

# Depot Medroxyprogesterone Acetate and Bone Mineral Density

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## Abstract

**Background:** Previous studies have suggested that depot medroxyprogesterone acetate (DMPA) may result in a reduction in bone mineral density (BMD). This study further explores this relationship. This study was undertaken to assess the association between long-term DMPA use and areal BMD (aBMD) in a uniform manner in a single private specialist practice over two decades.

**Methods:** Of 1,046 consecutive patients using DMPA in a single Melbourne specialist's practice between 1981 and 2013, from 1992 102 were referred for dual-energy X-ray absorptiometry (DXA) scans. Each was matched for age and body mass index with two participants from a reference group of 1,416 healthy female volunteers who underwent DXA scans at the Royal Melbourne Hospital.

**Results:** A total of 306 participants were included in this study, 102 cases and 204 referents. DMPA users had lower aBMD at first testing (median duration of DMPA use 4.3 years (IQR 2.6 - 6.7 years) compared with the reference group, and lower aBMD persisted in users 2 - 5 years post cessation of DMPA. These differences from the reference group were statistically and potentially clinically significant. There

was no evidence of accelerated bone loss at any site in the DMPA users during longitudinal observations on treatment, but the study had limited power to detect such an effect.

**Conclusions:** DMPA use was associated with aBMD deficits during and after treatment. The findings demonstrate that long-term, controlled, prospective studies with adequate sample size are required to evaluate the potential clinical impact of DMPA use on bone health outcomes.

**Keywords:** Depot medroxyprogesterone acetate; DMPA; Bone mineral density; BMD; Depo-Provera

## Introduction

DMPA became available in Australia in 1972 for the treatment of habitual abortion and premature labor, and a number of Australian doctors also started using it "off label" as a contraceptive in 1972. During this time, an expanding range of non-contraceptive benefits of DMPA became apparent. Due to the direct action of continuous progestogen exposure, as well as by suppressing ovarian estradiol secretion and the consequent lowering of circulating estradiol concentrations, it has proven particularly useful in the treatment of estrogen-dependent disorders such as endometriosis, recurrent candidiasis [1, 2, 3] and even endometrial hyperplasia and low-grade endometrial adenocarcinoma [4].

Concern was expressed regarding the potential effects of this suppressed circulating estrogen concentration on bone mineral density (BMD), and initial evidence of a potential, significant BMD effect was first reported by Cundy et al in 1991 [5] and Wark et al [6]. Cundy's study compared the BMD of 30 women who were using DMPA for a median of 10 years with 30 premenopausal and 30 postmenopausal controls. They found a reduction in bone density of 6.6-7.5% in DMPA users when compared with premenopausal controls [5]. This encouraged many others to investigate this relationship [7]. More recently, there has been a shift towards investigating the effects of DMPA on BMD in adolescents and young women. An observational prospective cohort study of 433 girls (including 58 on DMPA) showed that, while there did appear to be a decline in the first year of DMPA use, this did not reach the level of osteopenia and furthermore, appeared to stabilise at a normal

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(although lower) bone density, raising the need to consider issues of short and long-term clinical significance [8]. Despite these findings, several studies have also shown that there is significant bone gain following cessation of therapy, with the decline in BMD being reversed after discontinuation [9, 10, 11]. However, complete reversal did not always appear to occur in all subjects.

A number of authors have addressed potential safety issues and side-effects beyond BMD [12]. The most thoroughly investigated side-effect is the invariable change in the menstrual cycle, with 50 to 70% of women achieving amenorrhoea by 1 year of treatment. This is nowadays regarded as a bonus by most women. A substantial proportion of women will go through an initial phase of erratic spotting or light bleeding (30 to 60%), but this usually reduces greatly with each passing month. Very few women experience any heavy vaginal bleeding during treatment.

There have been inconsistent data regarding the effect of DMPA use on weight gain [12]. Other "side-effects" are rarely troublesome, and it has been proposed that the clinical benefits in prevention and treatment of dysmenorrhoea, endometriosis, endometrial hyperplasia and recurrent candidiasis could be greatly increased if DMPA was used more frequently for contraception [2, 3, 12].

The aim of this study was to explore changes in areal bone mineral density (aBMD) in long-term users of DMPA, managed in a uniform manner in a single private specialist practice. Since 1992, many of these DMPA users have had one or more BMD measurements (mostly in a single bone densitometry unit), and careful prospective records have been maintained on dates of BMD scans, DMPA injections and regular body weight measurements. Clinical outcomes were also recorded. The background of DMPA use in this private practice has been described in detail previously [1].

## Materials and Methods

Ethical approval for this study was provided by the Monash Health Human Research Ethics Committee (HREC Ref: 10316B) and cases gave consent for BMD studies and inclusion in medical research. The reference group all had volunteered and provided written informed consent to participate in observational studies of determinants of bone health conducted at the Royal Melbourne Hospital (RMH) Melbourne Health HREC Ref: 2003.0249, 2004.022 and 2004.021.

### Patient selection

This is a retrospective cohort study of consecutive patients presenting between 1981 and 2013 in a metropolitan solo private gynecology practice. During this time period, female patients received DMPA in the form of Depo-Provera® (Pfizer® Australia, West Ryde, NSW, Australia) for the treatment of a range of conditions including endometriosis, recurrent vaginal candidiasis, menstrual disorders, and for contraception. Initially, DMPA was obtained from the Upjohn Company, the original

manufacturers. From 1992 a subset of DMPA users was referred for dual-energy X-ray absorptiometry (DXA) scans on the request of their specialist and included in this study. These patients were referred for DXA if they had been on DMPA and there was an indication that they would continue long-term treatment with it. During the study period, all patients received 150 mg DMPA at 12 weekly intervals, for varying lengths of time. Some patients also received estrogen therapy in the early stages of the study for the initial control of breakthrough bleeding. No patients were menopausal at the time of commencement of DMPA treatment. Body weight was regularly recorded. Where body mass index (BMI) and smoking status were not specifically recorded, patients were directly contacted to confirm details of these factors.

### Reference group selection

For comparison of BMD changes, each DMPA patient was matched for age and BMI to two healthy research participants not using DMPA (reference group). The reference group was sourced from various bone health studies conducted at RMH between 1990 and 2012.

### Bone density measurements

Areal BMD was measured at the lumbar spine, total hip and femoral neck. All bone measurements for the reference group were obtained in a consistent manner in the Bone Densitometry Unit, Royal Melbourne Hospital. The majority of scans for DMPA users were performed using Hologic DXA scanners at RMH (n = 89) while a small number of scans were performed elsewhere using Lunar (Lunar Corp., Madison, WI, USA, (n = 11)) and Norland (Norland Corp., White Plains, NY, USA, (n = 2)) instruments. All Hologic scanners had been formally cross-calibrated according to manufacturer's specification. Results from Lunar and Norland instruments were standardised using an adjustment calculation from previously established cross-calibration equations, to provide internationally-accepted and standardised BMD scores [13-16].

### Statistical analysis

All data were analysed using Stata 12 (StataCorp, College Station, TX, USA). All continuous variables were tested for normality using the Shapiro-Wilk test prior to data analysis. Baseline differences between DMPA users and non-users were assessed using either a two-sample *t*-test or Wilcoxon rank-sum test for continuous data and Chi-squared test for categorical data.

Changes in aBMD measurements between baseline and follow-up points were calculated as the difference between corresponding measures, that is, each aBMD measurement (g/cm<sup>2</sup>) at follow-up minus the corresponding aBMD measurement at baseline. Regression analysis was used to assess the relationship between aBMD and duration of DMPA usage (or

**Table 1.** The Characteristics for the Study Cohort at the Time of Their First DXA

	DMPA users (n = 102)	Reference group (n = 204)	P
Mean age (SD)	37.6 (8)	38.1 (8.2)	0.623
Mean BMI (SD)	26.7 (6.0)	26.3 (5.4)	0.591
Smoking status (n (%))			< 0.001
Current/ex-smoker	23 (22.5)	67 (32.8)	
Never smoked	54 (52.9)	135 (66.2)	
Unknown	25(24.5)	2 (1.0)	
Median months of DMPA use before first DXA (IQR)	52 (31 - 80)	N/A	
First DXA scan results			
Total hip			
Areal BMD (g/cm <sup>2</sup> )	0.925 ± 0.177	0.996 ± 0.146	< 0.001
Neck of femur			
Areal BMD (g/cm <sup>2</sup> )	0.806 ± 0.151	0.877 ± 0.117	< 0.001
Lumbar spine			
Areal BMD (g/cm <sup>2</sup> )	1.014 ± 0.132	1.101 ± 0.153	< 0.001

DXA: dual-energy X-ray absorptiometry; DMPA: depot medroxyprogesterone acetate; BMI: body mass index (kg/m<sup>2</sup>); BMD: bone mineral density.

duration of follow-up for the reference group). Multivariate regression analysis was undertaken to determine whether the use of DMPA predicted the aBMD change while adjusting for other potential confounders such as age, BMI, smoking and estrogen use.

The relationships between the change in aBMD measurements and duration of DMPA use and its dosage were also assessed using multivariate regression analysis.  $P < 0.05$  was considered to be statistically significant for all tests. The final analysis included in the paper was based on annualised rate of change.

## Results

Since 1992, 102 patients underwent single or repeat studies of BMD. All of these patients had at least one densitometry measurement performed during the course of, or immediately following the cessation of DMPA. Data regarding baseline characteristics, dates and numbers of DMPA doses received, and bone densitometry results were retrieved from paper and electronic records (Table 1). In total, 306 participants were included in this study, 102 cases (82 with DXA scans performed during DMPA treatment, but not necessarily at DMPA commencement and 20 with DXA scans performed only after cessation of treatment) and 204 referents matched in a 1:2 ratio by age and BMI. The cohorts were of similar age at the time of their first scan; however, a higher proportion of the reference group appeared to be current smokers (Table 1).

The mean (SD) age of DMPA users at treatment initiation was  $37.6 \pm 8.0$  years with a median length of time of DMPA use of 4.3 years (IQR 2.6 - 6.7 years) at the time of the first DXA. The median (IQR) time of DMPA from first DXA to last DXA while taking DMPA was 3.5 (2 - 6.5) years. The median (IQR) time between first and last DXA after DMPA cessation

was 4.1 (2.3 - 5.2) years ( $n = 13$ ). The aim of Table 2 is to show the impact of DMPA on bone measures, which were calculated as change per year of follow-up.

Of the 102 cases, 29 (28.4%) used micronized estradiol-17 beta 2 mg daily at some stage during the treatment. Twenty-two used it to control breakthrough bleeding; usually estradiol 2 mg daily for less than 4 months and seven used it as a treatment for low BMD. The latter seven patients used estradiol for a median of 10 months (IQR 5 - 22, range 2 - 92 months). There was no correlation between total duration of previous estradiol use and the aBMD measured at the first DXA scan in DMPA users (data not shown). DMPA users had lower aBMD measurements at their first DXA compared with the reference group at all sites (Table 1). The differences were 0.071, 0.071, and 0.087 g/cm<sup>2</sup> for the total hip, femoral neck and lumbar spine respectively.

Throughout the clinical study period, patients had a variable number of bone densitometry measurements performed at different time intervals. Therefore, the measurements of aBMD change were adjusted for differences in time between measurements. Bone densitometry was performed during DMPA treatment in 82 patients (of whom 51-61% had one scan only and 31 had two or more scans) and, after DMPA cessation, in 42 DMPA users (of whom 29-69% had one scan only after DMPA cessation and 13 had two or more scans).

The results of crude and adjusted regression analysis indicate that prolonged use of DMPA resulted in BMD loss only at the lumbar spine (4.9% in the unadjusted analysis,  $P < 0.05$ ) (Table 2). It is important to note that DMPA users and non-users showed a similar overall rate of reduction in aBMD measures over time at the hip sites, while the DMPA group was using this agent. In unadjusted data, the rate of loss at the lumbar spine was marginally greater in the reference group than in DMPA users (Table 2). However, this difference became non-significant after adjustment for age, smoking and BMI (Table

**Table 2.** Crude and Adjusted Annualised BMD Changes (During DMPA Use for Cases) Intended to Show the Impact of DMPA on Bone Measures as Change per Year of Follow-Up (Only Those With at Least Two Visits Included)

	Crude		Adjusted <sup>‡</sup>			
	DMPA users <sup>†</sup> (n = 31)	Reference group (n = 62)	P	DMPA users <sup>†</sup> (n = 26)*	Reference group (n = 57)	P
Median (IQR) change in aBMD (g/cm <sup>2</sup> ) per year of follow-up						
Total hip	0 (-0.006 to 0.006)	-0.0016 (-0.0065 to 0.005)	0.504	0.001 (-0.001 to 0.003)	0.0005 (-0.004 to 0.003)	0.698
Femoral neck	-0.0024 (-0.0118 to 0.0012)	-0.0063 (-0.0109 to 0.0015)	0.718	-0.003 (-0.004 to 0.003)	-0.0043 (-0.006 to -0.002)	0.016
Lumbar spine	-0.0545 (-0.0848 to -0.0267)	-0.0809 (-0.1073 to -0.0427)	0.014	-0.083 (-0.087 to -0.080)	-0.0825 (-0.874 to -0.0790)	0.150
Median (IQR) percent change in BMD (g/cm <sup>2</sup> ) per year of follow-up (%)						
Total hip	0 (-0.6 to 0.6)	-0.2 (-0.7 to 0.5)	0.580	0.1 (-0.4 to 0.4)	0.2 (-0.04 to 0.4)	0.445
Femoral neck	-0.3 (-1.5 to 0.1)	-0.8 (-0.1 to 0.2)	0.651	-0.4 (-0.5 to -0.3)	-0.5 (-0.7 to -0.2)	0.445
Lumbar spine	-4.9 (-9.0 to -2.6)	-7.0 (-11.3 to -4.4)	0.045	-7.7 (-8.0 to -7.0)	-7.7 (-8.0 to -7.3)	0.781

Twenty patients had a DXA scan only post treatment cessation. <sup>†</sup>Adjusted for age, smoking status and BMI. DXA: dual-energy X-ray absorptiometry; DMPA: depot medroxyprogesterone acetate; BMD: bone mineral density. \*Five participants had missing data related to their smoking status and therefore they were not included in the adjusted analysis.

2).

Table 3 summarises the aBMD differences compared with controls in the 42 DMPA users who had at least one post-DMPA follow-up aBMD measurement.

### Discussion

The long-term use of hormones in gynecology frequently provokes controversy and difficulties with research. The long-term use of DMPA is no exception and this study over 21 years in one practice is intended to provide clinical perspective. This study reports the results of a unique dataset of BMD measurements taken from women using DMPA over varying lengths of time for a variety of indications, including the treatment of endometriosis and recurrent candidiasis as well as contraception, by the same gynecologist in a standardised manner between 1992 and 2013. It has demonstrated a statistically significant deficit in BMD in DMPA users. The clinical significance of this finding remains uncertain. However, this finding supports the cautious use of DMPA in women at risk for osteoporosis, the advisability of performing a baseline BMD in those likely to use it long term, and the need to balance these risks against those of alternative treatment, such as surgery for endometriosis.

Many publications have demonstrated small declines in various BMD measurements in women beginning use of DMPA for the first time [17], with potential detrimental effects on adolescent bone mass accrual only occurring when DMPA was used for greater than 12 months [18]. However, other studies have not been able to confirm this [19], with systematic review showing that after cessation of DMPA, BMD returns to normal as early as 24 weeks after cessation [20].

BMD is subject to influences from a number of physiological, pathological and lifestyle phenomena and hormonal therapy with agents such as DMPA, which is only one of these influences. This point is illustrated in a study by Lanza and associates [21], in which an increase in fracture risk was identified in DMPA users. However, this risk was present before commencement of DMPA, and did not increase further over the course of DMPA treatment, suggesting that this increased fracture risk could not be attributed to DMPA use. Meier et al [22] demonstrated a “slightly increased risk of fractures” in their long-term DMPA users not related to age. It is worth noting that any effect that DMPA might have on BMD appears to be comparable in magnitude to that experienced during lactation, which is considered a normal physiological variation [23].

There are a number of drawbacks, including the lack of baseline BMDs, of such a community study to demonstrate small adverse influences of DMPA usage on BMD. The study is relatively small and is therefore not designed to demonstrate small effects and only 31 women had two or more scans on DMPA and 13 had two or more scans post-DMPA.

A recent cross-sectional study which compared bone density in women using DMPA with those using a copper intrauterine device found a significantly increased rate of osteoporosis in DMPA users [24]. Furthermore, systematic review has found that DMPA use is associated with a reduction in BMD

**Table 3.** Difference in BMD Measures Between Cases and Control at Last DXA for the Reference Group and Last DXA Scan Post DMPA Cessation for Cases

	Crude			Adjusted†		
	DMPA users (n = 42)	Reference group (n = 204)	P	Cases (n = 42)	Reference group (n = 202)	P
Hip	0.858 (0.804 - 0.992)	0.993 (0.935 - 1.073)	< 0.001	0.959 (0.930 - 1.014)	0.973 (0.952 - 1.010)	0.089
Femoral neck	0.74 (0.676 - 0.803)	0.862 (0.787 - 0.944)	< 0.001	0.830 (0.792 - 0.886)	0.858 (0.828 - 0.903)	0.007
Spine	0.972 (0.894 - 1.053)	1.084 (1.001 - 1.186)	< 0.001	1.059 (1.041 - 1.083)	1.075 (1.059 - 1.101)	0.002

The median (IQR) between first and last DXA after DMPA cessation was 4.1 (2.3 - 5.2) years (n = 13). †Adjusted for age, smoking status and BMI. DXA: dual-energy X-ray absorptiometry; DMPA: depot medroxyprogesterone acetate; BMD: bone mineral density.

which may be prevented or ameliorated by estrogen supplementation [7]. However, studies could not be combined in meta-analysis because of excessive heterogeneity. The authors concluded that the effect on fracture risk of steroidal contraceptives could not be determined.

### Conclusions

DMPA use was associated with BMD deficits during and after treatment, the clinical significance of which remains uncertain. Our findings should alert the clinician to the need to monitor BMD in long-term users of this particularly useful treatment. Long-term, controlled, prospective studies with adequate sample size are required to evaluate the potential clinical impact of DMPA use on bone health outcomes.

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