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# Prevalence of Low Bone Mass and Osteoporosis in Long-Term Users of the Injectable Contraceptive Depot Medroxyprogesterone Acetate

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## Abstract

***Background:*** Bone mineral density (BMD) loss among depot medroxyprogesterone acetate (DMPA) users is a controversial issue. Aspects under debate include whether the number of years of use has any effect on continuous BMD loss, whether this loss will stabilise over the years of use or if it will progress to low bone mass, osteoporosis and an increased fracture risk. The aim of this study was to compare the difference in osteoporosis and low bone mass between DMPA and copper intrauterine device (Cu-IUD) users.
***Methods:*** This was a cross-sectional study that evaluated BMD at the lumbar spine and femoral neck in 47 long-term DMPA users and 41 Cu-IUD users as control group. BMD was measured by dual-energy X-ray absorptiometry. The participants were 27 to 57 years of age, had used either DMPA or a Cu-IUD uninterruptedly for at least ten years, had initiated use of the method prior to 40 years of age and had follicle stimulating hormone values <40 mIU/mL.
***Results:*** Findings showed that 68.1% and 36.6% of the DMPA and Cu-IUD users, respectively, had low bone mass and 29.8% and 2.4% of DMPA and Cu-IUD users, respectively, had osteoporosis. BMD decreased as the number of years of DMPA use increased.
***Conclusion:*** Long-term DMPA use was associated with low bone mass and osteoporosis in women who had used the method for 10 years or more. DMPA users with longer time of use showed a greater bone mass loss.

## Introduction

Depot medroxyprogesterone acetate (DMPA) is a highly effective, safe contraceptive method that has been in use worldwide for several decades.[1,2] However, there are controversies concerning long-time exposure and its effects on bone mineral density (BMD), not only during its use but also following discontinuation, after menopause, and with respect to fracture risk.[3] There is also concern regarding the use of DMPA over several years by adolescent girls before they achieve peak bone mass, and whether this would affect BMD in the future.[4–7]

It has been well established that DMPA users develop hypoestrogenism,[8,9] and that low endogenous estrogen is one of the principal causes of bone loss.[1] It has also been reported that DMPA users may experience progressive BMD loss throughout the first 5 years of use;[10–12] however, after that period, the body may adapt to hypooestrogenism, reducing bone mass loss and stabilizing bone turnover.[8] Furthermore, it has also been established that the decrease in BMD is reversible following discontinuation.[1,13]

Although it has been reported that long-term DMPA use does not increase the risk of low bone mass,[14] some researchers have been reported that use of this contraceptive method may increase fracture risk, principally in the fingers, toes, face and skull, and may increase the risk of other fractures compared to users of other contraceptive methods.[15] However, it is important to take into account that alcohol consumption and smoking habits could act as confounding factors.[16,17]

Evidence that any loss of BMD is recovered after DMPA discontinuation remains a subject of debate as far as long-term uninterrupted use is concerned.[3,6,7] Due to the scarcity of data on the long-term use of DMPA and its effect on BMD, the objective of this exploratory study was to compare any differences, if they exist, in low bone mass and osteoporosis between women who had used DMPA and those using a copper intrauterine device (Cu-IUD) uninterruptedly for 10

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years or more. The design of the study was based on the hypothesis that the body does not adapt to the hypoestrogenism caused by DMPA and that bone loss during long-term DMPA use may result in damage to bone health.

## Methods

This was a cross-sectional not blinded study conducted at the Human Reproduction Unit, Department of Obstetrics and Gynaecology, School of Medical Sciences, University of Campinas, Brazil. The Ethical Committee approved the study, and all the women signed an informed consent form prior to admission. Following a search of the archives of the family planning clinic up to the year 2013, 93 DMPA and 102 Cu-IUD users were identified. They had been using DMPA or Cu-IUD for at least 10 years uninterruptedly and attended the clinic regularly. An invitation letter was sent to all these women. Forty-eight of them agreed to participate and came to the clinic for BMD evaluation. All the women in both groups received small allowance for transportation and meals.

Two groups were formed: (1) the group of DMPA users and (2) a group of nonusers. For the first group, women of 27 to 57 years of age, who had been using DMPA (Depo-provera®, Pfizer) (intramuscular injection of 150 mg of the progestin every 3 months) uninterruptedly for at least 10 years (40 doses), who started using the method prior to 40 years of age and who had at least two consecutive (90 days apart) follicle-stimulating hormone (FSH) measurements <40 mIU/mL were enrolled in the study. Only one woman had FSH values >40 mIU/mL and was excluded. The nonuser group consisted of current users of the TCu380A copper intrauterine device (Cu-IUD) (Optima®, Injeflex) who had never used DMPA. Nonusers had had regular menstrual cycles for the 12 months preceding the study, had never used DMPA, and had not used any other hormonal contraceptive method for more than 6 months during their reproductive lives or in the 6 months preceding the study. Exclusion criteria consisted of chronic diseases (including diabetes mellitus, hyper or hypothyroidism, hyper- or hypoparathyroidism, hepatitis, cancer or pituitary diseases, inflammatory/rheumatologic conditions, and chronic renal failure. Women previously submitted to bariatric surgery or organ transplantation or women treated with steroids or seizure medications were also excluded from the study.

Bone mineral density was measured at the lumbar spine (LS) and femoral neck (FN) by dual-energy X-ray absorptiometry using a Lunar bone densitometer (GE Healthcare, Lunar Corporation). For the evaluation of osteopenia and osteoporosis, we used the World Health Organization (WHO) definition: $> -1.0$ standard deviation (SD) is normal BMD; $-1.0$ to $-2.5$ SD is low BMDs and; $< -2.5$ SD is osteoporosis.[32] To assess low bone mass and osteoporosis we used the T-score, which is the most important parameter for evaluating postmenopausal women. In our study, only 7 and 8 DMPA- and Cu-IUD-users, respectively, were under 40 years old. The Z-score would distort the result, because the woman would be compared with another person of the same age; consequently, the prevalence of osteoporosis could be affected and not reflect the reality. The assessment of BMD was performed by only one evaluator on the same equipment, and to increased reliability of the results, each day the evaluator measured a BMD with a phantom sample to reduce technical error of intraevaluator measurement.

Due to the fact that there are no similar studies to assess the prevalence of osteoporosis in long-term users of DMPA we were unable to estimate a sample size. Thus, we decided to conduct a pilot study and calculate the power of our sample based on the results of this pilot study, for an alpha error of 5% and a beta error of 13%; the sample size was calculated at 22 users and 22 nonusers for the assessment of BMD at the LS and FN. Considering this sample size, 47 DMPA users and 41 Cu-IUD users were enrolled, providing a power of over 80%. The demographic and clinical variables were compared using Student's *t*-test, the Mann-Whitney test, the chi-square test, and Fisher's exact test. To analyze the prevalence of low bone mass and osteoporosis the chi-square test was used. Comparison of mean BMD between the groups of DMPA users at the different years of use was performed using analysis of variance. The statistical analysis was performed using the SAS statistical software package for Windows, version 9.2 and all results were reported as mean ± SD. Significance was established at $p < 0.05$.

## Results

There were no differences between the two groups with respect to their sociodemographic variables (Table 1), with homogeneity being found for age, body mass index (kg/m$^2$),

Table 1. Some Sociodemographic Characteristics of the Women in the Two Groups at the Time of Evaluation

| | *Contraceptive method in use* | | |
|---|---|---|---|
| *Variables* | *DMPA* (n = *47*) | *Cu-IUD* (n = *41*) | p-*Value* |
| Age, years* | 45.7 ± 6.1 | 43.8 ± 6.1 | 0.17 |
| Age, median (range) | 46 (31–57) | 45 (27–54) | 0.16 |
| BMI; kg/m$^2$* | 27.3 ± 4.2 | 27.8 ± 4.4 | 0.60 |
| Years using the current method† | 14.8 ± 3.8 | 15.3 ± 4.0 | 0.49 |
| Ethnicity (white women)‡ | 17 (36.2%) | 18 (43.9%) | 0.54 |
| Married or living with a partner‡ | 35 (74.5%) | 39 (95.1%) | 0.0094 |
| In paid employment§ | 40 (85.1%) | 27 (65.8%) | 0.04 |
| *Previous contraceptive method used* | | | 0.46 |
| Combined oral contraceptives | 24 (51%) | 18 (43.9%) | |
| Cu-IUD | 8 (17%) | 4 (9.7%) | |
| Condom, natural or no methods | 12 (25.5%) | 15 (36.5%) | |
| ENG-releasing implant | 2 (4.2%) | 0 (0%) | |
| Combined monthly injectable | 1 (2.1%) | 4 (9.7%) | |
| Years using the previous method† | 3.7 ± 4.0 | 3.2 ± 3.6 | 0.26 |
| Physical activity ≥150 min/wk‡ | 11 (23.4%) | 9 (21.9%) | 0.91 |
| Domestic chores ≥150 min/wk§ | 42 (89.4%) | 39 (95.1%) | 0.15 |
| No alcohol consumption§ | 38 (80.8%) | 35 (85.4%) | 0.46 |
| No smoking§ | 35 (74.5%) | 35 (85.4%) | 0.36 |

*Student's *t*-test.
†Mann-Whitney test.
‡Chi-square$^2$ test.
§Fisher's exact test.
BMI, body mass index; Cu-IUD, copper intrauterine device; DMPA, depot medroxyprogesterone acetate; ENG, etonogestrel.

Table 2. Comparison of the Bone Mineral Density of DMPA and Cu-IUD Users by Age

| *Variable* | *Group* | n | *BMD mean ± SD* | *95% CI* | p-*Value** |
|---|---|---|---|---|---|
| *Age 27 to 36 years* | | | | | |
| L1–L4 | DMPA | 4 | 1.042 ± 0.073 | 0.925–1.159 | 0.0313 |
| | Cu-IUD | 7 | 1.205 ± 0.114 | 1.100–1.310 | |
| Femoral neck | DMPA | 4 | 0.886 ± 0.129 | 0.681–1.091 | 0.0568 |
| | Cu-IUD | 7 | 1.049 ± 0.114 | 0.943–1.155 | |
| *Age 37 to 46 years* | | | | | |
| L1–L4 | DMPA | 22 | 1.027 ± 0.127 | 0.971–1.084 | 0.0002 |
| | Cu-IUD | 18 | 1.182 ± 0.109 | 1.127–1.236 | |
| Femoral neck | DMPA | 22 | 0.903 ± 0.108 | 0.855–0.951 | 0.0637 |
| | Cu-IUD | 18 | 0.982 ± 0.153 | 0.906–1.058 | |
| *Age 47 to 57 years* | | | | | |
| L1–L4 | DMPA | 21 | 1.045 ± 0.133 | 0.985–1.106 | 0.0007 |
| | Cu-IUD | 16 | 1.199 ± 0.112 | 1.139–1.259 | |
| Femoral neck | DMPA | 21 | 0.925 ± 0.133 | 0.865–0.986 | 0.1849 |
| | Cu-IUD | 16 | 0.980 ± 0.102 | 0.925–1.034 | |

*Results were analyzed using Student's *t*-test; significance was established at $p < 0.05$.
95% CI, 95% confidence interval; BMD, bone mineral density; L, lumbar; SD, standard deviation.

and physical activity, all of which are factors that could influence BMD. No influence upon the results was observed regarding ethnicity. Albeit we did not obtain data about socioeconomic status of the women, the participants are patients from a Brazilian public service clinic and came from the low-income portion of the population. Thirty-three out of the 47 women in the DMPA group (68.1%) and 15 out of the 41 women in the Cu-IUD group (36.6%) were found to have low bone mass ($p = 0.002$). In addition, 14 of the 47 DMPA users (29.8%) and one of the 41 Cu-IUD users (2.4%) had osteoporosis ($p = 0.0008$).

No significant differences were found between the two groups with respect to whether low bone mass was present at the LS or the FN. Comparing the site of osteoporosis, there was a trend toward a higher prevalence of osteoporosis at the LS (13 women; 27.6%) when compared with the FN (1 woman; 2.4%) in DMPA users; however, this difference was not significant ($p = 1.0$). The mean BMD at the LS (L1–L4) among DMPA users was 1.037 ± 0.125, significantly lower than Cu-IUD users (1.192 ± 0.109; $p < 0.0001$), and at FN it was 0.9116 ± 0.119 and 0.9925 ± 0.128 among DMPA and Cu-IUD users, respectively ($p = 0.0029$). When the participating women were categorized by age and we performed a comparison of BMD between the two groups, it is shown that in all age groups it was lower BMD at the LS of DMPA users when compared to Cu-IUD users (Table 2).

Furthermore, comparison between DMPA users who had been using the method for 10 years, 11–15 years, or 16–23 years showed that BMD decreased as the number of years of DMPA use increased. Additionally, a significant decrease in BMD was found at the LS; however, no significant differences were found at the FN over the years (Fig. 1). Furthermore, users of Cu-IUD users showed no significant decrease in LS ($p = 0.4810$) and FN ($p = 0.9432$) with years of use.

## Discussion

Our results showed that around 30% of the women who had used DMPA for 10 years or more had osteoporosis, compared with only 3% of the nonusers. These results are more significant if we take into account that the two groups were homogeneous insofar as the risk factors for osteoporosis are concerned.

Investigators evaluating adolescent girls 12 to 18 years of age after 2 years of DMPA use reported that bone mass loss was insufficient to provoke osteopenia.[14] Nevertheless, longer periods of use, which obviously correlate with older age in users, may induce a reduction in BMD and consequently provoked low bone mass and osteoporosis and increasing fracture risk. There is no clear evidence regarding the relationship between DMPA use and an increased risk of fracture[3] despite the fact that some studies have shown a high risk of fracture in DMPA users compared with non-users.[15–17] However, there are some confounders that were not properly

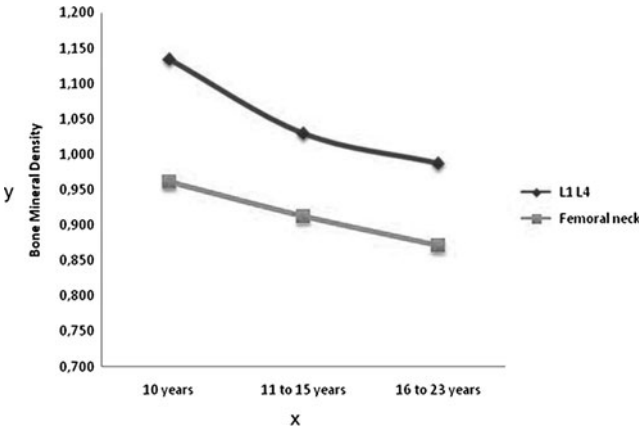


**FIG. 1.** Change in bone mineral density over time for depot medroxyprogesterone acetate (DMPA) users. Anova test: Lumbar spine (L1–L4), $p = 0.007$; femoral neck (FN), $p = 0.244$. Number of subjects using DMPA for each time of use studied: 10 years, 10 subjects; 11–15 years, 20 subjects; and 16–23 years, 17 subjects. Comparisons were made of users with the same time of use.

taken into account in those study populations,[1,3] and it is possible that the greater number of fractures in DMPA users could be accounted for by differences in the behavior of users compared to nonusers such as greater alcohol consumption, smoking and illicit drug abuse.[16,18] A firm association has been established between these habits and a higher incidence of fractures in the appendicular skeleton, but not with fragility fractures in the axial skeleton.[15]

Additionally, although the reduction in BMD in DMPA users has been well documented by some authors,[8,10–12,15,19] other investigators failed to replicate those results.[20,21] A greater loss was described in the initial years of use, varying in the different reports from around 0.4%[10,11] up to 3% per year.[12,19] Furthermore, some investigators suggested that BMD loss occurs in a linear fashion after a prolonged period of DMPA use,[8,10,22,23] however, this loss can be recovered within a short time, with a gain in bone mass of almost 5% two years after DMPA discontinuation.[24] Moreover, a United Kingdom–based researchers suggested that there is a balance with respect to BMD loss in long-term DMPA users and it is reasonable to speculate that there is an adaptation to the hypoestrogenism present during use.[8]

However, our study suggests that when DMPA is used uninterruptedly for long periods of time, loss of BMD may not stabilize. Thus, longitudinal studies are needed to confirm this hypothesis. These results were in agreement with the findings of other researchers showing that in long-term users (more than 10 years of use) of DMPA BMD was below the mean for the normal population, particularly at the LS,[8,10] and that women with FSH values ≥25.8 mIU/mL were associated with reduced BMD, possibly indicating that these women were in the menopausal transition.[25] However, when the region analyzed was the distal radius, no decrease in BMD was found in long-term users of DMPA.[20] In addition, attenuated rates of bone loss were found at the LS and FN[26] and the decrease in BMD at the distal and ultradistal radius was only statistically significant in women who had used DMPA uninterruptedly for as long as 13 to 15 years.[20]

These data may have an impact on family planning programs. It has been well established that DMPA is one of the most commonly used contraceptive methods in many settings; consequently, the impact of BMD loss with the resulting low bone mass and osteoporosis may constitute a public health problem. Nevertheless, scarce information is available regarding the duration of DMPA use in different national programs. The information currently available is derived from few studies that provide insight into the prevalence of long-term DMPA use around the world, since in many settings DMPA is administered in clinical rather than research settings. Nevertheless, there is information from some countries in which women have used DMPA for extremely long periods. For example, women are reported to have used DMPA for as long as 27 years in New Zealand, 23 years in Brazil, 16 years in the UK, and 15 years in China.[8,10,20,26] However, these studies analyze the mean BMD of DMPA users without categorizing by use of time, including users with 5–15 years of use of DMPA in a single analysis. Our study categorized the women according to the time of use and it is possible to observe that women using DMPA for a longer time showed a loss of BMD at LS.

Therefore, the recommendation given to physicians by the United States Food and Drug Administrationin 2004,[27] and then by the health authorities of the UK and Canada,[28,29] indicating that DMPA users were at risk of developing low bone mass and osteoporosis may be exaggerated. In fact, in the present study, an effect on BMD was only found in long-term users, as previously reported.[20] Nevertheless, it is important to take into account that in addition to DMPA use, other factors may affect BMD. Long-term users are older, and many of these women are in the menopausal transition; however, users and nonusers had the same mean age and therefore were influenced by the same decrease in BMD due to aging. Although some DMPA users were older than nonusers, users were not at postmenopause, because the FSH was at normal range. Furthermore, nonusers were menstruating regularly. Nevertheless we cannot ignore that hypoestrogenism are common among DMPA users. Age, calcium intake, sun exposure, coffee and alcohol consumption, and physical activity have a strong influence on BMD. Thus, factors related to lifestyle should be taken into account when BMD is evaluated.

The present study has some limitations, since subjects' family history of osteoporosis, fractures, calcium intake, coffee consumption, and sun exposure—well-known variables associated with bone mass loss—were not evaluated. However, Campinas is a Brazilian city in which there is sunshine throughout almost the entire year; consequently, exposure to sunlight is fairly constant. Though small, our study reached the sample size required for the study; however, with larger sample sizes the magnitude of difference could be detected mainly by differences in BMD was found even in the smaller subgroups.

According to the American College of Obstetricians and Gynecologists (ACOG)[1] and WHO,[30] DMPA is a safe and effective contraceptive. It also has some additional benefits related to the treatment of gynecological disorders such as its ability to reduce heavy menstrual bleeding, dysmenorrhea associated with endometriosis, the risk of ectopic pregnancy, sickle cell crises, and the incidence of bothersome perimenopausal symptoms. Nevertheless, the WHO guidelines regarding bone health and DMPA use suggested that the data are insufficient to determine whether the overall risks of continuing use of the method may outweigh the benefits in women over 45 years of age and in long-term users.[30] The UK National Institute for Health and Care Excellence states that new studies are needed to evaluate BMD recovery following discontinuation after long-term DMPA use and the risk of bone fractures in older women.[31]

According to the ACOG and WHO recommendations, the benefits of DMPA use surpass the risks. Nevertheless, our findings showed that DMPA use for 10 years or more has a deleterious effect on BMD, significantly reducing BMD and increasing the prevalence of low bone mass and osteoporosis compared with never users.

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### Author Disclosure Statement

No competing financial interests exist.

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