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Relationship between Weight and Bone Mineral Density in Adolescents on Hormonal Contraception

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Abstract

Study Objective—Since bone loss has been observed among adolescents on depot medroxyprogesterone acetate (DMPA), a clinical population that commonly experiences weight gain, we were interested in examining the direct relationship between body weight and bone mineral density (BMD) in adolescents on DMPA as compared to those on oral contraceptive pills (OC) or on no hormonal contraception (control).

Design—Prospective, Longitudinal study.

Setting—Four urban adolescent health clinics in a large metropolitan area.

Participants—Post-menarcheal girls, age 12 – 18 years, selecting DMPA, OC or no hormonal contraception.

Interventions—At baseline, 6, 12, 18, and 24 months, all study participants underwent measurement of weight and BMD of the hip and spine.

Main Outcome Measures—The correlation between weight and BMD, and the correlation between change in weight and change in BMD were assessed at each time point.

Results—Body weight was significantly ($p < .05$) positively correlated with femoral neck BMD and spine BMD at each time point regardless of contraceptive method. Change in body weight at 12 and 24 months was highly correlated with change in femoral neck BMD ($p < .0001$) for all treatment groups. No statistically significant correlation between change in weight and change in spine BMD was seen in the DMPA, OC or control subjects at 12 or 24 months.

Conclusion—Weight gain on DMPA may mitigate loss of BMD among adolescent users.

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Keywords

Adolescent; Contraception; Weight Gain; Bone Mineral Density

INTRODUCTION

The two most commonly reported adverse side effects associated with use of the contraceptive agent depot medroxyprogesterone acetate (DMPA) are weight gain and bone mineral density (BMD) loss. Overall, weight gain is reported in up to 54% of adolescents receiving DMPA,[1] and approximately 25% of adolescents experience substantial weight gain defined as either greater than 5% increase over baseline at 6 months or greater than 10% increase at 12 months.2 Weight changes are paralleled by significant increases in body fat with concomitant decreases in lean body mass.3-6

The balance of research also provides evidence that DMPA causes bone loss in adolescent users.[7-12] Mean change in spine bone BMD after two years of ranges from −1.5% to −6.0% in adolescents on DMPA as compared to +5.9% to +9.5% in adolescents off hormonal contraception.[7,11,13]

Body weight is generally a positive predictor of bone strength, of which BMD a major component.[14] Both body fat and lean mass are positively correlated with BMD, thus obesity can exert a protective effect against low BMD.[15,16]

Since bone loss has been observed among adolescents on DMPA, a clinical population that commonly experiences weight gain, we were interested in examining the direct relationship between body weight and BMD in adolescents on DMPA as compared to those on oral contraceptive pills (OC) or on no hormonal contraception (control).

METHODS

Subjects

The study population consisted of post-menarcheal girls, age 12 – 18 years, attending one of four urban adolescent health clinics in a large metropolitan area. Adolescent girls requesting contraception, and selecting either DMPA or OC, were eligible to participate. In addition, adolescent girls who planned to receive no hormonal contraception were eligible for enrollment as control subjects. The control group included adolescents who were abstinent and those using barrier contraceptive methods, although most were not sexually active.

Exclusion criteria for study participation included pregnancy or DMPA use within the preceding 6 months; OC use within the preceding 3 months; alcohol or drug dependence; medical condition (e.g. renal disease) or medication use (e.g. corticosteroids) know to be associated with the outcomes of interest; contraindication to estrogen use; weight exceeding 250 lbs (upper limit for DEXA scanner); and need for confidential contraceptive care. Subjects younger than 18 years gave written assent for participation, and written informed consent was obtained from a parent or legal guardian. Subjects aged 18 years provided their own written informed consent for participation. The study protocol was approved by the institutional review board of the participating institutions.

Data Collection

The present study represents a secondary analysis of weight and BMD data collected from May, 2000 through January, 2003. At baseline, 6, 12, 18, and 24 months, clinical and behavioral information was obtained from each study participant. Height and weight were

measured by using the same stadiometer (Easy Glide Bearing stature board) and Mettler-Toledo scale. Gynecologic age was calculated as the number of years since menarche. Tobacco use was reported as current use or non-use. Calcium intake was elicited with a focused 24-hour dietary recall, combined with the calcium Rapid Assessment Method.[17] Girls who consumed <1,300 mg/d of dietary calcium were counseled by a dietician; if the level of intake did not improve after 3 months, the participant was given a sample of Tums (500 mg; GlaxoSmithKline, Philadelphia, PA) to be taken once per day for 3 months. Physical activity was assessed with a survey that asked each participant to classify herself as inactive, normal, or active.

At baseline and at 6, 12, 18, and 24 months, all study participants underwent measurement of BMD that included L1–L4 lumbar vertebrae, total hip (left), femoral neck, trochanter, and Ward's triangle. The measurement technique used was dual-energy x-ray absorptiometry, using the model QDR 4,500-W fan-beam densitometer (Hologic Inc., Bedford, MA). The software used was QDR for Windows 11.2 (Hologic), which included a low-density measurement option. In vivo intra-individual coefficients of variation were 1.2% at the spine and 1.4% at the femoral neck; inter-individual coefficients of variation were 1.3% at the spine and 2.2% at the femoral neck. All scans were obtained within 4 weeks of the scheduled 6-month intervals.

Depot medroxyprogesterone acetate was administered every 12 weeks as a 150 mg, deep-IM injection (gluteus or deltoid). Girls in the OC group received an OC containing 20 mcg of ethinyl estradiol and 100 mg of levonorgestrel. Compliance with DMPA injections was assessed by chart review and was calculated as number of injections divided by number of prescribed injections (total of 9 injections over 24 mo) x 100. Compliance rates with OC use were assessed by monthly self-report and were calculated as the number of pills taken, divided by the number of pills prescribed (1 pill per day from date of initiation, for 24 mo) x 100. Participants who elected to change contraceptive methods during the study were withdrawn.

Statistical Analysis

To examine the relationships between weight and BMD across the treatment groups, Pearson correlation coefficient matrices were constructed of weight and bone measures by contraceptive group at 12 and 24 months. Both the correlation between weight and BMD and the correlation between change in weight and change in BMD were assessed at each time point. Since significant differences in age, tobacco use, physical activity and prior contraceptive use were seen between treatment groups at baseline, correlation coefficients were adjusted for these variables . Data analyses were conducted with SAS statistical software, version 9.1(SAS Institute Inc., Cary, NC).

RESULTS

The study population included 433 adolescent girls who selected either DMPA (n = 58), OC (n = 187), or represented the untreated control group (n = 188). Group compliance with DMPA injections was 99.4% (95% CI, 98.2% - 100%); group compliance with OC was 86.3% (95% CI, 86.26% - 86.34%). A total of 281 girls completed their 12-month study visit as follows: DMPA (n = 41, 71%), OC (n = 104, 56%), control (n = 136, 72%). A total of 184 girls completed their 24-month study visit as follows: DMPA (n = 27, 47%), OC (n = 62, 33%), control (n = 95, 51%).

Baseline data for the study population are presented in Table 1. Untreated controls were significantly younger than subjects on DMPA or OC. They were also significantly less likely to smoke and be physically inactive. The OC group had a higher body weight, spine

and femoral neck BMD than did the other two groups. The DMPA group was significantly more likely to have a history of prior contraceptive use. No statistically significant differences were identified among the groups regarding racial background, height, body mass index, and serum vitamin D levels.

Adjusted correlation coefficients between body weight and BMD at 12 and 24 zsmonths by contraceptive group are presented in Table 2. Body weight was significantly positively correlated with both femoral neck BMD and spine BMD at each time point regardless of contraceptive method.

Table 3 presents adjusted correlation coefficients between absolute changes in body weight and absolute changes in BMD by contraceptive group at 12 and 24 months. Change in body weight at 12 and 24 months was highly correlated with change in femoral neck BMD ($r = 1.0$, $p < .0001$) for all treatment groups. There was no statistically significant correlation between change in weight and change in BMD at the spine in either DMPA, OC or control subjects at 12 or 24 months. 12-month correlation coefficients were $r = -.101$ ($p = .63$), $r = -.082$ ($p = .45$) and $r = .100$ ($p = .30$) for DMPA, OC and control subjects respectively. 24-month correlation coefficients were $r = .098$ ($p = .77$), $r = -.012$ ($p = .94$) and $r = .048$ ($p = .71$) for DMPA, OC and control subjects respectively.

DISCUSSION

In this study, we found a very high correlation between body weight and BMD at all time points, regardless of treatment with hormonal contraception. The implication of these findings is that body weight and body fat may override the potential detrimental effect on bone seen with the use of DMPA and, to a lesser extent, very low dose oral contraceptives. The usual “culprit” for loss in BMD among DMPA users is estrogen deficiency induced by suppression of the hypothalamic-pituitary-ovarian axis without exogenous estrogen replacement.[18]

Two factors may explain our findings. First weight gain among adolescents on DMPA has been demonstrated to be secondary to gains in body fat rather than lean body mass.[3,4] It is well known that estrogen stores in body fat.[19] Therefore, it is possible that in women with increased body fat, more estrogen is available from their stored reserves. A second factor may relate to a biomechanical mechanism of weight on bone.[14] The bone and muscle comprise a unit, that, in the case of increased body weight, experiences increased mechanical strain. Increased strain, which is transferred through muscle to bone, results in the production of cytokines in the surrounding microenvironment. These cytokines are, at least in part, similar to those produced in the presence of estrogen and serve to increase bone formation and decrease bone loss.

The biomechanical theory may also help explain the impressive positive correlation between change in body weight and change in femoral neck BMD, which is not seen between weight change and change in BMD at the spine. More weight is transmitted per cubic inch of body structure through the hips than over the spine. Moreover, a wider variety of strain is transmitted by daily physical movements through the hip than through the spine. Hence, acute changes in weight would have a more immediate effect on femoral neck BMD than that of the spine. In fact, our results suggest that changes in weight are the predominant predictor of changes in femoral BMD regardless of hormonal contraceptive treatment.

Several sources of bias are present in our study. Since study subjects self-selected contraceptive method, rather than being randomized into treatment groups, confounding influences on the relationship between body weight and BMD may be unevenly distributed among treatment groups. In addition, the high attrition rate, particularly in the OC group,

may also have impacted study results. However, no significant differences were identified between subjects who did or did not finish the study, so we do not think this was a significant source of bias.

In conclusion, we found a statistically significant positive relationship between body weight and both femoral neck and spine BMD regardless of hormonal contraception. Our findings imply that weight gain on DMPA may mitigate loss of BMD among adolescent users.

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Table 1

Baseline Characteristics of Study Population[a,b]

Characteristic	Control (n = 188)	DMPA (n = 58)	OC (n = 187)	P-value
Chronological age (y)	14.8 ± 1.9	15.8 ± 1.6	16.0 ± 1.4	< .001
Gynecologic age (y)	2.7 ± 1.8	3.9 ± 1.8	4.0 ± 1.7	< .001
Race, n (% black)	119 (63)	37 (64)	114 (61)	0.87
Body weight (kg)	63.5 ± 16.5	60.5 ± 12.8	68.9 ± 17.1	< .001
Height (cm)	160.2 ± 9.7	161.7 ± 6.9	161.7 ± 6.6	0.15
Body mass index	25.8 ± 9.6	23.0 ± 4.1	26.3 ± 6.2	0.27
Spine BMD	0.98 ± 0.11	0.98 ± 0.09	1.03 ± 0.11	< .001
Femoral neck BMD	0.92 ± 0.15	0.92 ± 0.14	0.97 ± 0.14	0.007
Vitamin D (IU/d)	53.5 ± 36.5	66.0 ± 24.7	59.3 ± 33.9	0.61
Smoker, n (%)	10 (8)	14 (33)	37 (29)	<.001
Physical activity, n (%)				0.009
Active	99 (53)	78 (42)	22 (38)	
Normal	66 (35)	12 (6)	7 (12)	
Inactive	23 (12)	97 (52)	29 (50)	
No prior contraceptive use, n (%)	186 (99)	50 (86)	182 (97)	0.03

Note:

[a] All data are given as mean ± SD, unless indicated as n (%)

[b] Modified from Table 1. Cromer. Bone and contraception in adolescents. Fertil Steril 2008.[14]

Table 2

Correlation between Body Weight (kg) and Bone Mineral Density (BMD) at 12 and 24 months by Contraceptive Method

Pearson Correlation Coefficient[a] (p-value)	Weight vs. Femoral Neck BMD		Weight vs. Spine BMD	
	12 months	24 months	12 months	24 months
DMPA	.700 (< .001)	.929 (p < .001)	.514 (p = .01)	.584 (p = .05)
OC	.534 (< .001)	.541 (p < .001)	.514 (p < .001)	.470 (p = .004)
Control	.555 (< .001)	.513 (p < .001)	.457 (p < .001)	.432 (p = .002)

Note:

[a] Adjusted for age, smoking, physical activity and prior contraceptive use

Table 3

Correlation between Absolute Change in Weight (kg) and Absolute Change in Bone Mineral Density (BMD) at 12 and 24 months by Contraceptive Method

Pearson Correlation Coefficient[a] (p-value)	Δ Weight vs. Δ Femoral Neck BMD		Δ Weight vs. Δ Spine BMD	
	12 months	**24 months**	**12 months**	**24 months**
DMPA	1.000 (< .001)	1.000 (p < .001)	−.101 (p = .63)	.098 (p = .77)
OC	1.000 (< .001)	1.000 (p < .001)	−.082 (p = .45)	−.012 (p = .94)
Control	1.000 (< .001)	1.000 (p < .001)	.100 (p = .30)	.048 (p = .71)

Note:

[a] Adjusted for age, smoking, physical activity and prior contraceptive use