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Effects of long-term high-dose medroxyprogesterone acetate use on bone mineral density in postmenopausal women

Altuğ Semiz

Department of Obstetrics and Gynecology, Faculty of Medicine, İstinye University, İstanbul, Turkiye

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Corresponding Author: Altuğ Semiz, altug.semiz@gmail.com

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ABSTRACT

Aims: The aim of this study was to investigate the relationship between long-term depot medroxyprogesterone acetate (DMPA) use and bone mineral density (BMD) in postmenopausal women.

Methods: This study was conducted on 40 postmenopausal women who presented at the SSK Okmeydanı Training and Research Hospital Gynecology and Obstetrics Polyclinic. The sample for the study was randomly selected from postmenopausal women and divided into the control group (N=20) and the medroxyprogesterone acetate group (N=19).

Results: A total of 39 participants were included in this study, 19 cases and 20 controls. Long-term DMPA users had higher BMD compared with the control group. These differences from the control group were statistically and potentially clinically significant. The BMD in the control group has decreased significantly during one year of study. Based on the results, the long-term use of DMPA significantly affects the bone mineral density in postmenopausal women, increasing BMD.

Conclusion: Long-term use of DMPA was associated with improved BMD after treatment. The findings demonstrate the need for long-term, controlled, prospective studies with adequate sample size to evaluate the potential clinical impact of DMPA use on bone health outcomes in postmenopausal women.

Keywords: Depot medroxyprogesterone acetate, bone mineral density, osteoporosis, postmenopause, women

INTRODUCTION

The menopause period is considered one of the three main periods in a woman's life.[1] This period attracted more attention to be considered one of the natural processes of a woman's life instead of a disease experienced by women.[2] Women experience a different quality of life, acute onset, rapid, mostly irreversible changes in the menopause period.[3] The main reason for these changes is the decrease in estrogen due to ovarian insufficiency and the estrogen deficiency experienced in all systems with estrogen receptors. The changes experienced in the postmenopausal period are primarily divided into two groups: the short-term and the long-term. The changes occurring in the long term are more serious and effective. The two long-term changes are related to the cardiovascular system and osteoporosis. Osteoporosis is a progressive decrease in bone mineral density with systemic involvement.[4] Bone density decreases in this way, causing fracture formation due to microtrauma.[5] Osteoporosis, which could not be diagnosed until this point, where treatment options are limited. While there is no definitive cure for osteoporosis, treatment can help slow or halt the loss of bone density and reduce the risk of fractures.[6] This study's primary purpose was to investigate the consequences of long-term high-dose medroxyprogesterone acetate (DMPA) use on bone mineral density in postmenopausal women.

Osteoporosis is the most prevalent bone disease in humans, posing a significant public health concern.[7] It is more common in individuals of Caucasian descent, women, and the elderly.[8] Osteoporosis simply means decreased bone density. Osteoporosis is defined as "a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture".[9] Osteoporosis is among the important diseases seen in the elderly population. It is one of the systemic diseases frequently encountered in clinical practice, such as heart, stroke, diabetes and cancer. It is a significant public health issue that affects millions of people worldwide. Approximately 10 million Americans over the age

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of 50 have osteoporosis, and an additional 34 million are at risk of developing the disease.[10] Accurate statistics regarding the number of patients in Turkiye are not available.[11] However, in 2010, there were more than 24,000 hip fractures in individuals aged 50 years or older, with 73% occurring in women.[12]

DMPA is an injectable contraceptive that women widely use worldwide.[13] There are inconsistent information about the recovery of bone mass with long-term use of DMPA.[14] Because of the discussions, the use of the DMPA in women was decreasing.[15] Limited research was done on the role of DMPA in reducing osteoporosis and increasing bone quality in postmenopausal women. The majority of conducted studies focus on young women.[16-21] The leading cause of postmenopausal osteoporosis is estrogen deficiency.[22] However, recent studies have questioned the effect of progesterone used together with estrogen in hormone replacement therapy on bone density. There are three questions here.

What is the role of progesterone in natural internal balance? Is progesterone effective in bone metabolism, and/or what role does it play? Does progesterone have an additional effect on hormone replacement therapy?
In order to find answers to these questions, this study compared the bone densities of postmenopausal patients after one year of treatment by DMPA. The aim of this randomized controlled trial study was to investigate differences in BMD in long-term users of DMPA in postmenopausal women.

METHODS

This study is the scientific study of Altuğ Semiz master's thesis named "Effects Of Long-Term High-Dose Medroxyprogesterone Acetate Use On Bone Mineral Density In Postmenopausal Women", registered at the National Thesis Center with the number 103431 dated 2004. All procedures conducted in this study were in accordance with ethical guidelines and the principles outlined in the Declaration of Helsinki.

This study was conducted on 40 postmenopausal women who applied to the SSK Okmeydanı Training and Research Hospital Gynecology and Obstetrics Polyclinic between April 2001 and November 2002.

The sample for the study was selected randomly among postmenopausal women. The sample was divided into the control and medroxyprogesterone acetate groups (the case group). Twenty women were included in the study in the medroxyprogesterone acetate group, and the study was completed with 19 cases. One patient declined to participate in the study. The number of patients selected as the control group was 20 cases, and all patients completed the study. The number of women who entered menopause naturally was 30, and the number of women who had surgical menopause was 10. Premature menopause was not detected in the women. All patients in both groups underwent a complete gynecological examination.

In the case group, 20 mg medroxyprogesterone acetate (Farlutal tab. 5 mg. 2x2) was used orally for ten days during the second half of menstruation, and this treatment was continued for one year. No treatment was applied to the patients in the control group. Their follow-up was continued for one year. Patients in both groups received 1000 mg of calcium supplements per day.

The women included in the study were requested to meet the following criteria for the postmenopausal period: 6-12 months of secondary amenorrhea, FSH >25, LH >30, E2 <40, and normal prolactin levels in hormone measurements.

It was stipulated that the patients had not previously used any treatment for menopause or protection against osteoporosis, as this could affect the study results. In addition, it was ensured that the patients did not have any secondary problems predisposing to osteoporosis and that they had not received steroid treatment for any reason in the recent past. It was ensured that the patients did not use contraceptives and/or hormonal preparations for other reasons during the study period.

T-score ("Number of standard deviations above or below bone mineral density of age-matched controls") and Z-score ("Number of standard deviations above or below bone mineral density of young normal mean") were used to evaluate the hypotheses of this study. According to World Health Organization (WHO) criteria, osteoporosis is defined as T-score ≤−2.5. Osteopenia is defined as between T-scores (−1 and−2.5). Severe osteoporosis is defined as T-score >−2.5. Normal bone is defined as T-score >−1.[23]

Statistical Analysis

Minimum, maximum, mean (M), and standard deviation (SD) were used for descriptive characteristics for numerical values. The Shapiro–Wilk test was used as the normality test of continuous data. The Wilcoxon Signed-Rank test was used to compare the T-score and Z-score in the case and control groups. A general linear model was used to test the impact variables on each other. SPSS v22 was used for statistical analysis. A value of p 0.05 was accepted as statistically significant.

RESULTS

The patients in case group with a mean age of 49.2 years and a mean body weight of 76.36 participated in the study. Women in control group with a mean age of 49.65 years and a mean body weight of 74.85 participated in the study. Descriptive statistics of T-Score and Z-Score were presented according to the groups and are shown in Table 1.

In both groups, the difference between T-Score 1 and T-Score 2 was compared using the Wilkoxon Sign Ranks Test and the following results were obtained: in the study group, T-Score 2 value was higher than T-Score 1 in 15 cases, T-Score 2 value was lower than T score 1 in 3 cases and remained the same in 1 case (Table 2). According to these results, bone mineral density increased in 15 cases, decreased in 3 cases and remained the same in 1 case (n=19). In terms of Z-Scores, Z-Score 2 was higher than Z-Score 1 in 16 cases, Z-Score 2 was lower than Z-Score 1 in 3 cases and no equal cases were observed. With these results, according to Z-Scores, bone density increased in 16 cases compared to young adults and decreased in 3 cases (Table 2).

There is a significant difference in favor of loading between T-Score 1 and T-Score 2 and Z-Score 1 and Z-Score 2 in the case group (p<0.01). T-Score 2 value was found to be lower than T-Score 1 in 18 cases, and T-Score 2 value was found to be higher than T-Score 1 in 2 cases. As a result of these values, it was observed that bone mineral density decreased in 18 cases and bone mineral density increased in 2 cases.

Table 1. Descriptive statistics of T-Score and Z-Score

		N	Minimum	Maximum	Mean Rank	Std. Deviation
T-Score 1	Case	19	-3.2	1.6	-1.101	1.0991
	Control ranks	20	-2.8	1.2	-.700	1.2222
T-Score 2	Case	19	-2.17	1.70	-.4321	1.17547
	Control ranks	20	-3.00	0.85	-1.4270	.91680
Z-Score 1	Case	19	-2.18	1.03	-.7411	.85027
	Control ranks	20	-1.90	1.40	-.2285	1.07619
Z-Score 2	Case	19	-2.00	1.70	-.1137	1.04290
	Control ranks	20	-2.40	1.20	-.9065	.90604

Table 2. The comparison of study variables in case group

		N	Mean Rank	Sum of ranks	Z	p-value
T-Score 2-T-Score 1	Negative ranks	3[a]	8.83	26.50	-2.570	.010
	Positive ranks	15[b]	9.63	144.50		
	Ties	1[c]				
	Total	19				
Z-Score 2-Z-Score 1	Negative ranks	3[d]	11.33	34.00	-2.455	.014
	Positive ranks	16[e]	9.75	156.00		
	Ties	0[f]				
	Total	19				

a: TScore2<TScore1; b: TScore2>TScore1; c: TScore2=TScore1; d: ZScore2<ZScore1; e: ZScore2>ZScore1; f: ZScore2=ZScore1.

Z-Score 2 was lower than Z-Score 1 in 17 cases, Z-Score 2 was greater than Z-Score 1 in 1 case, and the two measurement results were the same in 3 cases. According to these results, bone density decreased in 17 cases, increased in 1 case, and remained the same in 3 cases in the average bone mineral density of the young adult population (Table 3).

General linear model was used to examine the effect of Medroxyprogesterone Acetate use on bone mineral density (Table 4 and 5). Statistically significant differences were found in both parameters of T-Score and Z-Score values ($p<0.01$).

The graphical representation of the change in bone mineral density in one year in patient groups using and not using Medroxyprogesterone Acetate can be expressed in Figure. T-Score and Z- score are statistically significant changes in both groups.

Table 3. The comparison of study variables in control group

		N	Mean Rank	Sum of ranks	Z	p-value
T-Score 2-T-Score 1	Negative ranks	18[a]	11.47	206.5	-3.793	<.001
	Positive ranks	2[b]	1.75	3.5		
	Ties	0[c]				
	Total	20				
Z-Score 2-Z-Score 1	Negative ranks	17[d]	9.91	168.50	-3.616	<.001
	Positive ranks	1[e]	2.50	2.50		
	Ties	2[f]				
	Total	20				

a: TScore2<TScore1; b: TScore2>TScore1; c: TScore2=TScore1; d: ZScore2<ZScore1; e: ZScore2>ZScore1; f: ZScore2=ZScore1.

Table 4. General Linear Model of T-Score

Groups	Factors	N	Mean	p-value	Std. error	95% confidence interval	
						Lower bound	Upper bound
Control	T-Score 1	20	-.700	<.001	.260	-1.227	-.173
	T-Score 2	20	-1.427	<.001	.235	-1.903	-.951
Case	T-Score 1	19	-1.101	<.001	.267	-1.642	-.559
	T-Score 2	19	-.432	<.001	.241	-.920	.056

Table 5. General Linear Model of Z-Score

Groups	Factors	N	Mean	p-value	Std. error	95% confidence interval	
						Lower Bound	Upper Bound
Control	Z-Score 1	20	-.229	<.001	<.001	-.669	.212
	Z-Score 2	20	-.907	<.001	<.001	-1.348	-.465
Case	Z-Score 1	19	-.741	<.001	<.001	-1.193	-.289
	Z-Score 2	19	-.114	<.001	<.001	-.567	.340

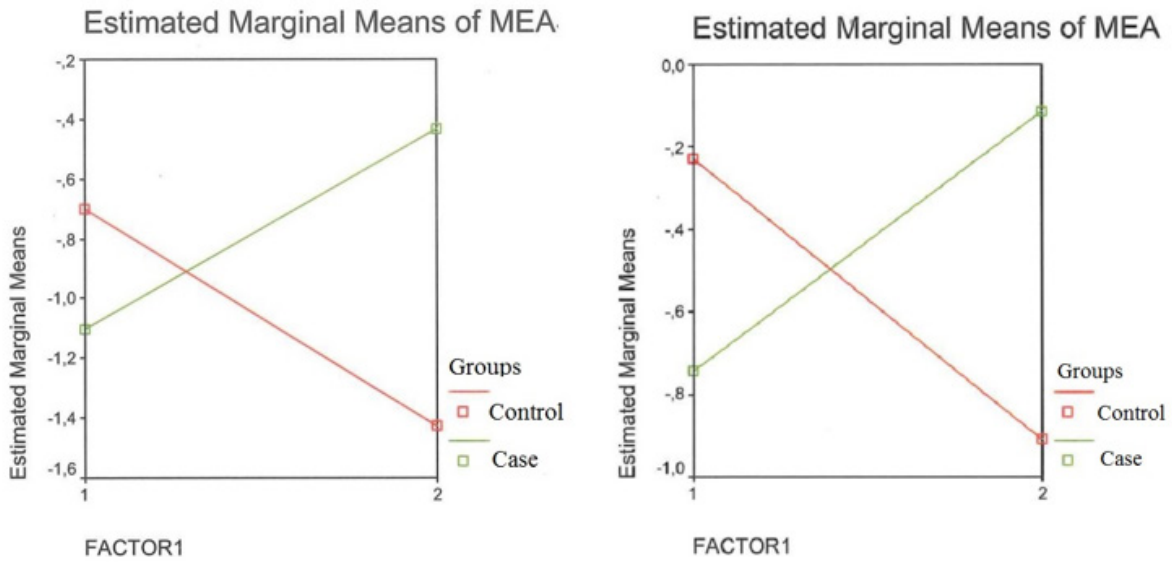

Figure. T-Score and Z-Score significant changes

DISCUSSION

The present study examined the impact of long-term high-dose DMPA use on bone mineral density in postmenopausal women. Based on the findings, the prolonged use of DMPA significantly impacts the bone mineral density of postmenopausal women and increases BMD. The impact of DMPA on bone density has sparked significant controversy. In this section, the current study's findings are compared and discussed in relation to the findings of previous studies.

Gallagher et al. [24] studied impact of high dose progesterone (20 mg medroxyprogesterone acetate) on bone mineral density. The study showed that medroxyprogesterone acetate significantly reduced the loss of bone mineral density from cortical bones of the skeletal system compared to placebo. Viola et al.[25] found a statistically meaningful distinction in forearm BMD measures between postmenopausal women who had been long-term users of DMPA and control group users. BMD was significant higher in the long-term users of DMPA. In this study, three comparisons were made between different time points: the first and third year, the second and third year, and the fourth and fifth year after menopause.[25] These results were in line with our study. In another study, Viola et al.[26] made the same comparison among menopausal women between 1 and 15 years. This study found no negative impact on forearm BMD measures in long-term DMPA users with less than 13 years of use. Sanches et al.[27] reported no significant differences between postmenopausal women who had used DMPA and control group women at 1 and 2-3 years periods in terms of the bone mineral density. Modesto et al.[28] reported that the long-term use of DMPA has been linked to low bone mass and osteoporosis in women who have utilized DMPA for ten years or more. Additionally, DMPA users with longer duration of use exhibited greater loss of bone mass. What is clear is that the reduction in BMD among DMPA users remains a controversial issue, and further studies considering other influencing variables are still needed. This study holds great value as it is one of the pioneering research in this area in Turkiye. Considering the importance of osteoporosis in elderly women, this study should be repeated with more samples in Turkiye to obtain more reliable results. These results can be the basis of treatment protocols in Turkiye.

This investigation has several limitations. One important limitation is the retrospective design. Additionally, the sample size is relatively small due to financial constraints. The study did not consider demographic characteristics such as calcium intake, smoking and BMI in the women, which may affect BMD. It is recommended that future research gather samples while taking these factors into account. Therefore, further studies with larger sample sizes are needed to clarify the effect of DMPA on BMD in postmenopausal women.

CONCLUSION

As a result of our study with a randomized control group and a one-year follow-up period observed that the use of 20 mg medroxyprogesterone Acetate daily in postmenopausal women was statistically significant in increasing BMD. A statistically significant decrease in bone density was observed in the control group. The tolerability of the drug was generally observed well.

According to results, it is revealed that progesterone has a positive influence on bone turnover and increases bone density. However, controlled and prospective studies with adequate sample size are needed to confirm our knowledge on of the clinical consequence of DMPA use on bone health outcomes.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study is the scientific study of Altuğ Semiz master's thesis named "Effects Of Long-Term High-Dose Medroxyprogesterone Acetate Use On Bone Mineral Densıty In Postmenopausal Women", registered at the National Thesis Center with the Decision No: 103431, Date: 2004.

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study had no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Altuğ Semiz

Altuğ Semiz was born on June 22, 1975, in İstanbul, Turkiye. He completed his medical education at İstanbul University, Cerrahpaşa Faculty of Medicine, between 1992 and 1998. Following his graduation, he began his career as an Assistant at the Obstetrics and Gynecology Clinic of S.S.K. Okmeydanı Hospital in İstanbul, where he worked from 1998 to 2003. He further advanced his training with a fellowship at King's College, Southampton Hospital in the UK, from 2003 to 2004. Upon returning to Turkey, he joined the IVF Unit at Şişli Memorial Hospital from 2005 to 2007. He then fulfilled his compulsory military service as an Obstetrics and Gynecology specialist at Sivas Military Hospital between 2007 and 2008. After completing his military service, he continued his career at Şişli Memorial Hospital, where he worked in the Obstetrics and Gynecology Clinic from 2008 until 2022. Since 2022, he has been serving as a Specialist in Obstetrics and Gynecology at İstinye University in İstanbul. Altuğ Semiz is proficient in English, having achieved an advanced level in YÖKDİL in 2024. Throughout his career, he has developed significant expertise in the fields of IVF, Obstetrics, and Gynecology, with extensive clinical and surgical experience.