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Predictors of Higher Bone Mineral Density Loss and Use of Depot Medroxyprogesterone Acetate

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Abstract

Objective—To identify possible predictive factors of higher bone loss, defined as at least 5%, at the spine or femoral neck, over time in depot medroxyprogesterone (DMPA) users.

Methods—Bone mineral density (BMD) was measured at the lumbar spine and femoral neck every 6 months in 240 white, black, and Hispanic women using DMPA. For purpose of analysis, an arbitrary value of at least 5% BMD loss from the baseline value after 24 months of DMPA use at either the lumbar spine or femoral neck was considered as higher BMD loss. Logistic regression analysis was then used to examine factors predictive of at least 5% BMD loss at either site.

Results—Of the initial 240 DMPA users, 95 completed 24 months of follow-up. Forty-five of the 95 DMPA users (47.4%) had at least 5% BMD loss at the lumbar spine or femoral neck by 24 months. Multivariable logistic regression model showed that at least 5% BMD loss was associated with current smoking (adjusted odds ratio [OR] 3.88, 95% confidence interval [CI], 1.26–11.96), calcium intake (in 100 mg) (OR 0.81, 95% CI, 0.65–0.99), and parity (OR 0.49, 95% CI, 0.29–0.82). Age, race or ethnicity, previous contraceptive use and body mass index were not associated with higher BMD loss.

Conclusions—The risk of higher BMD loss associated with DMPA use may be reduced by quitting smoking and increasing calcium intake. Having had a child is also protective.

INTRODUCTION

Depot medroxyprogesterone acetate (DMPA), approved by the US Food and Drug Administration (FDA) since 1992, functions as an effective, long-acting and reversible contraceptive for more than 2 million US women annually (1,2). In fact, it has been stated that the decline in unintended pregnancies in the US between 1987 and 1994 was partly due to increased use of this contraceptive (3,4). However, its adverse effect on bone mineral density (BMD) is a concern among clinicians, researchers and policy makers. Studies demonstrated that use of DMPA among adolescents and adults for 2–4 years results in a 1.5–6.8% loss of BMD at the spine and 3.6–7.7% at the hip or femoral neck (5–12). One limitation of these studies on this topic, however, is that they report mean bone loss. Thus, it has not been determined if certain women lose more bone mass while others do not. Furthermore, it has not been determined if it can be predicted who is at greatest risk of losing higher BMD while using DMPA.

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Several published studies have attempted to predict who is at increased risk of bone loss while using DMPA. For example, Clark et al (10) found that a greater percentage increase in fat mass was protective against bone loss at the spine and hip while women with higher baseline fat mass lost less hip bone mass over time. Berenson et al (11) found that DMPA users 16–24 years old lost more bone at the spine and femoral neck compared to those 25–33 years old. This same study reported that current smokers were more likely to lose bone mass at the spine while lean mass was protective at the femoral neck. However, information is lacking on clinically important predictors of higher bone loss which could be used in clinical practice. The purpose of this study was to identify possible predictive factors of higher bone loss, defined as at least 5%, at the spine or femoral neck over time in DMPA users.

MATERIALS AND METHODS

As part of a larger study, 805 non-Hispanic Black, non-Hispanic White, and Hispanic women between 16 and 33 years of age were recruited between October 9, 2001, and September 14, 2004. The methods for the larger study are reported in detail elsewhere (11). Briefly, recruitment was conducted to achieve a sample that was balanced by age group (16–24 years and 25–33 years), race (Black, White, Hispanic) and contraceptive method: nonhormonal (NH), oral contraceptives (OCPs), and injections (DMPA). Of the 805 women, five withdrew before completing the first visit, 92 had abnormal laboratory results, and five had T-scores < -2.5 on their bone scans. Thus, baseline data for the larger study were analyzed for 703 women. Those excluded (n=102) did not differ from women included in the analyses (N=703) on age, marital status, parity, or education (all $P > .05$). A total of 245 women selected OCPs, 240 chose DMPA, and 218 chose nonhormonal contraceptives. Comprehensive follow-up visits (e.g., phlebotomy, urine pregnancy testing, written questionnaires, calcium checklist (13) and bone densitometry) were conducted every 6 months following the initial interview while contraceptives were dispensed every 3 months and minor follow-up visits (i.e., anthropometry) were conducted every 3 months up to 36 months after the baseline visit. A registered dietician conducted a 24-hour recall of dietary intake annually.

Our analyses focused only on the DMPA users (N=240). Of the 240 initial users, 145 discontinued DMPA use sometime during the next two years, with 95 completing the study. There were no differences in baseline characteristics between DMPA users who completed the 24 months follow-up (n=95) and those who did not (n=145) with regard to age, race and BMI ($P > .05$). For the analysis purpose, an arbitrary value of at least 5% BMD loss from the baseline value after 24 months of DMPA use at any one of the two sites was considered as the higher BMD loss. The larger study had 58 DMPA users after 36 months of follow-up. However, a decision was made to use 24 months follow-up data (N=95) rather than 36 months data (n=58) to provide adequate sample size for the multivariable analyses. Bone densitometry, total body fat, percent body fat, and total lean mass, were measured using dual-energy X-ray absorptiometry (QDR 4500W Elite fan-beam densitometer [Hologic Inc., Bedford, MA]). All procedures were approved by the Institutional Review Board of the University of Texas Medical Branch.

Univariable comparisons were performed to compare the two groups (at least 5% vs. < 5% bone loss at the lumbar spine or femoral neck after 24 months of DMPA use) at baseline using the chi square test, Fisher's exact test, or Student *t* test as appropriate. Multivariable logistic regression was used to identify correlates of higher BMD loss after 24 months. Variables were screened for inclusion in an initial multivariable model. Candidate variables with $P \leq .20$ were included in the initial multivariable model while variable with $P > 0.20$ were excluded from the final model. The Hosmer-Lemeshow test (14) and area under the receiver operating characteristics (ROC) curve were used to assess the fit and predictive ability of the final model. All analyses were performed using STATA 10 (Stata Corporation, College Station, TX).

RESULTS

At baseline, the total sample ($N = 240$) had a mean age of 23.8 years with 72 blacks, 82 whites, and 86 Hispanics. Of the initial 240 DMPA users, 95 completed 24 months of follow-up. Forty-five of the 95 DMPA users (47.4%) had at least 5% BMD loss at the lumbar spine or femoral neck. A total of 50 women had <5% bone loss at both sites during the same period. The two groups (at least 5% BMD loss at spine or femoral neck vs. < 5% at the two sites) were similar in terms of race, height, weight, BMI, lean mass, fat mass, age at menarche, smoking, alcohol use, weight-bearing exercise, daily calcium intake, use of calcium supplements, and baseline spine and femoral neck BMD (Table 1). However, the former group of DMPA users were younger, less likely to have used DMPA in the past, and had lower mean parity than the latter group.

Variables that met the screening criteria for inclusion in the multivariable model were age, BMI, parity, previous use of DMPA, total calcium intake per day and current smoking while race/ethnicity was forced into the model. Variables with $P > .20$ (age and BMI) were excluded from the final model. The final logistic model yielded a P -value for the Hosmer-Lemeshow test of 0.25 and the estimated area under the ROC curve was 0.79 (confidence interval [C], 0.70–0.88). Adjusted odds ratios for the final logistic model are presented in Table 2. Higher BMD loss after 24 months of DMPA use was associated with current smoking (adjusted odds ratio [OR] 3.88, 95% CI, 1.26–11.96), calcium intake (in 100 mg) (OR 0.81, 95% CI, 0.65–0.99), and parity (OR 0.49, 95% CI, 0.29–0.82).

Figure 1(a) to 1(f) show the mean percentage BMD loss at the spine and femoral neck by smoking status, calcium intake and history of parity over 24 months with 6 months increment based on the available observations at each follow-up period. By and large, BMD loss was higher in women who were current smokers, never been pregnant and had daily calcium intake ≤ 600 mg (mean daily calcium intake) compared to their counterparts, although not all comparisons achieved statistical significant difference. Moreover, the difference in BMD loss substantially increased between the women with all three risk factors and without any risk factors [Fig (g) and Fig (h)].

Thirty-six month data were available for 27 of the 45 women who had at least 5% BMD loss at 24 months at either site. Data on these 27 women showed that the BMD loss increased at the spine from 5.3% to 5.8% and at the femoral neck from 5.7% to 7.7%, on average, between 24 and 36 months of use. In contrast, those who lost < 5% BMD by 24 months and had a scan at 36 months ($n=29$) experienced an average loss of 1.7% at the lumbar spine and 2.5% at the femoral neck by the 36 month visit as compared to 1.2% and 0.7% at 24 months, respectively.

DISCUSSION

This study examined the correlates of BMD loss associated with DMPA use based on a distinct cut-off point (at least 5% vs. <5%). We observed that almost half of DMPA users experience a bone loss of this magnitude within 2 years of initiating DMPA. Furthermore, these women continued to experience significant losses in BMD during their third year of use, especially at the femoral neck. These losses are of significant concern as they are likely to take an extended period of time to recover, especially at the hip. In a previous publication which included data on BMD changes after DMPA discontinuation, we reported that women regained an average of 2.4% BMD annually at the lumbar spine after they stop receiving injections (11). Bone lost at the femoral neck, however, recovered more slowly (1.6% per year). Clark et al observed that hip BMD was 4.7% below baseline 18 months after DMPA discontinuation among women who used this contraceptive for 24–36 months, demonstrating that this site was slow to recover in their study as well (10). The same study also reported spine BMD 2.9% below baseline a

18 months after DMPA discontinuation. In contrast, Kaunitz et al (15) observed more rapid recovery at the hip and femoral trochanter. These values were very close to their baseline levels after 96 weeks of DMPA discontinuation among women who used this contraceptive up to 5 years. However, spine and femoral neck BMD (1.2% and 3.1% lower than baseline level after 96 weeks, respectively) showed only partial recovery in that study, similar to the studies of Berenson et al (11) and Clark et al (10). Since the femoral neck is the most common fracture site after menopause, DMPA use for multiple years may place women at risk of future fractures if these detrimental changes are not completely reversible. Unfortunately, we were unable to examine reversibility among women who experienced a at least 5% lost in their BMD in the current investigation, as too few women were followed after discontinuation with this large of a loss. Thus, the reversibility of higher bone loss among DMPA users and the amount of time that it takes to return to baseline values needs to be explored in future studies.

This study reports that BMD loss is not a significant concern for all women who choose DMPA for contraception, as it is associated with certain risk factors. Those who had delivered a child, did not smoke and consumed at least 600 mg per day of calcium did not lose more than 2% of their BMD at the spine or hip over 24 months. Thus, concerns about their bone health are minimal. Furthermore, clinicians can counsel women who have a modifiable risk factor and wish to use DMPA that they can protect their bone health by quitting smoking and consuming a diet adequate in calcium. Given that the average calcium intake of 600 mg/day among women in this study is still far below recommended amounts (16), this counseling would probably benefit users of all types of contraceptives. Brochures which depict calcium rich foods could be disseminated as well as providing information on the role of calcium supplementation for those with inadequate dietary intake. Physicians may also wish to disseminate information about types of supplements and which are most efficiently absorbed. We observed that only about 8.9% of the women using DMPA took calcium supplements at least 4 days per week, demonstrating that few young women of reproductive age understand the importance of adequate calcium consumption. Finally, family planning visits could provide an opportunity to discuss smoking cessation programs in the local area as well as medications which can assist with their efforts to quit.

Another important finding of this study was that increased parity resulted in lower BMD loss. However, results of prior published studies on the relationship between parity and BMD are not consistent (17–19). Some studies showed higher BMD with increased parity in later life while others showed lower BMD or did not find any association. Pregnancy related changes in estrogen concentration, and increase in periosteal expansion and bone size due to weight gain during pregnancy could act as protective factors for BMD loss in later life.

Prevention of bone loss while using DMPA is not well understood and remains an important topic for future research. One option which has been suggested is to give estrogen supplementation. A double blinded placebo controlled trial in women with mean age of 37 years demonstrated that this can result in a 1% increase in spinal BMD per year among users of DMPA as compared to a 2.6% loss annually among those who did not take estrogen (20). Similar results were also found for the femoral and total body BMD although the statistical significance was less. Another study of adolescents DMPA users (mean age of 16 years) who had monthly estradiol cypionate injections showed a 2.8% spine BMD increase over 24 months compared to a 1.8% decrease in DMPA users who did not have estradiol injections (21). This study also showed a similar pattern at the femoral neck. Future studies which consider fracture as an outcome are needed to examine the practicality of using this supplement along with DMPA.

This study has several limitations. First, the sample size was small so there may be associations that we were unable to detect in our analyses. In addition, data such as calcium intake and

amount of exercise are subject to recall bias. Third, the discontinuation rate among DMPA users was high. However, this is a problem inherent to many contraceptive studies as there are many reasons that women may choose to change or discontinue their method (22–24). Fourth, the larger study did not randomize women to one of the three contraceptive groups as these methods have different efficacies and randomization could have led to unintended pregnancies. Finally, we did not have enough women in the at least 5% bone loss group who were followed after DMPA discontinuation to examine the reversibility of these findings among this subset.

In conclusion, women who have not delivered a child, smoke, and do not consume much calcium in their diet are at risk for higher bone loss while using DMPA. These women require additional counseling on how to decrease their risk of BMD loss in order to avoid placing their bone health at risk.

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A

G

Figure 1.

Mean percentage bone mineral density (BMD) loss in depot medroxyprogesterone acetate (DMPA) users at different follow-up visits by risk factor status. A, spine BMD by smoking status; B, femoral neck BMD by smoking status; C, spine BMD by daily calcium intake; D, femoral neck BMD by daily calcium intake status; E, spine BMD by pregnancy status; F, femoral neck BMD by pregnancy status; G, spine BMD by risk factor status; H, femoral neck BMD by risk factor status.

* Differences were significant at the $P < .05$ using Student t test.

Table 1

Characteristics of DMPA users by BMD loss category at baseline (<5% vs. ≥5%) (n=95)

Characteristic	≥5% BMD loss at lumbar spine or femoral neck (n=45)	<5% BMD loss at lumbar spine and femoral neck (n=50)	P Value
Age, mean, yr (SE)	22.5 (0.7)	24.8 (0.8)	.034
Race %			.714
Black	28.9	26.0	
White	37.8	46.0	
Hispanic	33.3	28.0	
Height, cm, mean (SE)	163.2 (1.0)	162.2 (1.0)	.493
Weight, kg, mean (SE)	70.5 (2.5)	74.5 (2.7)	.283
BMI, kg/m ² , mean, (SE)	26.6 (1.0)	28.3 (1.0)	.209
Lean mass, kg, mean (SE)	44.4 (1.1)	45.1 (1.1)	.644
Fat mass, kg, mean (SE)	24.4 (1.7)	27.5 (1.7)	.199
Fat mass, % of total, mean (SE)	33.1 (1.3)	35.6 (1.5)	.233
Age at menarche, y, mean (SE)	12.4 (0.3)	12.5 (0.2)	.831
Parity, mean (SE)	0.6 (0.1)	1.4 (0.2)	.003
Past use of pill (months), mean (SE)	13.8 (3.9)	25.1 (6.2)	.138
Past use of DMPA injection (no), mean (SE)	1.6 (0.5)	5.1 (1.2)	.012
High school graduate, %	71.1	74.0	.753
Relative with shortened height, % [¶]	37.8	42.0	.489
Relative with fracture history, % [†]	11.1	16.0	.675
Current smoker, %	44.4	32.0	.212
Alcohol use [*]	37.8	30.0	.423
Calcium intake, mg/day, mean (SE)	483.9 (29.8)	565.7 (39.7)	.109
Use of calcium supplements, % ^{**}	8.9	8.0	1.0
Weight-bearing exercise >120 min/wk,%	40.9	34.0	.489
Spine BMD, g/cm ² , mean (SE)	1.072 (0.018)	1.033 (0.012)	.078
Femoral neck BMD, g/cm ² , mean (SE)	0.924 (0.021)	0.894 (0.17)	.272

* At least 2–4 times/month

** At least 4–6 days/wk

¶ One or more close female relative (mother, sister, grandmother, or aunt) lost height (gotten shorter) as they grew older.

† One or more close female relative (mother, sister, grandmother, or aunt) suffered a broken hip, wrist, spine, or shoulder after the age of 45.

Table 2

Predictors of BMD loss $\geq 5\%$ at the lumbar spine or femoral neck in DMPA users over 24 months of use

Characteristics	Odds ratio (95% CI)
Race/ethnicity	
Black	Reference
White	0.34 (0.10–1.17)
Hispanic	0.90 (0.26–3.10)
Previous DMPA injection (#)	0.90 (0.80–1.02)
Parity	0.49 (0.29–0.82)
Total calcium intake	0.81 (0.65–0.99)
Current smoker	3.88 (1.26–11.96)

Based on logistic regression analysis

R-squared value: 0.20

Area under the ROC curve: 0.79

P value for Hosmer-Lemeshow goodness of fit test=0.25

Dependent variable: BMD loss ($\geq 5\%$ vs. $<5\%$)

Predictors: race/ethnicity (non-Hispanic black, non-Hispanic white, Hispanic), previous use of DMPA injection (# of injection), parity (continuous), total calcium intake (in 100 mg/day), current smoker (current smoker vs. not current smoker)