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ORIGINAL ARTICLE

Bone Mineral Density Among Long-term Users of Hormonal Contraception (Contraception and Bone Mineral Density)

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Abstract

Background: **Hormonal contraceptives that involve steroids have a high success rate and are commonly used. The use of these contraceptives can have positive and negative effects on health, including bone health. Some contraceptives may interfere with peak bone acquisition or may induce early bone mineral density (BMD) loss as they are provided for extended durations and at a time of life when many women have not yet reached the peak of bone development.**

Aim: **To assess the effect of long-term use of hormonal contraceptives (depot medroxyprogesterone acetate, Implanon, combined oral contraceptives) (≥3 years) among premenopausal women aged 28−40 years on BMD.**

Patients and methods: **This descriptive cross-sectional study was conducted on 70 female outpatients, who attended family planning clinics of Al Zahraa University Hospital and El Mahmoudeya Central Hospital from March 2021 to October 2021.**

Results: **There was a statistically significant difference regarding bone pain and duration of contraception and *T* score among studied groups except in the forearm. There was no statistically significant difference among all studied groups regarding demographic data, patient's classification, patient's parity, diet (milk, cottage cheese), and sun exposure.**

Conclusion: **BMD is reduced in females using depot medroxyprogesterone acetate and Implanon contraception for long-term duration and may be associated with osteopenia or osteoporosis. No significant changes in BMD were seen in women using combined oral contraceptives.**

Keywords: Bone mineral density, DXA scan, Hormonal contraception

1. Introduction

Contraceptives that include steroid hormones, such as those that are taken orally or injected, are among the most effective and extensively used methods of birth control. These contraceptives provide substantial contraceptive and non-contraceptive advantages to health, but they also have certain health hazards, such as those related to bone health.[1] Because contraceptives are taken for extended periods and during a stage of life in which many women have not yet reached the peak of bone formation, some contraceptives have the potential to interfere with peak bone acquisition or may induce early bone mineral density (BMD) loss, both of which could lead to osteopenia or osteoporosis in the future.[2]

In 2004, the United States Food and Drug Administration mandated that all depot medroxyprogesterone acetate (DMPA) packaging have a 'black box' warning. Despite this, the response from the vast majority of health organizations has been somewhat muted. The WHO, the American College of Obstetricians and Gynecologists, the National

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Institute of Public Health of Quebec, and the Centers for Disease Control and Prevention have released comments in favor of the continuing use of DMPA in adolescent and adult females beyond the suggested 2-year time restriction on the use of DMPA in adolescents and young women.[3]

There is very little research that has been done regarding the link between the use of subdermal implants and BMD. The effect is still debatable at this point.[4] As for the combined oral contraceptive (COC) pill, the spectrum of effects of combination hormonal contraceptives on bone health is complex and still not entirely understood.[5]

This research aimed to investigate the effects of using hormonal birth control for an extended period (>3 years) among premenopausal women on the BMD at the lower lumbar vertebra, femur neck, and forearm at the family planning unit.

2. Patients and methods

This descriptive cross-sectional study was carried out on 70 female outpatients, who attended the family planning unit of Al-Zahraa University Hospital and El Mahmoudeya Central Hospital from March 2021 to October 2021.

Women of childbearing age (28–40 years), who are current users of a hormonal or nonhormonal contraception for at least 3 years were included. Of those included, 37 women use hormonal contraception, DEMPA (15), Implanon (nine), and COC (13), and 33 women use nonhormonal contraception intrauterine device (IUD) (25) and safe period (eight).

We excluded medical conditions and medications that could affect bone metabolism such as: women who were or had recently been using anticonvulsants, corticosteroids, thiazide diuretics, medications for the treatment of thyroid illness, or hormone therapy for postmenopausal symptoms were excluded from the trial, as were women who were nursing or had recently stopped breastfeeding. Diabetes mellitus, chronic renal failure, hyperthyroidism, hypoparathyroidism, hepatitis, cancer, and pituitary problems are all examples of chronic illnesses that affect women.

2.1. Methodology

All women were recruited after confirmation of inclusion and exclusion criteria. Written and verbal informed consent was obtained, as well as the approval of the Ethics Committee of the Faculty of Medicine for Girls, Al-Azhar University. They were subjected to personal history, complete history taking (medical, surgical, obstetric, contraception history), present complaint of low back pain and general bone pain. BMD was measured using dual-energy radiograph absorptiometry, and a general physical was performed, including measurements of height and weight and the calculation of BMI. BMD results were interpreted as osteopenia (T score between -1 and -2.5), osteoporosis (T score$\geq$2.5), normal (T score greater than -1), and osteoporosis (T score$\geq$2.5) according to the definition provided by the WHO.[6]

Statistical analysis method of the data: The IBM SPSS software program, version 20.0, was used to do the analysis once the data were entered into the computer (IBM Corporation, Armonk, New York, USA). The qualitative data were characterized using numbers and percentages. It was determined by the application of the Kolmogorov–Smirnov test that the distribution was normal. The range (both the lowest and the maximum), the mean, and the SD were used to characterize the quantitative data. At the 5% level, significance of the results that were obtained was evaluated.

3. Results

Table 1.

There was no statistically significant difference in age, occupation, or BMI across all groups analyzed, and 90% of the women in this dataset are stay-at-home mothers (Figs 1 and 2).

There were no statistically significant differences in sex parity among all groups tested.

Table 2 shows that back pain was more prominent in IUD users followed by COC users with no statistically significant difference and generalized bone ache was higher in COC users followed by DMPA users with a statistically significant difference (Table 3).

Table 4 shows that there is a negative significant correlation between BMD (femur neck) and patient age, while no statistically significant correlation was found between BMD indices and patient's BMI, duration of contraception and duration of lactation at all examination sites.

Table 5 shows that the duration of contraception use was significantly more prolonged in COC, IUD, and DMPA users, DMPA users had significantly lower adjusted mean BMD at the lumbar spine and femoral neck. Implanon users had significantly lower adjusted mean BMD at the femoral neck, a slight decrease at the lumbar spine but with no significant statistical difference. COC had a slight increase in BMD at the lumbar spine with no significant statistical difference and no significant difference in forearm BMD between all studied groups.

Table 1. Groups' demographic information used in research.

	DEMPA ($N = 15$) [n (%)]	Implanon ($N = 9$) [n (%)]	COC ($N = 13$) [n (%)]	IUD ($N = 25$) [n (%)]	Safe period ($N = 8$) [n (%)]	P value
Age (years)						
Minimum–maximum	31–40	28–40	31–40	30–40	30–39	$H = 3.820$ $P = 0.431$
Mean ± SD	36.07 ± 2.685	36.00 ± 4.472	36.00 ± 3.606	36.12 ± 3.219	33.75 ± 2.915	
Occupation						
Housewife	13 (86.7)	9 (100)	12 (92.3)	21 (84.0)	8 (100)	$\chi^2 = 3.151$ $P = 0.533$
Employee	2 (13.3)	0	1 (7.7)	4 (16.0)	0	
Height (cm)						
Minimum–maximum	150–165	157–169	158–173	150–170	155–170	$H = 10.194$ $P = 0.104$
Mean ± SD	158.73 ± 3.369	163.22 ± 4.236	165.69 ± 4.803	160.96 ± 5.303	164.00 ± 4.375	
Weight (kg)						
Minimum–maximum	60–90	70–95	65–105	62–98	70–98	$F = 1.551$ $P = 0.198$
Mean ± SD	74.60 ± 8.166	81.00 ± 10.259	83.46 ± 10.627	79.64 ± 9.874	80.88 ± 10.750	
BMI (kg/m^2)						
Minimum–maximum	23.5–35.0	26.0–36.0	24.0–35.0	25.0–36.0	25.0–36.0	$F = 0.333$ $P = 0.854$
Mean ± SD	29.30 ± 3.081	30.24 ± 3.550	30.18 ± 3.098	30.56 ± 3.415	30.06 ± 4.028	

COC, combined oral contraceptive pill; F, analysis of variance test; H, Kruskal–Wallis test; IUD, intrauterine device; χ^2, χ^2 test.
*Statistically significant at P value less than 0.05.

4. Discussion

Our results demonstrated that long-term DMPA use had a negative impact on BMD with both lumbar spine (LS) and femoral neck (FN) BMD considerably decreased to the levels of at least osteopenia compared with never users.

The suppression of LH and FSH production by DMPA causes anovulation and, to varying degrees, estrogen insufficiency in its users. Hypoestrogenism, caused by decreased estrogen production, is connected with decreased bone mass or BMD as a result of an increase in bone resorption markers. This conclusion may be predicted among DMPA users because low estrogen levels are the leading cause of bone mineral loss in women. However, progestogen seems to have a trophic impact on BD, which mitigates this effect.[7]

In the current research, etonogestrel-releasing implants were linked to a modest decrease in BMD in the LS and FN, although this difference was not statistically significant when compared with copper IUD users. Similar results were seen for BMD in the forearm.

Furthermore, serum estradiol levels were lower in DMPA users compared with those who had Norplant implants.[8]

The favorable effect of levonorgestrel on bone density may result from the drug's direct action on the bone, its influence on free estradiol levels, or its effect on glucocorticoid osteoblast receptors.[9]

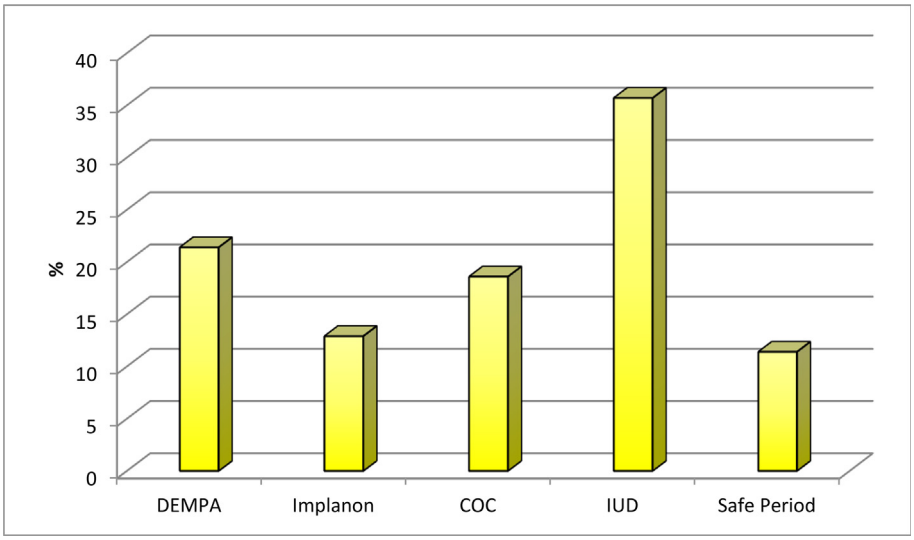

Fig. 1. Distribution of the studied sample according to patient classification.

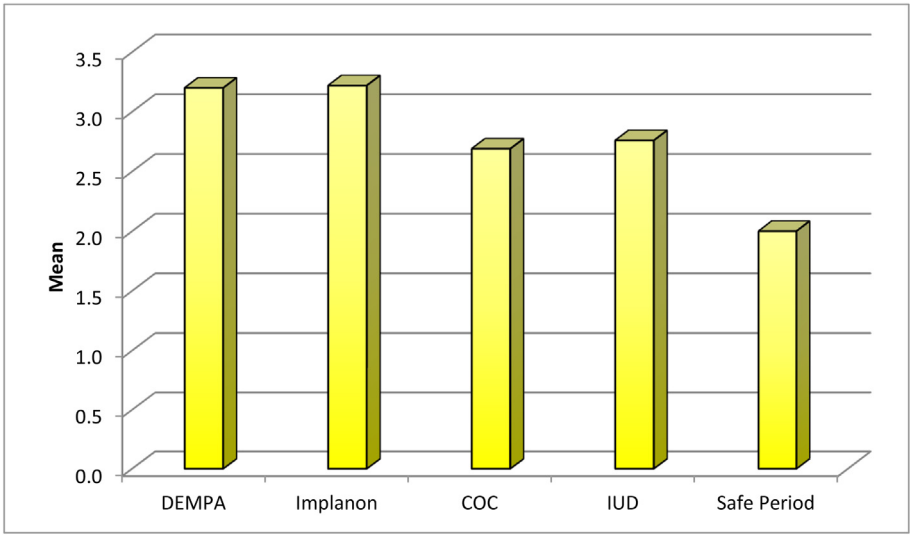

Fig. 2. Patient equality comparisons among study groups.

Table 2. Patients' complaints among studied groups.

	DEMPA ($N = 15$) [n (%)]	Implanon ($N = 9$) [n (%)]	COC ($N = 13$) [n (%)]	IUD ($N = 25$) [n (%)]	Safe period ($N = 8$) [n (%)]	P value
Back pain	11 (73.3)	6 (66.7)	10 (76.9)	22 (88.0)	3 (37.5)	$\chi^2 = 8.457$ $P = 0.076$
Bone pain	12 (80.0)	4 (44.4)	13 (100)	18 (72.0)	4 (50.0)	$\chi^2 = 11.03$ $P = 0.026$*

COC, combined oral contraceptives; IUD, intrauterine device.

Table 3. There was no statistically significant difference in this table among the groups tested and their diet (milk, cottage cheese), or their exposure to sunlight.

	DEMPA ($N = 15$)	Implanon ($N = 9$)	COC ($N = 13$)	IUD ($N = 25$)	Safe period ($N = 8$)	P value
Milk (times/week)						
Minimum–maximum	1–7	2	2–7	2–14	3–7	$H = 9.164$ $P = 0.057$
Mean ± SD	3.20 ± 2.280	2.0 ± 0.000	5.22 ± 2.167	4.47 ± 3.281	5.67 ± 2.309	
Cottage (g/w)						
Minimum–maximum	100–500	200–250	100–500	100–500	100–250	$H = 5.575$ $P = 0.233$
Mean ± SD	192.86 ± 142.678	225.00 ± 27.386	321.43 ± 172.861	192.31 ± 111.516	185.71 ± 69.007	
Sun exposure (h/w)						
Minimum–maximum	1–4	1–3	1–3	1–3	1–2	$H = 2.199$ $P = 0.699$
Mean ± SD	1.92 ± 1.256	1.44 ± 0.726	1.69 ± 0.855	1.40 ± 0.645	1.33 ± 0.516	

COC, combined oral contraceptive pill; H, Kruskal–Wallis test; IUD, intrauterine device.

Table 4. Correlation between DXA indices and patient age, BMI, duration of contraception, and duration of lactation.

	Spine		Femur neck		Forearm	
	r	P	r	P	r	P
Age	−0.164	0.175	−0.270	0.024*	0.047	0.701
BMI	0.076	0.529	0.028	0.818	0.150	0.216
Duration of Contraception	−0.250	0.835	0.057	0.639	0.126	0.298
Duration of lactation	−0.099	0.447	−0.195	0.132	−0.195	0.131

DXA, dual-energy X-ray absorptiometry.

Table 5. Duration of contraception and T score among the studied groups.

	DEMPA ($N = 15$)	Implanon ($N = 9$)	COC ($N = 13$)	IUD ($N = 25$)	Safe period ($N = 8$)	P value
Duration of contraception (years)						
Minimum–maximum	3–12	3–6	3–13	3–13	3–7	$H = 10.257$ $P = 0.036$*
Mean ± SD	6.60 ± 2.558	4.67 ± 1.414	7.00 ± 3.028	6.24 ± 2.990	4.00 ± 1.414	
T score						
Spine						
Minimum– maximum	−2.5 to −0.5	−1.1 to 1.2	−0.7 to 2.5	−0.6 to 1.9	−0.3 to 1.4	$F = 32.775$ $P < 0.001$*
Mean ± SD	−1.33 ± 0.477	−0.03 ± 0.775	1.22 ± 0.744	0.25 ± 0.564	0.71 ± 0.636	
Femur neck						
Minimum–maximum	−1.3 to 1.5	−0.7 to 0.9	−2 to 1.7	−0.9 to 1.7	−0.6 to 1.6	$F = 3.449$ $P = 0.013$*
Mean ± SD	−0.07 ± 0.741	0.03 ± 0.572	0.59 ± 0.678	0.58 ± 0.667	0.70 ± 0.780	
Forearm						
Minimum–maximum	−1.3 to 0.9	−0.6 to 0.3	−0.8 to 0.5	−1.0 to 0.9	−0.8 to −0.1	$F = 1.173$ $P = 0.331$
Mean ± SD	−0.46 ± 0.550	−0.12 ± 0.311	−0.19 ± 0.451	−0.41 ± 0.533	−0.34 ± 0.277	

COC, combined oral contraceptives; IUD, intrauterine device.

This study found that COCs with 30 g of ethinyl estradiol were associated with a modest increase in LS BMD among COC users, but that this effect did not vary significantly from that seen among Cu-IUD users. Similar results were seen with regard to BMD in the FN, and the forearm.

Estrogen's function is the suppression of bone resorption, which may explain why it has a protective effect on BMD. Interleukin 6 (IL-6) increases bone resorption, whereas estrogen prevents osteoblast manufacture of IL-6. When estrogen binds to its receptors, transcription of several genes is triggered and changed. The IL-6 receptors may potentially be blocked by estrogen. The estrogen-dependent regulatory factors tumpr necrosis factor-α and the OPG/RANKL/RANK system are modified slightly yet collectively by estrogen to prevent bone resorption.[10]

A cross-sectional investigation by Modesto *et al.*[11] demonstrated that long-term DMPA use was associated with low bone mass and osteoporosis in women who had used the method for 10 years or more, which is consistent with our conclusion.

However, Viola *et al.*[12] did not detect a deleterious effect on BMD among long-term DMPA users with less than 13 years of use but they used the forearm as the site of measurement, which may be less sensitive.

In keeping with our study finding, Liu *et al.*[13] support that there is good evidence that oral contraceptives have a positive effect on BMD in premenopausal women.

However, Sordal *et al.*[14] in their study observed that COCs did not affect BMD.

Decreased BMD was also seen by other researchers. Very low doses of OCPs in adolescents have been linked to mild bone loss, according to research by Almstedt *et al.*[15]

Postmenopausal women who took estrogen (EE) levels of 15–25 mg daily did not lose bone density, and those who used EE doses of 25 mg or more per day gained bone.[16]

Studies in premenopausal women have shown that oral contraceptives do not have an effect or enhance bone density. By contrast, the use of COCs in adolescents who have not achieved peak bone mass compromises bone mineral acquisition.[5]

Heller *et al.*[17] and Pongsatha *et al.*[18] observed that women who used etonogestrel-releasing implants had significantly reduced BMD, which is consistent with our study's findings.

However, Modesto *et al.*[4] found no significant changes in BMD among the ENG-releasing implant users, but the study related to the relatively short duration of use of contraceptives.

However, Di *et al.*[19] found a significant increase in BMD, but the study was limited because there was no group not using a progestogen-only contraceptive.

The question of whether or not the alterations in BMD caused by current DMPA use are reversible is more crucial. We were unable to see BMD recovery in our study because we stopped following up with ex-DMPA users.

Evidence suggests that DMPA use over the long term decreases BMD; however, this effect is transient and reversible.[19] After being stopped, BMD is much higher, and these gains are maintained in subsequent assessments. BMD in the spine and hips returned to pretreatment levels after 1–2 years of treatment cessation and 3–5 years of the last DMPA injection, respectively.[20]

Due to a lack of sufficient data on fracture incidence, the risk of clinical bone fragility (i.e. bone fracture) arising from the use of hormonal contraceptives in women is still unknown.[21]

Multiple studies and meta-analyses have evaluated the influence of DMPA on fracture risk; however, analyses that include all skeletal fracture sites rather than those associated with fragility provide little insight into the potential for fracture related to low BMD. Among studies that focused on osteoporosis-related fractures, there was a signal for a small increase in fracture risk for DMPA users versus nonusers.[21]

4.1. Conclusion

We conclude that long-term use of DMPA contraception reduces BMD and may be linked to osteopenia and osteoporosis in women. BMD decreases considerably at the FN in long-term etonogestrel-releasing implant users, while BMD decreases somewhat but not significantly at the LS in this population.

Conflicts of interest

There are no conflicts of interest.

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