued by the patient after 1 year because of being lost to follow-up. Intramuscular DMPA injection was stopped permanently, and her menstruation came back 9 months thereafter.

## Outcome and follow-up

The patient was lost to follow-up after 12 months but presented at the hospital again 18 months after the hip fracture incident due to pain at the surgical site. Serial X-ray of the left hip revealed avascular necrosis (AVN) of previous screw fixation at the left femoral head, as shown in Fig. 2A, B, C. Total left hip arthroplasty was performed uneventfully, as shown in Fig. 2D. After the operation, she was able to go back to work. Repeated DEXA at the last follow-up (24 months after stopping DMPA) showed improvement of osteoporosis, as revealed in Fig. 3. Over a 30-month period, a BMD percentage change at the right femoral neck increased to 26.7% when compared with the initial BMD at the time of fracture. Currently, the patient is only taking oral calcium and vitamin D2 supplement and is advised to maintain healthy lifestyle with fall prevention.

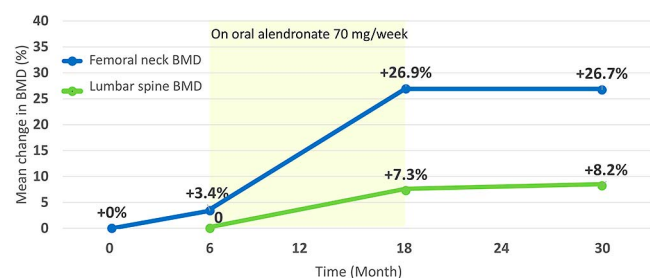


**Figure 2**

Serial X-ray of left hip revealed flattening of the outer portion of the left femoral head from avascular necrosis (A) at the time of immediate post-operation, (B) at 12 months later, (C) at 18 months later and (D) total left hip arthroplasty was performed to treat avascular necrosis.

## Discussion

Intramuscular DMPA injection inhibits endogenous estrogen production, resulting in hypoestrogenism and bone loss. Even though a decline in BMD has been shown to be completely reversible once DMPA is discontinued in a previous study (2), the skeletal effects of DMPA might vary depending on the peak bone mass and lifestyle habits of each individual patient. Estrogens play an important role in bone health through actions on osteoblasts, osteoclasts and osteocytes via the estrogen receptor (6). The pathophysiology of DMPA-induced bone loss is complex, and several mechanisms contribute to its development and progression (7). Previous reports showed that the risk of clinical bone fragility resulting from hormonal contraceptives use remains uncertain due to insufficient data on fracture incidence (4). Most studies have relied on BMD as a surrogate marker. However, there is no established 'fracture threshold'



**Figure 3**

Mean percentage changes in BMD after stopping DMPA.

based on BMD among pre-menopausal patients. As a result, several organizations still recommend DMPA as an excellent and low-cost method of contraception for patients who desire a long-term, reversible contraceptive method. Our case challenged this notion and the bone effects of DMPA must be discussed with patients who would continue a long-term use of DMPA. Moreover, hormonal contraceptives are increasingly used for indications other than contraception, such as acne, hirsutism and dysmenorrhea. Careful consideration by weighing the risks and benefits for progestin-only contraceptive should be made, especially in younger women who plan to receive the treatment for more than 2 years.

Estrogen acts differently at trabecular and cortical sites, and data showed that trabecular bone may be more susceptible to hypoestrogenism (6). Among women using DMP, the greatest bone loss occurs in the first few years of use and is dose-related. Bone loss has been observed in females of all ages using the standard dose of DMPA (150 mg intramuscularly every 12 weeks) and a greater decline in BMD was found in the femoral neck than spine BMD over a 3-year period (−4.2% versus −6.0%) (2). In a population-based, case–control study of adult women from the United Kingdom, an increase in adjusted odds ratio for incident fractures was highest (more than 3 times) among women under age 30 with longer DMPA exposure when compared with control cases (8). Therefore, use of DMPA for more than 2 years should be cautioned, especially in younger women, from its negative effect on bone health. Given the mechanism of action of BMD loss following use of DMPA, it is most likely that the discontinuation of DMPA rather than vitamin D supplementation in this patient that led to the observed partial recovery in BMD. Health promotions including smoking cessation, increased physical activity and adequate calcium and vitamin D intake should be actively counseled among adolescents and younger women considering initiating DMPA.

Our present case also highlights that the patient's clinical presentation is important for interpreting genetic sequencing results. The pathogenicity of VUS could not be done through a functional analysis of the detected variants in resource-limited settings. Therefore, detailed family studies, clinical data and careful follow-up are needed to clarify the role of this variant. HPP is a multi-systemic disease caused by loss-of-function sequence variation in *ALPL*, which leads to deficient tissue-nonspecific alkaline phosphatase (ALP) that is essential for bone mineralization. It can appear at different ages. In adults, the symptoms of HPP are often misdiagnosed as osteoporosis and inappropriate treatments with bisphosphonates or denosumab could lead to atypical fracture (9). Identification of rare *ALPL* VUS challenges in deciphering the clinical relevance whether this patient has HPP and bisphosphonate should be discontinued. The underrepresentation of non-European ancestry groups

in current genomic databases complicates the interpretation of their genetic test results. Fortunately, the possibility of HPP in this patient had been disregarded from repeated normal ALP level and extended family members testing. Recent advances in next-generation sequencing technology have greatly increased the number of VUS encountered in clinical practice and clinicians should be knowledgeable to manage with this problem.

In summary, we present a diagnostic challenge in a premenopausal woman with an unusual fracture history and osteoporosis. The fracture risk from long-term use of DMPA, which is widely used as progestogen-only contraceptive method in low and middle-income countries, should be carefully considered. Women who choose to use a long-term DMPA should be counseled on healthy lifestyle habits and consider BMD monitoring to detect early-onset osteoporosis.

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#### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the work reported.

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#### Patient consent

Written informed consent was obtained from the patient for publication of the submitted article.

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#### Author contribution statement

Y T wrote the initial draft of the article. Y T, V V, S N, T H contributed to the editing process. Y T was involved in the direct care of the patient, investigation and follow-up of patient.

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