

DMPA's effect on bone mineral density: A particular concern for adolescents

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Contraceptive DMPA reduces bone mineral density.
 Supplement with calcium and vitamin D and urge exercise.

Practice recommendations

- Discuss the potential for decreased bone mineral density in using depot-medroxyprogesterone acetate (DMPA) with any woman who is thinking of it as a means of contraception (C).
- Recommend to women that they take 1300 mg of calcium and 400 IU of vitamin D when using DMPA (C).
- Consider prescribing estrogen replacement if DMPA is going to be used for more than 2 years (C).

Strength of recommendation (SOR)

- A Good-quality patient-oriented evidence
 B Inconsistent or limited-quality patient-oriented evidence
 C Consensus, usual practice, opinion, disease-oriented evidence, case series

sample sizes and methodological flaws. Moreover, most studies have shown that BMD change is reversible after discontinuation of DMPA.

Experts recommend counseling young women about DMPA's possible effects on bone. But they caution against limiting its use based on the insufficient research to date (SOR: C). Analysts estimate that the availability of DMPA has contributed significantly to decreased adolescent pregnancy rates in the United States over the last 10 years.² This article reports on a systematic review of the literature concerning DMPA and BMD.

Reason for concern

A 1991 study by Cundy et al³ was the first to examine the relationship between DMPA and BMD and found that DMPA users had significantly lower BMD than nonusers. DMPA delivers high doses of progestin and inhibits ovulation in most women. Consequently, DMPA can decrease serum estradiol levels. Low serum estradiol levels have also been linked to lower BMD levels in women who are in menopause or who have eating disorders.

Adolescence is a time of bone building. The chief reason for interest in the asso-

Among adolescent women who use contraception, the injectable progestin-only depot-medroxyprogesterone acetate (DMPA, Depo-Provera) is second in popularity only to oral contraceptive pills.¹ A very real drawback with DMPA, however, is a resultant hypoestrogenic state that has been linked to lowered bone mineral density (BMD).

Although several studies have demonstrated a relationship between DMPA use and lower BMD among adults and adolescents (strength of recommendation [SOR]: B), many of them had small

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ciation between DMPA and decreased BMD is the potential risk of future osteoporosis and osteoporotic fractures for women using DMPA during adolescence. A mature woman's BMD at any given time is related to her peak bone mass and subsequent rate of decline. Ninety percent of peak bone mass (the highest level of BMD achieved during one's lifetime) is determined by age 18 in women.⁴ Between the ages of 18 and 30, women gain the last 10% of their maximum bone density. After age 30, bone resorption outpaces bone formation and women start to lose bone slowly.⁵ This decline continues until menopause, when women experience a more rapid decline in BMD related to sudden withdrawal of estrogen.

Factors that affect peak BMD. Several factors influence the level of peak bone mass a woman will reach—genetics, race, hormonal milieu, and lifestyle factors.^{4,5} As for lifestyle, it's been shown that both anorexia and the female athlete triad cause low estrogen levels, and the resultant loss of BMD may not be recovered.^{6,7}

Pregnancy, too, is known to be a state of increased bone turnover and resorption,^{8,9} and pregnancy during adolescence may also negatively impact BMD. A small 2002 study compared teenagers who had been pregnant with age-matched controls who had not been pregnant, and found that hip bone density in the adolescent mothers was lower by approximately 10%.¹⁰

Use of bone-affecting medications by adolescents is worrisome because they are still building bone at a high rate.

■ What the literature tells us

Studies of adult women. Studies examining the relationship between DMPA use and BMD have yielded varying results (**TABLE 1**). Most of them show that using DMPA over a course of 2 years decreases BMD by 5% to 10%. New users have the most significant decreases in BMD, suggesting the decline levels off after 2 years of use (SOR: B).¹¹⁻¹³ However, most early studies were cross-sectional and small,

and thus had limited power to determine causality. In addition, these trials were not randomized, and they may have suffered from bias because treatment groups were volunteers.

Three recent prospective studies^{12,14,15} found that bone density losses recover after discontinuation of DMPA. Kaunitz¹⁵ followed women for up to 2 years after DMPA discontinuation and found that BMD recovered almost completely (-0.2% at hip and -1.19% at lumbosacral [LS] spine at 2 years). However, only a small number of women were studied post-discontinuation for the full 2 years. Clark¹² followed women for up to 18 months after discontinuation and found that those who had used DMPA still had significantly lower BMD (-4.7% at the hip and -2.9% at the spine).

These studies established that bone density decreases with the initiation of DMPA, but none of them addressed the key issue of whether BMD remains at lower levels long term (ie, decades) and thereby increases future fracture risk.

Studies of adolescents. Fewer studies have examined the relationship between DMPA use and BMD in adolescents (**TABLE 2**). Most available studies have small sample sizes and methodological limitations (high dropout rates, different age criteria, and significant differences in the comparison groups). In this population, DMPA seems to cause a mild decrease in BMD. There are not enough data to evaluate BMD recovery after DMPA discontinuation. Therefore, it is hard to extrapolate the information about BMD in an adolescent to future fracture risk.

One study examined serum estradiol levels and BMD in 22 adolescents ages 15 to 19 years who were new users of DMPA.¹⁶ Only 6 participants were still using DMPA at 1 year, and 4 used it throughout the 2 years of the study. The trend over 2 years was toward decreasing BMD. Serum estradiol levels were low, but were not correlated with BMD.

Another related study measured bone biochemical markers in 3 groups: 53 ad-

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In women, 90% of peak bone mass is determined by age 18.

olescents ages 12 to 18 starting DMPA; 165 adolescents starting oral contraceptive pills; and 152 adolescent women not using hormonal contraception.¹⁷ There was no relationship between bone biochemical markers and BMD at either the LS spine or the femoral neck.

■ Can estrogen therapy counteract DMPA's effect?

If decreased BMD in women taking DMPA is due to low estradiol levels, it is logical that a trial of estradiol supplementation would mitigate the negative effect. Indeed, a bone-protective effect of supplemental estrogen therapy has been found in studies of young women with amenorrhea secondary to the female athlete triad. Similarly, in postmenopausal women with low serum estradiol levels, supplemental estrogen therapy helps maintain BMD.¹⁸

Two randomized trials have evaluated the use of supplemental estrogen on the adverse effects of DMPA on bone.^{19,20} The trial by Cromer et al¹⁹ randomized 123 adolescent women ages 12 to 18 to receive either estrogen supplementation or placebo. They found that the participants in the estrogen group had BMD gains vs BMD losses among those in the placebo group over the 2-year period of the study (2.8% vs -1.8% at the LS spine, and 4.7% vs -5.1% at the femoral neck; $P < .001$ for both). The limitations to this study include a high dropout rate (53 participants had left by 24 months) and incomplete data collection due to early stoppage of the study.

Cundy et al²⁰ studied 38 adult women who had been on DMPA for at least 2 years and had below-average LS spine BMD. Nineteen women were randomized to receive estrogen supplementation and underwent bone density tests every 6 months; 19 women were also in the comparison placebo group. In the estrogen supplementation group, there was significant attenuation of lowering BMD that increased throughout the trial. However, only 26

subjects completed the 2-year study.

■ Limit DMPA use to 2 years? Experts disagree

The FDA, in 2004, placed a black box warning on DMPA: "Women who use Depo-Provera Contraceptive Injection may lose significant bone mineral density. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of Depo-Provera Contraceptive Injection during adolescence or early adulthood, a critical period of bone accretion, will reduce peak bone mass and increase the risk of osteoporotic fracture later in life. Depo-Provera Contraceptive Injection should be used as a long-term birth control method (eg, longer than 2 years) only if other birth-control methods are inadequate."²¹ In light of these FDA guidelines, many practitioners have started limiting patients' use of DMPA to 2 years.

The Society of Adolescent Medicine has produced clinical guidelines for treating adolescents who do well on DMPA for contraception (SOR: C, expert opinion).²² The guidelines recommend, among other things, that physicians:

- continue prescribing DMPA to adolescent girls needing contraception, while providing adequate explanation of benefits and potential risks.
- consider ordering a dual-energy x-ray absorptiometry (DEXA) scan to evaluate a patient's risk.
- keep in mind that duration of use need not be restricted to 2 years.
- recommend 1300 mg calcium plus 400 IU vitamin D and daily exercise to all adolescents receiving DMPA.
- consider estrogen supplementation in those girls with osteopenia (or those at high risk of osteopenia who have not had a DEXA scan) who are otherwise doing well on DMPA and have no contraindication to estrogen.

The World Health Organization similarly published recommendations stat-

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Reduction of bone mineral density with DMPA appears to level off after 2 years.

TABLE 1

DMPA's effect on BMD in adult women: What the studies reveal

AUTHOR (TYPE OF STUDY)	# OF PARTICIPANTS/ POPULATION DESCRIPTION	OUTCOME MEASURE	RESULTS	COMMENTS
Gbolade, 1998²⁴ (cross-sectional)	N=185 Ages 17-52 (mean 33) Using DMPA for 1-16 years	DEXA of LS spine and femoral neck	Z-score lower at LS spine ($P<.001$) but not at the femoral neck ($P=.25$)	No significant association between duration of DMPA use and Z-score
Ryan, 2002²⁵ (cross-sectional)	N=32 Ages 19-53 Using DMPA >2 years Low serum estradiol level or menopausal symptoms	DEXA of LS spine and femoral neck	Z-scores were lower at both femoral neck (-0.84; 95% confidence interval [CI], -1.17 to -0.52) and LS spine (-0.32; 95% CI, -0.62 to -0.02)	18 women had osteopenia at LS spine 3 women had osteoporosis at LS spine
Petitti, 2000²⁶ (cross-sectional)	n=350 (DMPA) n=695 (control) Ages 30-34 Using DMPA ≥ 2 years Control group: women who never used hormonal contraception	SXA of wrist	BMD was lower for DMPA current users vs nonusers 0.465 vs 0.471 g/cm ² in midshaft ulna ($P<.001$) 0.369 vs 0.382 g/cm ² in distal radius ($P<.001$)	Large WHO-sponsored, multinational study Past users of DMPA had bone densities not significantly different from nonusers Large variations in BMD among sites
Wanichsetakul, 2002²⁷ (cross-sectional)	n=34 (DMPA) n=62 (comparison) Ages 30-34 Using DMPA ≥ 2 years Comparison groups of women on no steroid contraception in prior 6 months	DEXA of LS spine, distal radius, and femoral neck	BMD at femoral neck and distal radius was not different between DMPA users and controls ($P=.335$ and $P=.398$) DMPA users had lower BMD at LS spine ($P=.007$)	Study conducted in Thailand
Beksinska, 2005²⁸ (cross-sectional)	n=127 (DMPA) n=161 (comparison) Ages 40-49 Using DMPA ≥ 1 year	DEXA of radius and ulna	No significant difference in BMD at distal radius ($P=.26$) or ulna ($P=.21$)	Higher BMD was associated with higher BMI Higher FSH levels were associated with lower BMD
Tang, 2000²⁹ (cohort)	N=59 Ages 37-49 Using DMPA for a mean of 10 years	DEXA of LS spine and femoral neck Annual measurements for 3 years	Small annual decreases in BMD at LS spine (-0.44%), femoral neck (-0.4%), and Ward's triangle (-1.05%)	Duration of DMPA use not related to BMD Decreases in BMD less than projected for age Study conducted in China
Scholes, 2002¹³ (cohort)	n=183 (DMPA) n=258 (comparison) Ages 18-39 Comparison group not exposed to DMPA	DEXA of LS spine and proximal femur Measurements every 6 months for 4 years	Total hip and LS spine BMD were lower for DMPA users ($P=.002$ at LS spine; $P<.005$ for proximal femur)	New users lost bone faster than longer-term users Women who discontinued DMPA showed increasing BMD levels, which reached levels of nonusers after 30 months 33% dropout rate among both groups at 3 years, 44% of DMPA users discontinued use within first 6 months of the study

TABLE 1

DMPA's effect on BMD in adult women: What the studies reveal (continued)

AUTHOR (TYPE OF STUDY)	# OF PARTICIPANTS/ POPULATION DESCRIPTION	OUTCOME MEASURE	RESULTS	COMMENTS
Cundy, 1994¹¹ (cohort)	n=36 (DMPA) n=18 (comparison) Ages 25-51 (mean 41-45) 14 women had used DMPA for ≥3 years and discontinued 22 women were long- term DMPA users Individuals in comparison group were never users of DMPA	DEXA of LS spine and femoral neck Measured twice in each woman	Group I (discontinuers) BMD change at LS spine 3.4% per year (1.6% to 5.2%) and at femoral neck 0.8% per year (-1.8% to 3.4%) Group II (long-term users) BMD change at LS spine -0.2% per year (-2.0% to 1.6%) and at femoral neck -1.1% per year (-2.6% to 0.4%) Group III (nonusers) BMD change at LS spine 0.3% per year (-2.2% to 2.8%) and at femoral neck -1.5% per year (-3.2% to 0.2%)	BMD in LS spine in both groups of DMPA users was 9% lower than control group at baseline
Berenson, 2001³⁰ (cohort)	n=33 (DMPA) n=59 (comparison) Ages 18-33 New users of DMPA Comparison group not using any hormonal contraception	DEXA at LS spine 2 measurements for each participant 12 months apart	Adjusted percent change in BMD for DMPA users was -2.7% (-4.44% to -1.05%) and in nonusers was -0.37% (-1.98% to 1.25%), <i>P</i> =.01	39% dropout rate among both groups
Merki-Feld, 2000³¹ (cohort)	N=36 Ages 30-45 Using DMPA ≥6 months	Quantitative CT of radius Measured twice over 12 months	Trabecular bone mass increased 1.6% (<i>P</i> =.8) Cortical bone mass decreased 0.6% (<i>P</i> <.04)	Duration of DMPA use was not associated with BMD change
Clark, 2004¹⁴ (cohort)	n=178 (DMPA) n=145 (comparison) Ages 18-35 New users of DMPA Comparison group not using hormonal contraception	DEXA of LS spine and total hip Measured every 3 months for 2 years	At 24 months, change in BMD in DMPA users was -5.8% (SE=0.096) at hip and -5.7% (SE=0.034) at LS spine Significant difference between DMPA group and comparison group (<i>P</i> =.001)	Dropout rate 22% in both groups over 2 years Duration of use predicted decrease in BMD Among DMPA users, increasing BMI was protective against BMD loss at hip
Kaunitz, 2006¹⁵ (cohort)	n=248 (DMPA) n=360 (comparison) Ages 25-35 New users of DMPA Comparison group not using hormonal contraception	DEXA LS spine, total hip, femoral neck, and trochanter Measured at baseline and every 48 weeks for up to 5 years	Mean decrease in BMD in DMPA users was 5.16% (±3.6) at hip and 5.38% (±3.57) at LS spine At 96 weeks after discontinuation, change was -0.20% at hip and -1.19% at LS spine	Decreases in BMD were linearly associated with duration of use up to 5 years 17% of DMPA group and 33% of comparison group completed entire 5 years of study
Clark, 2006¹² (cohort)	n=178 (DMPA) n=145 (comparison) Ages 18-35 New DMPA users Comparison group not using hormonal contraception	DEXA total hip and LS spine Measured every 3 months for up to 4 years	Mean change in BMD in DMPA users was -7.7% (±0.11) at hip and -6.4% (±0.36) at LS spine DMPA users of 24-36 months had BMD of -4.7% (hip) and -2.9% (spine) compared with baseline 18 months after discontinuation	Most loss was noted first 2 years after initiation of DMPA Most users of DMPA up to 2 years returned to baseline BMD by 3 years 36% dropout rate in both groups after second year of study Only 45% of DMPA group completed 4 years of study

BMD, bone mineral density; BMI, body mass index; CT, computed tomography; DEXA, dual-energy x-ray absorptiometry; DMPA, depot-medroxyprogesterone acetate; FSH, follicle-stimulating hormone; LS, lumbosacral; SE, standard error; SXA, single-energy x-ray absorptiometry; WHO, World Health Organization.

TABLE 2

DMPA's effect on BMD in adolescent women: What the studies reveal

AUTHOR (TYPE OF STUDY)	# OF PARTICIPANTS/ POPULATION DESCRIPTION	OUTCOME MEASURE	RESULTS	COMMENTS
Scholes, 2004³² (cross-sectional)	n=81 (DMPA) n=93 (comparison) Ages 14-18 Current users of DMPA, range of 1-13 injections (mean 3)	DEXA proximal femur and LS spine	Neither total hip ($P=.1$) nor spine ($P=.19$) BMD was significantly lower in DMPA users	17 non-DMPA users were taking OCPs DMPA users were more likely to be African American and to have a previous pregnancy
Beksinska, 2007³³ (cohort)	n=115 (DMPA) n=144 (comparison) Ages 15-19 New users of DMPA Comparison group not using hormonal contraception	DEXA of distal radius and ulna	No significant difference in BMD between groups ($P=.88$)	51 DMPA users completed the study vs 91 nonusers of hormonal contraception Majority of cohort was African American
Cromer, 2004³⁴ (cohort)	n=53 (DMPA) n=152 (comparison) Ages 12-18 New users of DMPA Comparison group not using hormonal contraception	DEXA of femoral neck and LS spine Measured at baseline, 6 months, and 12 months	LS spine BMD decreased in DMPA group 1.4% and increased in control group 3.8% ($P<.001$); femoral neck BMD decreased in DMPA group 2.2% and increased in control group 2.3% ($P<.001$)	45% dropout rate by 12 months in the DMPA group
Lara-Torre, 2004³⁵ (cohort)	n=58 (DMPA) n=19 (comparison) Ages 12-21 New DMPA users Comparison group ages 15-19 not using any hormonal contraception	DEXA of LS spine Measured at baseline and every 6 months for 2 years	DMPA group had significantly more BMD changes than control group at each check: -3.02% at 6 months ($P=.014$); -3.38% at 12 months ($P=.001$); -4.81% at 18 months ($P<.001$); -6.81% at 24 months ($P=.01$)	DMPA group was more likely to be African American DMPA group had dropout rates of 54% at 12 months and 64% at 24 months
Scholes, 2005³⁶ (cohort)	n=80 (DMPA) n=90 (comparison) Ages 14-18 Baseline users of DMPA (duration of use from 1 to 13 injections)	DEXA of hip, spine, and whole body Measured at baseline and every 6 months for 24-36 months	Significant BMD decreases in DMPA users at each check vs comparison group in hip and spine ($P=.001$), but not in whole-body BMD ($P=.78$) Most discontinuers had regained BMD back to baseline by 12 months	18.9% of non-DMPA users were taking OCPs 61 participants discontinued DMPA during the study DMPA group more likely to smoke and to have been pregnant

BMD, bone mineral density; DEXA, dual-energy x-ray absorptiometry; DMPA, depot-medroxyprogesterone acetate; LS, lumbosacral; OCPs, oral contraceptive pills.

ing that no restriction should be placed on the use of DMPA due to bone effects (SOR: C, expert opinion).²³

Formulate a reasonable approach

As with any other potentially harmful medication, weigh the risks and benefits of DMPA for the individual patient. It is unclear whether BMD lost during DMPA use completely recovers or even what the time frame for that recovery is. Whether the potential risk for future fracture is increased is unknown, but it certainly is cause for concern. Discuss potential risks with any woman who wants to use DMPA for contraception. Routine calcium and vitamin D supplementation for women using DMPA may be helpful and is unlikely to be harmful.

There is not enough evidence to recommend for or against routine screening of BMD in long-term users of DMPA. Research should evaluate the efficacy of estrogen supplementation in women on prolonged DMPA. Long-term studies could provide more information regarding BMD recovery over several years. ■

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Disclosure

The author reported no potential conflicts of interest relevant to this article.

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How this systematic review was conducted

A search of PubMed, the Cochrane database, and all references from primary reviewed articles was performed in 2007 using the terms depot-medroxyprogesterone acetate, bone mineral density, osteoporosis, osteopenia, injectable contraception, progestin-only contraception, Depo-Provera, and DMPA. Studies qualified for analysis if they contained data about bone density in women who had used some type of progestin-only injectable contraception. All types of studies were included. Excluded were studies that did not use BMD as an outcome measure or that re-analyzed data published elsewhere.

Bone mineral density is traditionally used as a surrogate measure of fracture risk in postmenopausal women. However, most of the women included in the reviewed studies were young and at low risk of fracture. The relationship between bone density in premenopausal women and fracture risk later in life is unclear. There are no available studies relating injectable progestin-only contraception with future osteoporotic fractures.

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FAST TRACK

Recommend calcium and vitamin D supplementation with DMPA use.

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