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Contraception 73 (2006) 470–487

Contraception

Review article

Progestogen-only contraception and bone mineral density: a systematic review

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Received 14 December 2005; revised 28 December 2005; accepted 28 December 2005

Abstract

Questions have been raised about the effects of progestogen-only contraceptive use on bone health, particularly among young women who have not yet reached peak bone mass and perimenopausal women who may be starting to lose bone mass. We conducted a systematic review that evaluated the association between progestogen-only contraceptive use and fracture risk or bone mineral density (BMD). We identified 39 articles from MEDLINE and EMBASE, published through July 2005. One study reported that depot medroxyprogesterone acetate (DMPA) users were more likely to experience stress fractures than nonusers; this association was not statistically significant after controlling for baseline bone density. In cross-sectional studies, the mean BMD in DMPA users was usually below that of nonusers, but within 1 SD. In longitudinal studies, BMD generally decreased more over time among DMPA users than among nonusers, but women gained BMD upon discontinuation of DMPA. Limited evidence suggested that use of progestogen-only contraceptives other than DMPA did not affect BMD.

Keywords: Contraception; Progestogen; Bone mineral density; Fracture; Systematic review

1. Introduction

Questions have been raised about the effects of progestogen-only contraceptive use on fracture risk and bone mineral density (BMD), particularly among young women who have not yet reached peak bone mass and among perimenopausal women who may be starting to lose bone mass. Concern is greatest for women using depot medroxyprogesterone acetate (DMPA), due to its relatively hypoestrogenic effect. A systematic review published in 2001 reviewed 10 cross-sectional and 7 longitudinal studies and concluded that mean BMD was lower in DMPA users than in nonusers, but that the difference was within 1 SD from the nonusers [1]. Results from that review for Norplant use were conflicting. In addition to concern about bone loss, a key issue is whether women can regain sufficient bone mass after discontinuing use of progestogen-only contraceptives.

The objective of this systematic review was to determine whether progestogen-only contraceptive use has an adverse effect on fracture risk or BMD, especially among younger (<18 years) women and older (>45 years) women. The review examined the following progestogen-only contraceptive methods: DMPA, norethisterone enantate (NET-EN), levonorgestrel and etonogestrel implants, and progestogen-only pills.

2. Materials and methods

The MEDLINE and EMBASE databases were searched for all articles published between 1966 and July 2005 by using the following search terms: [Medroxyprogesterone 17-Acetate/ and (contracept: or inject: or depo or depot)] or [(depot medroxyprogesterone or depo medroxyprogesterone or depotmedroxyprogesterone or depomedroxyprogesterone) or dmpa.tw.] or [net en.tw. or norethisterone-enantate] or [(norplant: or uniplant or jadelle or implanon) or ((levonorgestrel or etonogestrel) and (implant:))] or [(levonorgestrel and intrauterine device) or mirena.tw.] or [(exp Progestational Hormones/ or progestin:.tw.) and (contracept:) and (oral.tw. or pill.tw. or pills.tw. or tablet.tw. or tablets.tw.)] and (bone density) or (bone or osteo:) or fracture. Although fracture was the primary outcome of interest, the search also targeted articles that assessed BMD among progestogen-only contraceptive users. We searched reference lists of identified articles and relevant review articles for additional citations of interest. We did not consider abstracts of conference presentations, dissertations and case studies.

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doi:10.1016/j.contraception.2005.12.010

2.1. Study selection and inclusion criteria

We selected primary research articles that examined the effects of progestogen-only contraceptive use on fracture risk or BMD. If there was more than one report of the same study, we used the most recent publication; this approach resulted in the exclusion of three reports of studies with subsequent publications [2-4].

2.2. Study quality assessment and data synthesis

We summarized and systematically appraised the evidence through the use of standard abstract forms. We

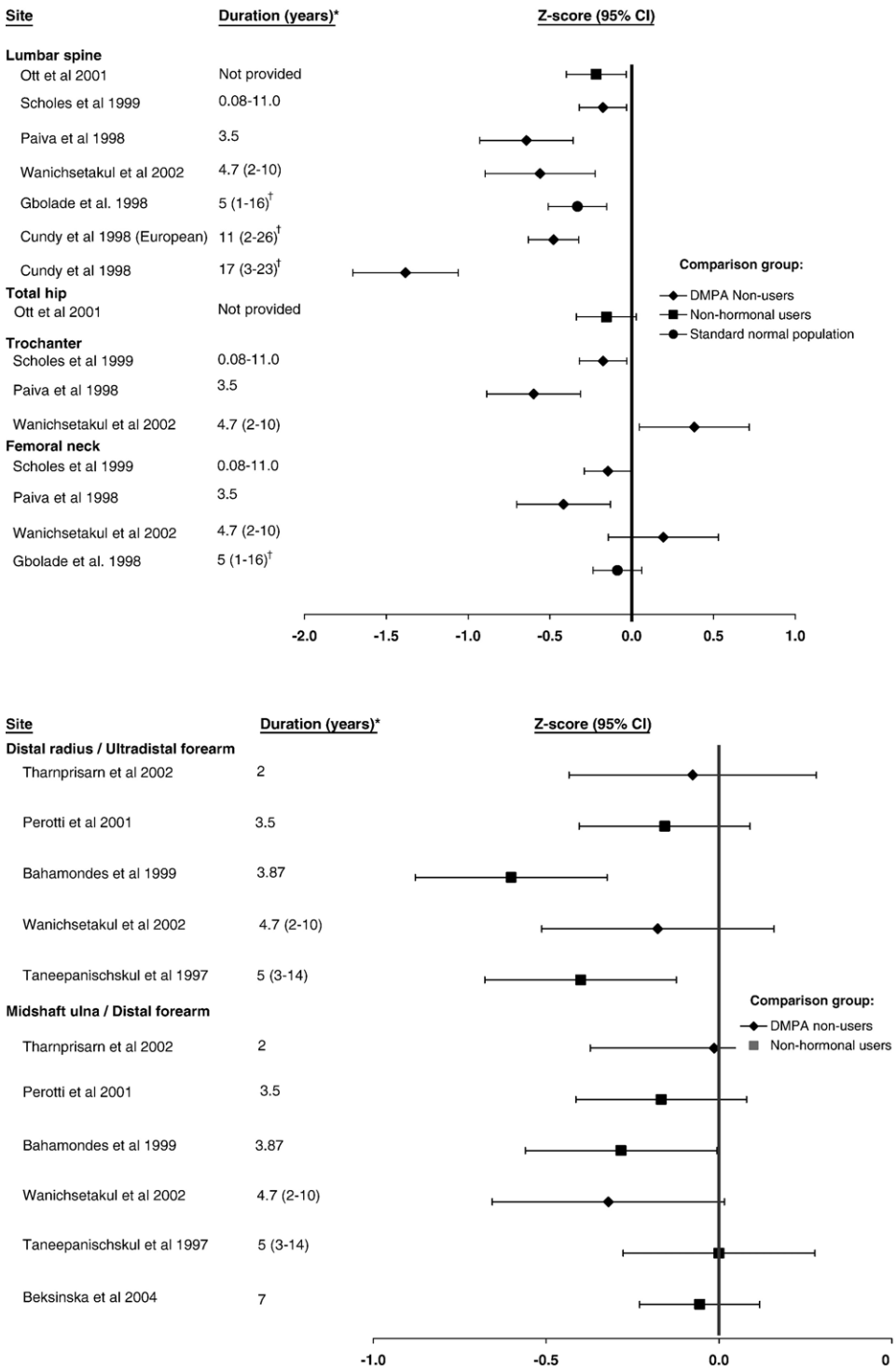

Fig. 1. Cross-sectional studies of BMD at spine and hip sites and at forearm sites in adult women using DMPA and in nonusers, by duration of DMPA use. *Z*-score = number of standard deviations between mean BMD among DMPA users and nonusers. *Mean and/or range, except where median is indicated (†).

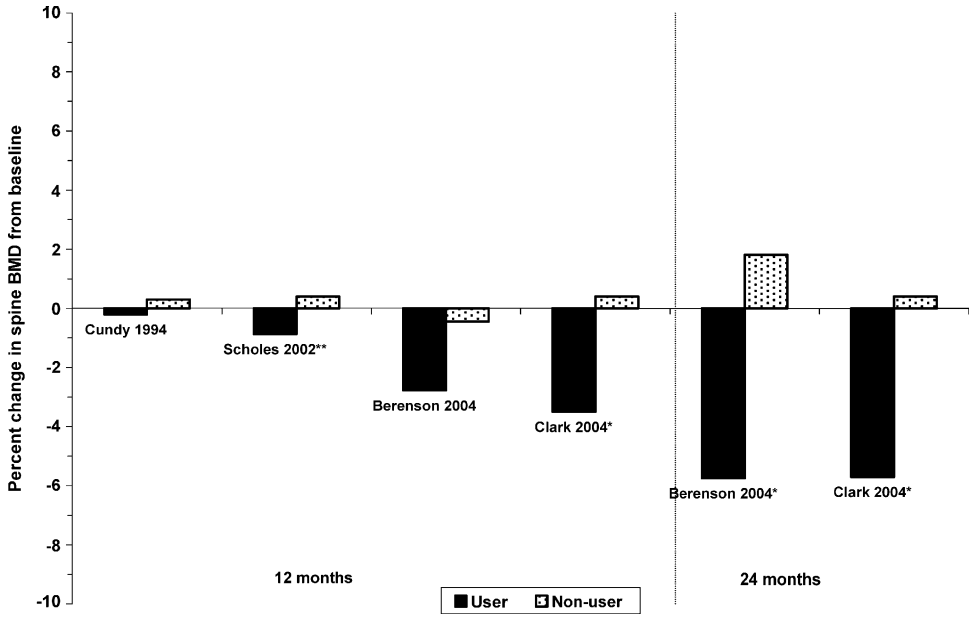

Fig. 2. Longitudinal studies of changes in BMD in the spine in adult women who used DMPA and in nonusers, by difference in mean percent change in BMD from baseline. *Significant difference between DMPA users and nonusers. **Statistical significance not reported.

assessed the quality of each piece of evidence by using the system for grading evidence developed by the United States Prevention Services Task Force (USPSTF) (Appendix A). Because the studies identified addressed disparate study objectives, measurement of outcomes, and duration of contraceptive use, we were unable to calculate summary odds ratios.

Many of the cross-sectional studies reported the differences in BMD between users and nonusers of progestogen-only contraceptives as a *Z*-score. In this context, the *Z*-score expresses the difference in BMD among progestogen-only contraceptive users according to the standard deviation among nonusers [1]. Therefore, the *Z*-score represents the number of standard deviations between the mean BMD in users and the mean BMD in nonusers. When compared to a standard normal population, this statistic is called a *T*-score. The World Health Organization (WHO) uses the *T*-score as a measure of clinical significance of BMD. Values within

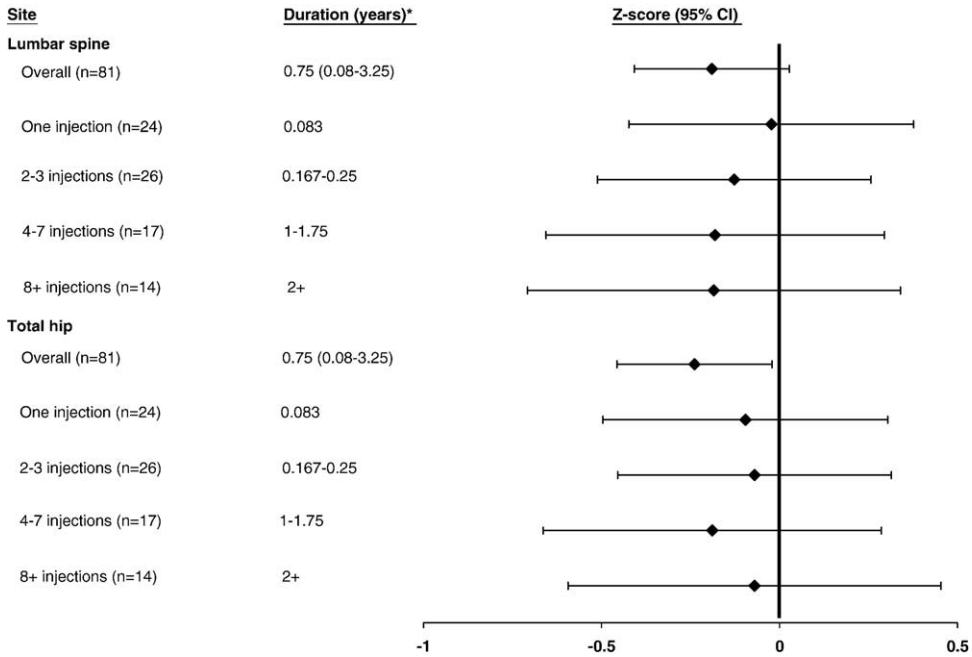

Fig. 3. Cross-sectional study by Scholes et al. [29] of BMD at spine and hip sites in adolescent women who used DMPA and in nonusers, by duration of DMPA use. *Z*-score = number of standard deviations between mean BMD among DMPA users and nonusers. Overall *Z*-scores are unadjusted; all other *Z*-scores are adjusted for age, ethnicity, smoking, body mass index, calcium intake and weight-bearing exercise. *Mean and/or range.

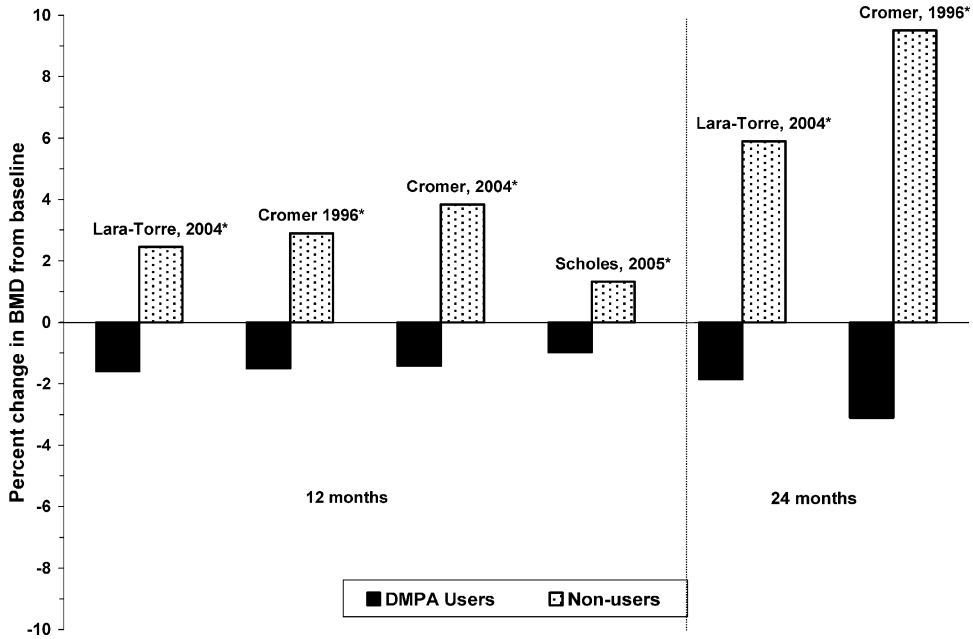

Fig. 4. Longitudinal studies of changes in BMD in the spine in adolescent women who used DMPA and in nonusers, by difference in mean percent change in BMD from baseline. *Significant difference between DMPA users and nonusers.

1 SD of the standard normal population are considered normal; osteopenia is defined as more than 1.0 SD below normal; osteoporosis is defined as more than 2.5 SD below normal [5].

Studies that reported mean BMD values or percent change in mean BMD according to contraceptive use were included in summary graphs (Figs. 1–5). For the cross-sectional studies, *Z*-scores were plotted by anatomic site, duration of contraceptive use and comparison group. *Z*-scores were calculated by subtracting the mean BMD of the comparison group from that of the progestogen-only contraceptive group, then dividing by the standard deviation for the comparison group [1]. Thus, a *Z*-score of −1.0 would indicate that BMD in progestogen-only contraceptive users was 1 SD below that of nonusers. Confidence intervals for the *Z*-scores were constructed using the following standard error formula: standard error= $1/\sqrt{(\text{sample size of progestogen-only contraceptive users})}$.

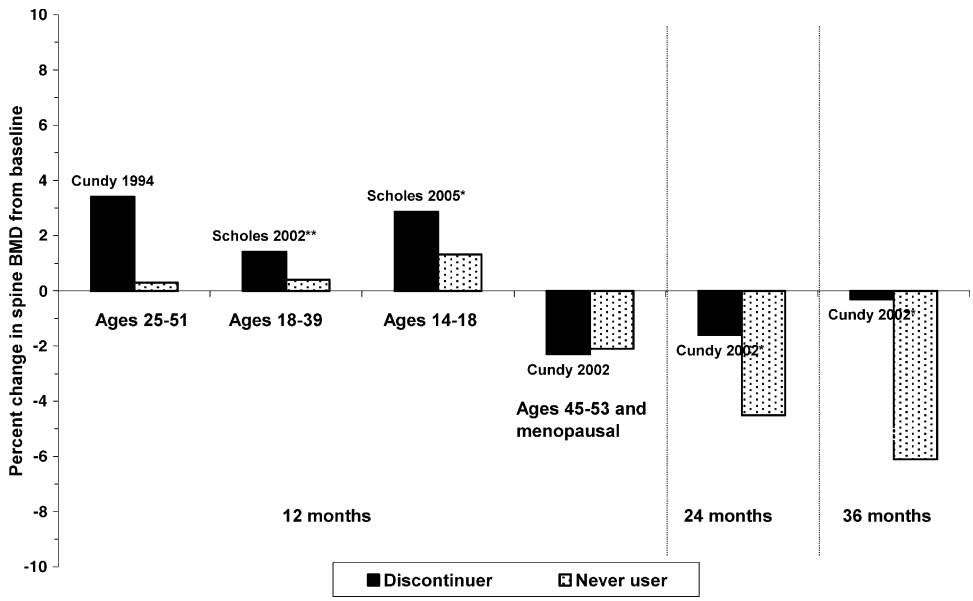

Fig. 5. Longitudinal studies of changes in BMD in the spine in adolescent and adult women who discontinued use of DMPA and in nonusers, by difference in mean percent change in BMD from baseline. *Significant difference between DMPA users and nonusers. **Statistical significance not reported.

3. Results

From 163 articles identified by the search strategy, 39 met the inclusion criteria. One study examined fracture as an outcome [6]. The other 38 studies examined BMD (Tables 1 and 2). Thirty-two studies examined use of DMPA [7–38], eight reports of seven studies examined levonorgestrel implants [15,18,23,31,39–42] and one study each examined etonogestrel implants [43], progestogen-only pills [44] and NET-EN [21]. We did not identify any studies that examined the effects of the levonorgestrel-releasing intrauterine system on fracture risk or BMD.

3.1. Fracture risk

In a longitudinal investigation of 3758 female US Army recruits, bone density was measured at baseline by using quantitative ultrasound of the heel and reported as the speed of sound (SOS) through bone [6]. Women were then followed for 8 weeks of basic training for occurrence of stress fractures. The mean age of the study population was 21.1 years (range 16–35 years); 169 DMPA users and 2629 nonhormonal users were included. DMPA use at baseline was associated with higher risk of stress fracture during follow-up only among non-Hispanic white women [relative risk (RR) 1.71; 95% CI 1.01–2.90]. However, the investigators reported that this association became nonsignificant when adjusted for SOS at baseline (RR and 95% CI not given). The relationship between DMPA use and SOS was not reported.

3.2. Current DMPA use and BMD

We identified 15 reports of cross-sectional studies [7–21] that examined current DMPA use and BMD in adult women, generally older than age 18 years (Table 1; Fig. 1); three reports did not contain enough information to include in the graph [18-20]. Overall, DMPA users had lower BMD than nonusers; *Z*-scores were generally greater than −0.5. The results suggested a trend of lower bone density with longer duration of DMPA use for the spine but not for the hip or forearm. However, information on duration was poorly reported and included wide ranges.

We identified seven longitudinal studies of changes in BMD among primarily adult DMPA users (Table 2) [22–28]. In one study, BMD measured in the forearm increased among the Norplant users, while the DMPA users had a nonsignificant decrease from baseline (0.41%) over 6 months [23]. Two studies examined whether administering estrogen to DMPA users would prevent bone loss [27,28]. One study found no significant differences in forearm BMD at baseline or over 12 months among 33 DMPA users and 10 nonusers, aged 30–45 years [28]. During the second year, seven DMPA users who had lost more than 1% bone mass in the first year received treatment with either calcium (1000 mg daily) or conjugated estrogens (0.625 mg every other day) for 12 months; by the end of 2 years, there were no differences in BMD for treated and nontreated DMPA users compared with baseline values. In the second study, 38 premenopausal women with low spinal BMD who were currently using DMPA were randomly assigned to receive conjugated estrogens (0.625 mg daily) ($n=19$) or placebo ($n=19$) [27]. At the end of 2 years, the treatment group had gained a mean 1% spinal BMD, and the placebo group had lost a mean 2.6% spinal BMD ($p<.002$); a similar trend of smaller magnitude was seen at other anatomic sites.

The remaining four longitudinal studies were directly comparable, i.e., they included a comparison group of women not using DMPA and reported spine or hip BMD (Fig. 2) [22,24–26]. Two studies enrolled continuing DMPA users [22,24], and two enrolled new users [25,26]. In all four studies, loss to follow-up was substantial (approximately 60% lost), due to loss from the study or change in contraceptive methods. All four studies reported decreases in BMD among DMPA users compared with BMD among nonusers over time; the magnitude and significance of the decreases varied by study. Cundy et al. [22] reported nonsignificant decreases in BMD after 12 months of follow-up (differences of −0.5% for the spine and 0.4% for the femoral neck between DMPA users and never users). Scholes et al. [24] reported an annualized mean rate of change in BMD for the spine and total hip over 3 years; DMPA users had a mean change in spinal BMD of −0.87% per year compared with 0.4% in nonusers (difference −1.27%), and a significant mean change of −1.12% for the total hip compared with −0.05% in nonusers (difference −1.07%). Berenson et al. [25] reported a significant adjusted mean 2.77% decrease in spinal BMD after 1 year and total decrease of 5.74% after 2 years, which represented a −7.54% difference from nonusers. Clark et al. [26] observed a decrease in hip BMD of 2.8% at Year 1 and 5.8% at Year 2 among DMPA users compared with a total change of "less than 1% in the nonusers"; BMD of the spine decreased 3.5% and 5.7% at Years 1 and 2, respectively, in DMPA users compared with a change of less than 0.4% in nonusers. Although the mean changes were relatively small in this study, participants who were in the upper quartile of total spine BMD loss had mean decreases of 6.8% and 9.0% at Years 1 and 2, respectively.

3.2.1. Young age (<18 years)

Two cross-sectional studies examined DMPA use among adolescent girls, primarily younger than 18 years of age (Table 1) [12,29]. In a cross-sectional analysis of 148 adolescents, aged 14–18 years, DMPA users had lower mean BMD in the hip, spine and whole body than did nonusers, although the differences were not significant (Fig. 3) [29]. Analysis of duration of DMPA use found a slight decreasing trend for BMD at the spine ($p=.06$) with greater number of injections, but not at the hip ($p=.21$) or whole body ($p=.71$). The second cross-sectional study enrolled 550 women aged 15–54 years and examined age at initiation of DMPA use [12]. Bone mineral density was 7.5% lower among DMPA users than among nonusers, but this deficit

Table 1
Cross-sectional studies of effects of current and past use of progestogen-only contraceptives on BMD

Author, year	Population [age (years), country]	Treatment group	Comparison group	Duration of use	Outcome	BMD measures	Results	Adjustments	Quality
Cross-sectional studies of current DMPA use									
Virutamasen et al., 1994 [19]	25–45, Thailand	75 DMPA users (3 groups)	147 nonusers	3–5, 6–7, >7 years	Trabecular bone pattern (Singh's index)	Radiograph of femoral neck	No difference	Age	II-3, Fair
Taneepanichskul et al., 1997 [16]	24–48, Thailand	50 DMPA users	50 IUD users	3–14 years	Mean BMD±SD	Distal and ultradistal forearm (DEXA)	No difference in mean BMD among DMPA Norplant, and IUD users	Age, BMI, income, parity	II-3, Fair
Taneepanichskul et al., 1997 [15]			41 Norplant users	Mean=59 months					
Paiva et al., 1998 [9]	20–45, Brazil	72 DMPA users	64 nonusers	≤1 year	Mean BMD±SD	Lumbar spine, femoral neck, Ward's triangle, trochanter (DEXA)	Mean BMD significantly lower at all sites; only mean BMD for lumbar spine >1 SD below standard normal population	None. Sub-analysis on 47 users and 47 controls matched on age and BMI	II-3, Fair
			Lifetime hormonal contraceptive use <2 years	Mean=42 months	% with BMD*T*-score <−1				
Gbolade et al., 1998 [11]	17–52, United Kingdom	185 DMPA users	–	1–16 years	Mean BMD (95% CI)	Lumbar spine, femoral neck (DEXA)	Mean BMD for lumbar spine significantly lower compared with standard normal population; no difference in femoral neck BMD	Age	III, Fair
				Median=5 years	Z-score based on standard normal population				
Cundy et al., 1998 [12]	15–54, New Zealand	200 DMPA users	350 nonusers from other studies	2–26 years	Mean BMD*Z*-score (95% CI)	Lumbar spine (DEXA)	*Z*-score −0.65 (95% CI −0.80, −0.49); women starting DMPA at age <21 years and who used DMPA for >15 years had the lowest *Z*-scores	None	II-3, Fair
				Median=12 years					
Tang et al., 1999 [20]	34–46, Hong Kong	67 DMPA users	218 nonusers	5–15 years	Mean BMD	Lumbar spine, femoral neck, Ward's triangle, trochanter (DEXA)	Mean BMD significantly lower in all sites	None; no significant differences in baseline characteristics	II-3, Fair
				Median=6 years					

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Table 1 (*continued*)

Author, year	Population [age (years), country]	Treatment group	Comparison group	Duration of use	Outcome	BMD measures	Results	Adjustments	Quality
Cross-sectional studies of current implant use									
Scholes et al., 1999 [8]	18–39, United States	183 DMPA users	274 nonusers	1–133 months	Mean BMD±SE	Lumbar spine, femoral neck, trochanter, whole body (DEXA)	Mean BMD significantly lower in all sites for ages 18–21 years; not significantly decreased for other age groups	Age; DMPA users more likely to be nonwhite, smokers, physically active	II-3, Fair
Bahamondes et al., 1999 [17]	35–45, Brazil	50 DMPA users	50 nonhormonal users	≥1 year Mean=46.4 months	Mean BMD±SD	Midshaft and distal forearm (SXA)	Mean BMD significantly lower at distal forearm and nonsignificantly lower at midshaft	Age, weight, race	II-3, Fair
Pettiti et al., 2000 [18]	30–34, 7 countries	133 DMPA users	652 nonhormonal users	≥2 years; median=3 years	Mean BMD	Distal radius, midshaft ulna (SXA)	Mean BMD was significantly lower in both sites, but <1 SD	Age, BMI	II-3, Fair
Ott et al., 2001 [7]	18–39, United States	115 DMPA users	72 nonhormonal users	Not provided	Mean BMD±SD	Lumbar spine, whole body, proximal femur (DEXA)	No significant difference	None; more DMPA users (56.5%) ever pregnant than nonusers (30.6%)	II-3, Fair
Perrotti et al., 2001 [14]	30–34, Brazil	63 DMPA users	63 never users	≥2 years; mean=42 months	Mean BMD±SD	Distal and ultradistal forearm (SXA)	No significant difference in BMD	Age; stratified by race	II-3, Fair
Tharnprisarn et al., 2002 [13]	15–30, Thailand	30 DMPA users	30 OC users	≥ 2 years Mean=25 months	Mean BMD±SD	Distal and ultradistal forearm (DEXA)	No significant difference in BMD	None; no significant differences in baseline characteristics	II-3, Fair
Wanichsetakul et al., 2002 [10]	30–34, Thailand	34 DMPA users	62 nonusers No use of hormonal contraceptives for >6 months	2–10 years Mean=56 months	Mean BMD±SD	Lumbar spine, femoral neck, Ward's triangle, trochanter, ultradistal and distal radius (DEXA)	Mean BMD significantly lower in lumbar spine; no differences at other sites	None; no significant differences in baseline characteristics	II-3, Fair
Scholes et al., 2004 [29]	14–18, United States	81 DMPA users	93 nonusers	1–13 injections Median=3 injections	Mean BMD±SE	Proximal femur, posterior–anterior lumbar spine, whole body (DEXA)	Mean BMD at all sites not significantly lower, after adjustment for confounding variables. Nearly significant trend (p=.06) in lower BMD for spine with longer duration DMPA use	Age, BMI, ethnicity, smoking, calcium intake, weight-bearing activity	II-3, Fair
Beksinska et al., 2005 [21]	40–49, South Africa	127 DMPA users	161 nonhormonal users	Median 84 months	BMD (g/cm^2) and 95% CI	Radius and ulna (DEXA)	No significant differences in BMD	None for difference in BMD	II-3, Fair

Cross-sectional studies of past DMPA use									
Orr-Walker et al., 1998 [37]	60 (mean), New Zealand	34 DMPA users	312 never users	Median = 3 years	Mean BMD ± SE	Lumbar spine, femoral neck, Ward's triangle, trochanter, whole body (DEXA)	No significant difference in BMD	Age, body weight	II-3, Fair
Petitti et al., 2000 [18]	30–34, 7 countries	32 DMPA users	652 never users	Median < 3 years	Difference in BMD from never users (g/cm^2)	Distal radius and midshaft (SXA)	No significant difference in BMD	Center, age, BMI, years of lactation, years since last lactation, partner's occupation	II-3, Fair
Vanderjagt et al., 2005 [42]	23–50, Nigeria	90 Norplant users	25 nonhormonal users	1–4 years	Difference in ultrasound measurements	Quantitative ultrasound of heel bone, stiffness index	No differences between Norplant users and nonhormonal users	Age, BMI	II-3, Fair
Petitti et al., 2000 [18]	30–34, 7 countries	261 Norplant users	652 never users	Median = 4.2 years	Difference in BMD from never users (g/cm^2)	Distal radius and midshaft (SXA)	Mean BMD significantly lower at midshaft and nonsignificantly lower at distal radius; all changes < 1 SD from never users	Center, age, BMI, years of lactation, years since last lactation, partner's occupation	II-3, Fair
Taneepanichskul et al., 1997 [15]	19–48, Thailand	41 Norplant users (> 1 year)	50 DMPA users	Mean = 2.6 years	Mean BMD ± SD (or SE — not stated)	Distal and ultradistal forearm (DEXA)	No significant differences between Norplant users, DMPA users and IUD users	None	II-3, Fair
Intaraprasert et al., 1997 [39]			50 IUD users						
Cross-sectional studies of past implant use									
Petitti et al., 2000 [18]	30–34, 7 countries	47 past Norplant users	652 never users	24–36 months (n = 9); 37–48 months (n = 7); 48+ months (n = 31)	Difference in BMD from never users (g/cm^2)	Distal radius and midshaft (SXA)	No significant difference in BMD	Center, age, BMI, years of lactation, years since last lactation, partner's occupation	II-3, Fair
Cross-sectional studies of current NET-EN use									
Beksinska et al., 2005 [21]	40–49, South Africa	102 NET-EN users	161 nonhormonal users	Median = 49 months	BMD (g/cm^2)	Radius and ulna (DEXA)	No significant difference in BMD	None	II-3, Fair

BMI: body mass index; DEXA: dual energy x-ray absorptiometry; SE: standard error; SXA: single X-ray absorptiometry; OC: oral contraceptives; CI: confidence interval.

Table 2
Longitudinal studies of effects of current and past use of progestogen-only contraceptives on BMD

Author, year	Population [age (years), country]	Treatment group	Comparison group	Duration of use before study	Follow-up	Outcome	BMD measures	Results	Adjustments	Quality
Longitudinal studies of current DMPA use										
Cundy et al., 1994 [22]	25–51, New Zealand	(1) 14 DMPA users discontinued during follow-up (2) 22 continuing DMPA users	17 never users	Median = 10 years for both groups	2 years	% change in BMD (95% CI)	Lumbar spine, femoral neck (DcXA)	Mean BMD lower at baseline (significant at spine, not at femoral neck); no change at follow-up (median 12 months)	None	II-2, Fair
Naessen et al., 1995 [23]	20–45, Sweden; RCT	9 DMPA initiators	10 Norplant initiators	Initiators	6 months	% change in BMD (95% CI)	Distal and proximal forearm (SPA)	Nonsignificant decrease from baseline in mean BMD at 6 months	None	I, Fair
Cromer et al., 1996 [31]	12–21, United States	15 DMPA initiators	17 nonhormonal users	Mean = 2.2 years at baseline	2 years	% change in BMD (95% CI)	Lumbar spine (DEXA)	Mean BMD significantly decreased at Years 1 and 2	Age, race, exercise, weight	II-2, Fair
Merki-Feld et al., 2003 [28]	30–45, Switzerland	36 DMPA users	10 nonusers	Mean = 42.2 months	1 year	Mean BMD (SD); annual % change	Radius (peripheral quantitative computed tomography)	No significant changes over 12 months	Duration of DMPA use, age, smoking, BMI, weight, calcium intake, physical activity, gravidity, lactation, age at menarche, estradiol levels	II-2, Poor
Tang et al., 2000 [36]	37–49, China	59 continuing DMPA users	–	Mean = 10 years (range 8–18)	3 years	Annual % change in BMD (95% CI) *Z*-scores	Lumbar spine, femoral neck, Ward's triangle, trochanter (DEXA)	Significant decrease in BMD at all sites over 3 years, except trochanter; *Z*-scores at year 3 smaller than at baseline	None	II-3, Poor
Scholes et al., 2002 [24]	18–39, United States	72 continuing DMPA users 110 discontinued DMPA use during follow-up	258 nonusers (includes COC users)	Baseline: median = 11.3 months (range 0.3–133)	3 years Measurements every 6 months	Annualized % change in BMD (95% CI)	Lumbar spine, total hip, whole body (DEXA)	Mean BMD decreased over 3 years; greatest decrease in first year; discontinuers of DMPA gained BMD and were similar to non-DMPA users at end of follow-up	Age, ethnicity, smoking, weight, calcium intake	II-2, Good
Busen et al., 2003 [30]	15–19, United States	6 DMPA initiators	–	Initiators	2 years; loss 73% at Year 1 and 82% at Year 2	Annual % change in BMD (95% CI)	Lumbar spine, femoral neck (DEXA)	Mean BMD decreased significantly at both sites in Year 1 and nonsignificantly at Year 2	None	II-3, Poor

Longitudinal studies of current DMPA use

Cundy et al., 2003 [27]	<45, New Zealand	19 women randomized to DMPA+0.625 mg conjugated estrogen daily	19 women randomized to DMPA+placebo pill	Median = 11 years	2 years	Mean % change in BMD	Spine, femur, total body by DEXA at baseline, 6, 12, 18 and 24 months	DMPA/E group gained 1% BMD at spine, while DMPA/ placebo group lost 2.6% BMD over 2 years	Groups well-matched at baseline	I, Fair
Lara-Torre et al., 2004 [32]	12–21, United States	58 DMPA initiators	19 nonhormonal users 71 COC users	Initiators	2 years	% change in BMD (95% CI)	Lumbar spine (DEXA) at 6, 12, 18 and 24 months	Mean BMD (6 months) and median BMD (12–24 months) decreased among DMPA users during 2 years vs. COC users and controls	None	II-2, Fair
Berenson et al., 2004 [25]	18–33, United States	47 DMPA users	86 COC users 58 nonhormonal users	Initiators	2 years	% change in BMD (95% CI)	Lumbar spine (L1–L4) by DEXA at baseline, 12 and 24 months	DMPA users averaged 5.7% loss from 0 to 24 months compared with controls; linear trend in BMD loss from 0 to 24 months ($p < .001$)	Age, race/ethnicity, exercise, calcium intake, smoking, BMI	II-2, Good
Cromer et al., 2004 [33]	12–18, United States	370 DMPA initiators	152 abstinent or nonhormonal users	Initiators	12 months	Mean % change in BMD and BMAD (SD)	Spine, femoral neck	Mean BMD decreased 1.4% at the spine and 2.2% at the femoral neck, significantly different from increases of 3.8% at the spine and 2.3% at the femoral neck for controls	Race, chronological age, body weight	II-2, Good
Clark et al., 2004 [26]	18–35, United States	178 DMPA initiators	145 nonhormonal users	Initiators	24 months	Mean % change in BMD (SD)	Spine, total hip	Mean BMD decreased significantly at spine and hip, rate of loss slowed over 24 months at spine but not at hip	None for mean change	II-2, Good
Scholes et al., 2005 [34]	14–18, United States	80 DMPA users at baseline	90 nonusers at baseline	30% new users; median = 12 months among current users	24–36 months	Mean change in BMD (95% CI)	Hip, spine, whole body by DEXA at baseline, 6, 12, 18, 24, 30 and 36 months	Decreased BMD in DMPA users over time compared with nonusers at hip and spine, but not total body	BMD at baseline, ethnicity, pregnancy, age at menarche, age, smoking, calcium, body fat	II-2, Good
Cromer et al., 2005 [35]	12–18, United States	65 randomly assigned to DMPA+monthly injections of 5 mg estradiol cypionate	58 randomly assigned to DMPA+monthly injections of saline (placebo)	Initiators	12–24 months	Mean % change in BMD and BMAD	Spine, femoral neck by DEXA at baseline, 12, 24 months	Significantly lower BMD for DMPA/ placebo users at 12 and 24 months than DMPA/E users	Body weight, baseline BMD	I, Fair

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Table 2 (*continued*)

Author, year	Population [age (years), country]	Treatment group	Comparison group	Duration of use before study	Follow-up	Outcome	BMD measures	Results	Adjustments	Quality
Longitudinal studies of past DMPA use										
Cundy et al., 1994 [22]	25–51, New Zealand	14 DMPA users, stopped at start of study	17 never users	Median = 10 years	2 years	BMD (95% CI)	Lumbar spine, femoral neck (DEXA)	At 1- and 2-year follow-up, significant increase in spine BMD in past DMPA users	None	II-2, Fair
Cundy et al., 2002 [38]	45–55, New Zealand	16 past DMPA users; 5 with HRT and 11 with no HRT	15 never users, no HRT	Median = 12 years	3 years	Mean change in BMD ± SD	Lumbar spine, femoral neck (DEXA)	Non-HRT group maintained BMD over 3 years, except for significant loss at spine at Year 1; HRT group gained BMD over 3 years; control group significantly lost BMD over 3 years	None	II-2, Fair
Scholes et al., 2002 [24]	18–39, United States	110 discontinued DMPA use during follow-up	258 nonusers (includes COC users)	Baseline: median = 11.3 months (range 0.3–133)	3 years Measurements every 6 months	Annualized % change in BMD (95% CI)	Lumbar spine, total hip, whole body (DEXA)	DMPA discontinuers gained BMD, similar to non-DMPA users at end of follow-up	Age, ethnicity, smoking, weight, calcium intake	II-2, Good
Scholes et al., 2005 [34]	14–18, United States	80 DMPA users at baseline, 61 discontinued during the study	90 nonusers	3–62 months, with 98% having at least 6 months of use	Mean = 14 months	Mean change in BMD (95% CI)	Hip, spine, whole body by DEXA at baseline, 6, 12, 18, 24, 30, 36 months	Discontinuers gained more bone than nonusers during follow-up and reached levels at least as high as those of nonusers	Baseline BMD, ethnicity, pregnancy, age at menarche, age, smoking, calcium, body fat	II-2, good
Longitudinal studies of past DMPA use										
Naessen et al., 1995 [23]	20–45, Sweden, RCT	10 Norplant initiators	9 DMPA initiators	6 months	6 months	% change in BMD (95% CI)	Distal and proximal forearm (SPA)	Significant increase in mean BMD at 6 months	None	I, Fair

Cromer et al., 1996 [31]	12–21, United States	7 Norplant users	17 nonhormonal users	Mean = 2.7 years at baseline	2 years	% change in BMD (95% CI)	Lumbar spine (DEXA)	Mean BMD increased at Years 1 and 2, similar to controls	Age, race, exercise, weight	II-2, Fair
Di et al., 1999 [40]	25–40, China; RCT	29 Norplant initiators	31 domestic implants/initiators (China)	1 year	1 year	% change in BMD	Lumbar spine, proximal femur (DEXA)	Significant increases in BMD over 1 year (2.4% increase in spine for Norplant users); no significant differences between Norplant and Chi nese implant users	None	I, Fair
Diaz et al., 1999 [41]	18–35, lactating women; Chile	29 Norplant initiators	51 IUD initiators	Initiators	12 months postpartum and 12 months after weaning	Mean BMD±SE	Whole body, lumbar spine, femoral neck, trochanter (DEXA)	No significant differences during lactation or weaning	None	II-2, Fair
Beerthuizen et al., 2000 [43]	18–40, Netherlands, Chile, Finland	46 Implanon initiators	30 IUD users	Initiators	2 years	Mean BMD±SD	Lumbar spine, femoral neck, Ward's triangle, trochanter, distal radius (DEXA)	No significant differences over 2 years	None	II-2, Fair
Longitudinal studies of current and past use of progestogen-only pills in lactating women										
Caird et al., 1994 [44]	28–41, United Kingdom	9 lactating POP users	12 lactating, barrier method users	Initiators	12 months	Mean BMD±SE	Lumbar spine (DEXA)	POP users lost significantly less BMD than barrier methods users at 6 months, and at 1 year had higher BMD than at baseline	None	II-2, Fair

RCT: randomized controlled trial; SPA: single photon absorptiometry; BMAD: bone mineral apparent density; POP: progestogen-only pills.

was magnified for women who started DMPA use before age 21 years and for those who began to use DMPA before age 21 years and used it for 15 years or more.

Six longitudinal studies examined DMPA use and BMD among adolescents (Table 2) [30–35]. One small noncomparative study reported statistically significant BMD losses in the spine and femoral neck from baseline of about 3.5% at 1 year and 2.5% at 2 years [30]. However, this study was limited severely by small sample size and large loss to follow-up. Another study randomized new DMPA users, aged 12 to 18 years, to monthly injections of estradiol cypionate ($n=65$) or monthly placebo injections ($n=58$) [35]. After 24 months, the group receiving estradiol cypionate had gained 2.8% BMD at the spine, whereas the placebo group had lost 1.8% ($p<.001$); at the femoral neck, the group receiving estradiol cypionate had gained 4.7% BMD and the placebo group had lost 5.1% ($p<.001$).

The other four longitudinal studies included comparison groups of participants who were not using DMPA (Fig. 4) [31–34]. All of these studies found significant decreases in BMD in DMPA users compared with nonusers over time. Cromer et al. [31] studied 15 DMPA users and 17 nonhormonal users, ages 12–21 years, and reported statistically significant decreases in mean spine BMD over 2 years; the mean percent difference in BMD between the two groups was −4.38% at Year 1 and −12.61% at Year 2. This difference was due to both loss of BMD in the users (−3.12% at Year 2) and gain in the nonusers (9.49% at Year 2). Lara-Torre et al. [32] studied 58 DMPA initiators, 19 nonhormonal users and 71 COC users, and found significant mean BMD decreases in DMPA users compared with those in nonusers at 6, 12, 18 and 24 months (there were no differences between COC users and nonhormonal users). By 24 months, DMPA users had lost a mean 1.85% BMD and nonusers had gained a mean 5.89% BMD. Cromer et al. [33] enrolled 53 DMPA users, 165 OC users and 152 nonhormonal or abstinence users, ages 12 to 18 years, and found a mean 1.4% decrease in spinal BMD among DMPA users after 12 months compared with a mean 3.8% increase in the nonuser group; for the femoral neck, there was a mean 2.2% decrease in the DMPA users and a mean 2.3% increase in the nonusers. Scholes et al. [34] studied 170 adolescents aged 14 to 18 years who were either current DMPA users ($n=80$, 30% new users, 70% current users with mean duration of use about 12 months) or who were not using DMPA ($n=90$); 78% of participants completed 24 months of follow-up. After adjustment for covariates, the annualized mean percent change over 24 months in DMPA users was −1.81% at the hip, −0.97% at the spine and 0.73% for the whole body. Among nonusers, the mean percent changes were −0.19%, 1.32% and 0.88% for the hip, spine and whole body, respectively.

3.2.2. Older age (>45 years)

Three studies examined BMD among women of older reproductive age, currently using DMPA (Tables 1 and 2) [11,20,36]. A cross-sectional study included 185 DMPA users in the United Kingdom, aged 17–52 years [11]. For women aged 40–49 or 50–52 years, there were no significant differences in BMD compared with the normal population mean (Caucasian women from the UK, US and Scandinavia). In a second cross-sectional study, 67 Chinese women (mean age 43 years) who had used DMPA for 5 years or more had significantly lower levels of BMD at the spine, femoral neck, trochanter and Ward's triangle than 218 women who had never used DMPA (mean age 40 years) [20]. A prospective follow-up of 59 DMPA users from this study over 3 years found small but statistically significant losses of BMD at the lumbar spine (−0.4%), femoral neck (−0.4%) and Ward's triangle (−1.05%), but not of the trochanter (0.1%, not significant) [36]. However, *Z*-scores were smaller at follow-up, suggesting that although the study population lost BMD over the follow-up period, they may have lost less BMD than the standard normal population. No effect was seen with duration of DMPA use, except for a weak correlation between duration of DMPA use and mean BMD at the femoral neck ($r=-0.265$; $p=.043$).

3.2.3. Duration of DMPA use and rate of BMD change

Two studies that enrolled continuing DMPA users examined loss of BMD by duration of use [24,36]. One found no differences by duration of use [36]. The other reported that the mean amount of change in BMD decreased with increasing cumulative DMPA use and that those with 1 year or less of DMPA exposure had a higher rate of loss than those with more than 1 year of use [24].

Three studies that enrolled women who were initiating DMPA were able to directly observe the rate of change in BMD [25,26,34]. Berenson et al. [25] reported an adjusted mean 2.77% decrease in spinal BMD during Year 1 and an adjusted mean 3.24% decrease during Year 2, implying greater loss during the second year than the first, although confidence intervals overlapped. Clark et al. [26] observed that the rate of loss of hip BMD among DMPA users was linear throughout the 2-year follow-up, but the rate of loss of spinal BMD was not linear and seemed to decelerate at approximately 18 months of DMPA use. In the only study to examine the rate of change in BMD among adolescents, new users lost more BMD than continuing users, and the adjusted mean change in BMD decreased with increasing cumulative use of DMPA [34].

3.3. Past DMPA use and recovery of BMD

We identified two cross-sectional studies that examined recovery of BMD in adult women who had discontinued DMPA use (Table 1) [18,37]. Among 346 postmenopausal women (mean age 60 years), 10% reported prior use of DMPA for a mean of 3 years and a median age of 45 years at discontinuation (median 2 years before menopause) [37]. No significant differences were observed in mean BMD for former DMPA users and nonusers for any of five sites

(lumbar spine, femoral neck, Ward's triangle, trochanter and total body). No correlation was found between mean BMD and duration of DMPA use, age at initiation of DMPA use, age at discontinuation of DMPA, or time between discontinuation and menopause. The second cross-sectional study examined BMD in 32 former DMPA users and 695 women who had never used hormonal contraceptives; no difference in forearm BMD was found, even for those who had used DMPA for 4 years or more [18].

Three longitudinal studies examined recovery of BMD after discontinuation of DMPA use in adults (Table 2; Fig. 5) [22,24,38]. Cundy et al. [22] studied 14 women (median age 41 years, range 25–49) who had discontinued DMPA use (median duration of use 10 years, range 3–17 years) and 18 never users (median age 44 years, range 26–51). After 1 year of follow-up, the former DMPA users gained 3.4% spinal BMD ($p<.001$ from baseline) compared with 0.3% among the never users (nonsignificant from baseline). Bone mineral density in the femoral neck increased by 0.8% among the former users compared with a decrease of 1.5% for never users, a nonsignificant difference. Among eight former DMPA users who completed 2 years of follow-up, the mean increase in spinal BMD was 3.0% at 12 months and 6.4% at 24 months. The study of Scholes et al. [24] found that DMPA discontinuers gained bone throughout follow-up at rates greater than those for nonusers, regardless of duration of DMPA use. The annualized mean percent changes in BMD were 1.41% per year for the spine among women who had discontinued DMPA compared with 0.40% for nonusers, and 1.03% and −0.05% at the hip for those who discontinued and for nonusers, respectively. By about 30 months after discontinuation, former DMPA users had BMD levels similar to those of nonusers, although BMD of the hip was recovered more slowly than spinal BMD. A third longitudinal study examined BMD in former DMPA users, aged 45 to 55 years, who had used DMPA for at least 5 years and who had reached menopause — five women discontinued DMPA and started hormone replacement therapy (HRT); 11 women discontinued DMPA and did not use HRT; and 15 women had undergone natural menopause, had never used DMPA and did not use HRT during the study period [38]. At baseline, the mean BMD was 10% lower in the spine and 15% lower in the hip among the former DMPA users than among never users. During follow-up, former DMPA users not using HRT had stable BMD measurements at the spine and hip at Years 1, 2 and 3, with the exception of a statistically significant loss of BMD in the spine at Year 1 (−2.3%). The five women who had used DMPA and subsequently used HRT gained BMD at both sites, with statistically significant increases in Years 2 and 3. In contrast, the control group had statistically significant decreases in BMD at both sites over all 3 years. The authors hypothesized that there is an estrogen-sensitive component of bone that is lost during DMPA use, and that this is the same component lost early in menopause. Therefore, DMPA users may have already experienced loss of BMD due to estrogen-deficiency and do not experience the rapid bone loss of early menopause.

3.3.1. Adolescents

In the only study to look at recovery of BMD after discontinuation of DMPA among adolescents (14–18 years) [34], 38 girls who discontinued DMPA had significantly greater increases in BMD at 12, 18 and 24 months at the spine, hip and whole body compared with 84 nonusers (Table 2; Fig. 5). The annualized adjusted mean percentage changes in BMD among discontinuers were 1.34%, 2.86% and 3.56% for the hip, spine and whole body, respectively, compared with −0.19%, 1.32% and 0.88% for the same sites in nonusers. Discontinuers continued to gain BMD throughout follow-up, and the amount of gain did not differ by the duration of DMPA use. By 12 months of follow-up, adjusted mean BMD values for discontinuers were at least as high as those for nonusers at all sites and at all subsequent follow-up periods.

3.4. Other progestogen-only methods

Three reports of two cross-sectional studies and five longitudinal studies of current users of progestogen-only implants (primarily Norplant, but one study of Implanon) found either no significant differences in BMD (or, in one study, in quality of bone as measured by calcaneal ultrasound) or increases in BMD compared with nonusers.[15,23,31,39–43] However, in the largest cross-sectional study of 610 Norplant users and 695 nonhormonal users, mean BMD at the midshaft of the ulna was lower among exclusive users of Norplant than among nonhormonal users [18]. This difference was statistically significant, but was within 1 SD of the mean BMD in the nonusers. This study also examined past use of Norplant and found no significant difference in BMD at the forearm compared with never users [18]. The single study of Implanon followed 44 Implanon users and 29 non-hormone-medicated intrauterine device (IUD) users for 2 years and found no differences in BMD (spine, femoral neck, Ward's triangle, trochanter, distal radius) between baseline and follow-up or between Implanon and IUD users [43]. The only study of progestogen-only pill use evaluated breast-feeding women and found that pill users lost less BMD than nonusers [44]. The only study of NET-EN also showed no difference in BMD between NET-EN users and nonhormonal users in a cross-sectional analysis [21].

4. Discussion

4.1. Does use of progestogen-only contraceptives affect fracture risk?

Information on progestogen-only contraceptive use and fracture risk is limited to one study that did not find a significant association between DMPA use and risk of stress fracture in female military recruits, after controlling for baseline bone density, as measured by quantitative ultra-

sound [6]. It is possible that at study entry, DMPA users had lower bone density than nonusers, which may have led to greater fracture risk in the DMPA users. Unfortunately, no information on the association between baseline bone density and DMPA use was given.

4.2. Does current use of progestogen-only contraceptives affect BMD?

Overall, current DMPA users had lower mean BMD than nonusers did and greater declines in BMD over time. The amount of the deficit varied among studies; some found statistically significant differences in BMD between DMPA users and nonusers and others did not. Among the cross-sectional studies, the deficits in BMD among DMPA users were generally within 1 SD of the mean BMD for the nonusers. In the longitudinal studies of adult women, rates of change in BMD over time differed; most of the studies enrolled continuing DMPA users and reported decreases of less than 1% per year. However, the two studies that enrolled women initiating DMPA use found larger decreases of about 2–3% per year [25,26]. Studies that examined rate of BMD loss by duration of DMPA use showed either no effect of duration or that the rate of loss decreased over time, with the greatest amount of loss during the first year of use [24–26,36].

Results from two cross-sectional studies and six longitudinal studies among adolescents showed decreased BMD in current DMPA users compared with that for nonusers [12,29–35]. Findings in one of these studies suggested that initiation of DMPA before age 21 was associated with decreased BMD, especially for duration of use longer than 15 years [12]. The differences in BMD in DMPA users and nonusers were due to loss of BMD in the users and gain in BMD in the nonusers, and ranged from 2% to 3% for the first year of DMPA use. Although this range is higher than those reported in many of the adult studies of DMPA use and BMD, it is comparable to those for adult studies that enrolled women initiating DMPA use; all of the adolescent studies enrolled DMPA initiators. One study examined the rate of BMD loss among adolescent DMPA users and found that new users lost more BMD than continuing users did; the adjusted mean change in BMD decreased with increasing cumulative use of DMPA [34].

Data are limited, but studies of current users of progestogen-only contraceptives other than DMPA generally reported no differences in BMD for users compared with that for nonusers. Women using levonorgestrel implants had similar or higher BMD compared with that for nonusers [15,23,31,39–42], with the exception of a large cross-sectional study that reported small but statistically significant lower BMD for Norplant users compared with that for nonusers [18].

4.3. Do former DMPA users regain BMD after DMPA discontinuation?

Studies that examined recovery of BMD among women discontinuing DMPA use reported increases in BMD, generally at rates higher than those for nonusers [22,24,34]. Evidence suggests that spinal BMD may be recovered more quickly or in greater amounts than hip BMD [22,24,34]. In one of the adult studies, former DMPA users had similar levels of BMD in the spine and hip than never users by 30 months after discontinuation [24]. In a study of adolescents, mean BMD levels for participants who discontinued DMPA reached the levels of those who had never used DMPA by 12 months [34]. Limited evidence suggests that women who discontinue DMPA use before menopause can regain lost bone mass, that women who discontinue DMPA when they reach menopause do not experience the rapid period of bone loss that non-DMPA users experience and that postmenopausal women who previously used DMPA have BMD levels similar to those of women who have never used DMPA [37,38]. These findings need to be confirmed in larger studies with longer follow-up. No studies have examined fracture risk in postmenopausal women or BMD in the later postmenopausal years, when fracture risk is highest, among former DMPA users. No studies of progestogen-only methods other than DMPA examined changes in BMD after discontinuation of the contraceptive method.

4.4. Limitations

A primary limitation of this body of evidence is the lack of information about the relevant clinical outcome — fracture risk. The only study identified that examined fracture risk had several limitations and reporting problems [6]. Without knowing the final adjusted relative risk for DMPA use, the baseline BMD values, and whether other potential confounders were included, it is difficult to interpret these results. The body of evidence on fracture was therefore given a quality rating of "II-2, Poor." The body of evidence on progestogen-only contraceptive use and BMD also has several limitations including differences in the quality of the study designs (e.g., longitudinal vs. cross-sectional), site of BMD measurement, adjustment for confounding, duration of participant follow-up and loss to follow-up, inclusion of a control group and choice of controls, and demographic differences in population groups studied. Overall, the cross-sectional studies received a "II-3, Fair" quality rating and the longitudinal studies received a "II-2, Fair" quality rating.

Because of the lack of evidence on the potential effects of progestogen-only contraceptive use on risk of fracture, the clinical significance of the observed changes in BMD remains unclear. The findings indicate that DMPA users lose BMD, but this loss is generally less than 10% or within 1 SD from the mean BMD in the nonusers, and BMD remains within the normal range [5]. It is unclear whether BMD serves as a good surrogate for subsequent fracture risk among premenopausal women [45,46]. Bone mineral density is only one marker of bone strength and does not take into account bone size or bone architecture [47]. Loss of BMD during DMPA use may be analogous to changes in BMD during pregnancy and lactation. Evidence suggests that women fully recover bone that is lost during pregnancy

and lactation, and parity and cumulative duration of breast-feeding have generally not been associated with later decreased BMD or increased fracture risk [48–50]. A study of adolescent mothers suggested that those who breast-fed subsequently had higher BMD values of the proximal femur than adolescent mothers who did not breast-feed, and BMD values similar to those of nulliparous adolescents [51].

5. Conclusion

Depot medroxyprogesterone acetate users have lower BMD than nonusers, but deficits are usually within 1 SD of the mean BMD of nonusers, so the clinical significance of these findings is unclear. The differences in BMD among adults were almost completely due to decreased BMD in DMPA users; in adolescents, differences in BMD were due to decreased BMD in DMPA users as well as increased BMD in nonusers. Recovery of BMD occurs after discontinuation of DMPA, most likely at rates higher than those in nonusers. However, it is still unclear whether adult women can regain BMD to baseline levels and whether adolescents can reach peak bone mass after discontinuation of DMPA. The relationship between these changes in BMD during the reproductive years and future fracture risk is unknown. Although evidence is limited, women using other forms of progestogen-only contraceptives do not appear to have lower BMD than nonusers.

Acknowledgments

This review was supported by resources from the World Health Organization, the US Centers for Disease Control and Prevention (CDC), the US Agency for International Development (USAID) and the US National Institute of Child Health and Human Development (NICHD).

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the funding agencies.

Appendix A. Study quality assessment

Individual study: Each study was given a rating of either Level 1, Level II-1, Level II-2, Level II-3, Level III based on the study design (Appendix Table 1). Each study was also given a rating of poor, fair or good based on the criteria for grading the internal validity of a study (Appendix Table 2). A good study meets all criteria for that study design; a fair study does not meet all criteria but is judged to have no fatal flaw; and a poor study contains a fatal flaw.

Body of evidence: The quality of the body of evidence was the highest rating given to an individual study. If the results were inconsistent, the quality of the body of the evidence was lowered by one level, if results were consistent, then the quality of the body of the evidence was left at the original level.

Appendix Table 1
Levels of evidence

Levels of evidence	
Level 1	Evidence obtained from at least one properly designed randomized controlled trial.
Level II-1	Evidence obtained from well-designed controlled trials without randomization.
Level II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
Level II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be due to this type of evidence.
Level III	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert communities.

Source: US Preventive Services Task Force. Guide to clinical preventive services, 2nd ed. Alexandria, Virginia: International Medical Publishing, 1996. p. 862.

Appendix Table 2
Criteria for grading the internal validity of individual studies

Study design	Criteria
Systematic reviews	Comprehensiveness of sources/search strategy used. Standard appraisal of included studies. Validity of conclusions. Recency and relevance.
Case-control studies	Accurate ascertainment of cases. Nonbiased selection of cases/controls with exclusion criteria applied equally to both. Response rate. Diagnostic testing procedures applied equally to each group. Appropriate attention to potential confounding variables.
Randomized controlled trials (RCTs) and cohort studies	Initial assembly of comparable groups: For RCTs: adequate randomization, including concealment and whether potential confounders were distributed equally among groups. For cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts. Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination). Important differential loss to follow-up or overall high loss to follow-up. Measurements: equal, reliable and valid (includes masking of outcome assessment). Clear definition of interventions. All important outcomes considered. Analysis: adjustment for potential confounders for cohort studies, or intention-to-treat analysis for RCTs.
Diagnostic accuracy studies	Screening test relevant, available for primary care, adequately described. Study uses a credible reference standard, performed regardless of test results. Reference standard interpreted independently of screening test. Handles indeterminate results in a reasonable manner. Spectrum of patients included in study. Sample size. Administration of reliable screening test.

Source: Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med 2001;20(3 Suppl):21–35.

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