

IS LONG-TERM USE OF HORMONAL CONTRACEPTIVES A RISK FACTOR FOR OSTEOPOROSIS ?

*Kamal Anwar**, *Soad Mosaad *** and *Amany Shalaby ****

Department of Obstetrics and Gynecology*, Forensic Medicine and Clinical Toxicology** and
Clinical Pharmacology***. Faculty of Medicine, Mansoura University, Mansoura, Egypt.

ABSTRACT

Objective : To study the effect of long-term use of different forms of hormonal contraceptives on bone mineral density (BMD)

Design : A prospective study

Setting: Fertility Care Unit, Mansoura University Hospitals.

Subjects and Methods: One hundred healthy women aged 25-49 years who chose long term hormonal contraceptives were recruited in the study. Women had to fulfill a set of inclusion and exclusion criteria. Those women were categorized into five groups, each comprised twenty women. All groups were well balanced with respect to age, height, weight and body mass index. Those who used combined oral contraceptives (group 1), Norplant subdermal implants (group 2), Implanon subdermal implants (group 3), injectable Depo-Provera (group 4) and Control group used non-hormonal intrauterine contraceptive device Tcu 380A (group 5). After 3 years of contraceptive use, bone mineral density (BMD) of lumbar spine (L2-L4) was measured for all women using dual energy X-ray absorptiometry (DEXA). BMD measurements (g/cm^2) were expressed as Z-scores to assist in the interpretation of BMD results. BMD and Z-scores in different groups were compared using Anova Test with Post Hoc Test (Turkey HSD) for multiple comparisons between groups.

Results: Of 100 women, 9 women were excluded from analysis and a total of 91 women made up the final sample; 18 used combined oral contraceptives (group 1), 19 used Norplant (group 2), 19 used Implanon (group 3), 18 used Depo-Provera (group 4) and 17 used non-hormonal IUD Tcu 380A (group 5). Age, height and body mass index were not significantly different among the groups. Mean BMD at lumbar spine (L2-L4) was 1.205 (group 1), 1.182 (group 2), 1.11 (group 3) 0.842 (group 4) and 1.113 (group 5). There were significant differences in BMD values at lumbar spine between different groups. Depo-Provera group was associated with a lower BMD than the other groups whereas the combined oral contraceptive group was associated with a higher BMD. Mean z-scores were -0.34 (group 1), -0.37 (group 2), -0.5 (group 3), -2.26 (group 4) and -0.5 (group 5). Multiple comparisons by using Post Hoc Tests (turkey HSD) demonstrated that BMD and Z-scores in Depo-Provera users were significantly lower than that of other groups. All women using Depo-Provera experienced osteoporotic changes with a Z-score ranging from -2.02 to -2.4.

Conclusion: Depo-Provera was associated with a significantly lower BMD; hence its long term use is a potential risk factor for osteoporosis. Combined oral contraceptives and Norplant were associated with increased BMD while Implanon had no effect. These results have a great importance in cases of medico-legal examination of women who used Depo-Provera for a long duration as a simple trauma may lead to fractures.

Corresponding author : Dr. Kamal Anwar, Mansoura University Hospitals, Mansoura, Egypt.

INTRODUCTION

Osteoporosis is a major health problem facing women throughout the developed and developing countries. Osteoporosis is defined as a condition of generalized skeletal fragility in which bone strength is sufficiently weak that fractures may occur with a minimal trauma⁽¹⁾. Fortunately, bone mineral density (BMD) assessment is used to establish the diagnosis of osteoporosis, predict future fracture risk and monitor changes in bone mineral density due to medical conditions or therapy. BMD has an inverse relation to the risk of fracture. The lower the BMD the greater the risk⁽²⁾.

Prospective studies have demonstrated multiple risk factors associated with the development of osteoporosis and subsequent fragility fractures. Disturbance of endogenous steroid hormones is one of these risk factors⁽³⁾. Most cases of osteoporosis are caused by increasing bone resorption due to decreased estrogen production following menopause. Studies have shown that lower doses of hormonal replacement therapy are effective in improving bone mineral density (BMD) in postmenopausal women⁽⁴⁾.

In the last few years, there is a great health concern regarding the detrimental effect of hormonal contraceptive use on bone mineral density. However, most of the studies assessed the effect of short term use of these contraceptives on bone mineral density (BMD) and the results were not conclusive and contradictory. Therefore, the purpose of the present work was to study the effect of long-term use of different forms of hormonal contraceptives (combined oral contraceptives, subdermal Norplant, subdermal Implanon and injectable Depo-Provera) on bone mineral density. Wanichsetakul et al.⁽⁵⁾ defined long term use as > 2 years.

SUBJECTS & METHODS

This study was carried out at Fertility Care Unit,

Mansoura University Hospital from August 2003 to August 2006. One hundred women who chose long-term use of hormonal contraceptives participated in the study. Thorough history was taken from all women including: age, special habits (smoking or alcohol), concomitant medications, presence of systemic diseases and current or past contraceptive use. Also, obstetric and lactation histories were obtained.

Women had to fulfill a set of exclusion and inclusion criteria. The most important exclusion criteria were:

- 1- Chronic diseases affecting bone metabolism
- 2- Use of any medication affecting calcium metabolism
- 3- Significant scoliosis that hinders the BMD measurement at lumbar spine
- 4- Vigorous exercises or heavy work
- 5- Current pregnancy or lactation
- 6- Use of hormonal contraceptives within the past six months

The most important inclusion criteria were:

- 1- Age between 25-49 years
- 2- Good physical and mental health
- 3- Weight between 80-130% of ideal
- 4- Six months interval following termination of pregnancy and lactation.

After obtaining an informed consent, full clinical examination was performed to assess health status. Women were weighed using a platform beam balance and their heights were measured by using a vertical measuring rod attached to the weighing scale. Body mass index was calculated as weight in kilograms divided by the square of the height in meters.

Eligible women were categorized into five equal groups, each comprised twenty women.

Group 1: comprised women using combined oral contraceptives (low-dose contraceptive pills) contain 30ug. ethinyl estradiol

Group 2: comprised women using subdermal implant, Norplant

Group 3: comprised women using subdermal implant Implanon

Group 4: comprised women using injectable Depo-Provera

Group 5: A control group comprised women using non hormonal intrauterine contraceptive device (Tcu 380A)

To avoid a significant baseline variation between different groups, we aimed at a balance with respect to age, height, weight and body mass index.

Bone mineral density measurement was performed in the anteroposterior position at lumbar spine (L2-L4); a site that contains high percentage of trabecular bone. These measurements were performed after 3 years of contraceptive use. The equipment used in this study was the dual energy x-ray absorptiometry (DEXA); Lunar, DPX-IQ system (Lunar corporation, Madison, USA) (Fig 1). The dual energy X-ray absorptiometry equipment measures area of bone in cm^2 and bone mineral content (in grams) and expresses density as grams / cm^2 . It also allows comparison to different reference populations (6).

How is bone mineral density (BMD) of an individual expressed?

To assist in the interpretation of bone mineral density results, the bone mineral density of an individual is expressed as a relation to two norms: the expected BMD for the referenced same-age population (Z-score) or young healthy adult (T-score). Because normal values decrease with age, it is convenient to express data in term of z-scores (age-matched comparisons) which represent the number of standard deviation away from the mean. Negative z-score indicates that individual's bone mass is lower than the referenced same-age population. This denotes that something may cause bone to deteriorate faster than that attributable to age and primary osteoporosis alone. Therefore, BMD measurements (g/cm^2) were transformed into

standard deviation (SD) scores thus providing Z-scores (equivalent to T-Scores) by means of the following equation(7) :

Z-score = recorded BMD-mean BMD of reference population / SD of BMD of reference population

Statistical analysis :

It was performed using SPSS (Statistical Package for Social Sciences) version 10. Data was presented as a mean \pm SD. Analysis of variance (Anova test) was used for comparisons between groups with Post HOC tests (Turkey HSD). For multiple comparisons between different groups, Pearson correlation coefficient was used to calculate correlation between variable. $P < 0.05$ was considered to be statistically significant(8).

RESULTS

Nine women were excluded from analysis as they had discontinued use of contraception before they completed three years use. So, a total of 91 women made up the final sample; 18 used combined oral contraceptives (group 1), 19 used Norplant (group 2), 19 used Implanon (group 3), 18 used Depo-Provera (group 4) and 17 used non-hormonal IUD Tcu 380A (group 5). Most of the studied women were in the fourth decade of life as shown in table I. All women had been pregnant in the past and all have children. Demographic characteristics of the 5 groups showed that there were no significant variations between different groups as regards age, height and body mass index (table II).

Mean bone mineral density (BMD) measurements were 1.205 ± 0.02 in (group1) 1.182 ± 0.35 (group 2); 1.11 ± 0.028 (group 3), 0.842 ± 0.05 (group 4) and 1.113 ± 0.015 (group 5). There was a statistical significant variation between different groups where F test = 198.32, $P = 0.0001$. In Depo-Provera users (group 4), BMD was lower than all the other groups whereas in oral contraceptive users (group 1), BMD

was higher than others as shown in table III and figure 2.

Z-scores percentages and Z-scores of different groups at lumbar spine (L2-L4) are presented in figures 3 and 4. Mean Z-scores of BMD measured was -0.34 ± 0.052 (group 1), -0.37 ± 0.067 (group 2), -0.5 ± 0.063 (group 3), -2.26 ± 0.014 (group 4) and -0.5 ± 0.068 (group 5). Z-scores of BMD measured in Depo-Provera users (group 4) ranged from -2.0 to -2.4. All women in this group had a low bone mass (osteopenia) according to WHO criteria for osteoporosis (1994) (9).

Multiple comparisons by using Post Hoc Tests (Turkey HSD) revealed a statistical significant variation of BMD between different studied groups as shown in (table IV). BMD and age-matched Z scores of Depo-Provera users (group 4) was statistically significantly decreased ($P < 0.001$) when compared with that of the other groups.

Reports of BMD measurement are presented in figures 5 and 6; typically include the following :

- Image of the bone within lumbar spine (L2-L4)
- The BMD expressed in g/cm². The bone mineral content of the scanned region.
- Normal values based on the reference database
- The T-and Z-scores based on comparison of the patient's BMD with the reference database. The results are also presented as a percentage of the mean values of the reference population.

DISCUSSION

Osteoporosis occurs in 5% to 20% of women most often between the ages of 50 and 75 years (10). Although clinicians and women more commonly focus on osteoporosis prevention in older women, helping young women to achieve and maintain a normal bone mass represents an approach in preventing postmenopausal fracture. Bone mass reaches its peak between 20-30 years and bone mass

starts to decline at age of 35 years. Most women in this study were in the fourth decade of life. This ensures that bone mass has been completed and age related bone loss has not yet been established.

Steroidal contraceptive use has been associated with changes in bone mineral density in women and conflicting results have come from different studies. However, concern about bone health may influence the recommendation and use of these effective contraceptives globally (11).

Combined oral contraceptives are used by numerous women very often throughout a prolonged period of time. The close relationship between estrogen and bone turnover raises the question of the potential bone impact of oral contraceptives. In this study, combined oral contraceptives were associated with a significant high bone mineral density when compared with the other contraceptives used.

The effect of oral contraceptives may depend on duration of use, timing and dosage levels. Oxford Center for Evidence Based Medicine levels of evidence reported a positive effect of oral contraceptives on bone mineral density in perimenopausal women when bone loss starts and the positive influence is significantly dependent on the length of treatment. However adverse effects were reported in women before age of 20 years, possibly because taking oral contraceptives at younger ages interferes with achieving peak bone mass (12). As regards the dosage, studies demonstrated that low dose oral contraceptives (30 µg ethinyl estradiol) seem to be associated with a more positive effect on bone mass than ultra-low dose oral contraceptives (20 µg ethinyl estradiol) (13).

Norplant increases bone mineral density in women of all ages. Cromer et al (14) compared bone mineral density in adolescent girls receiving Norplant and Depo-Provera. After two years, bone mineral density increased a total of 9.3% in Norplant users and 9.5% in control subjects but decreased a total of

3.1% in Depo-Provera users. Also, Cromer and Harel (15) reported a significant increase of 2.4% in BMD at lumbar spine after one year of Norplant use. Our study supports the work of the others as it showed that Norplant users had a mean higher bone mineral density than Implanon, Depo-Provera and Controls (1.182 vs 1.11, 0.842, 1.113) respectively.

In Implanon users, we found a nearly equal BMD to the control who used non hormonal intrauterine contraceptive devices as a method for contraception. This finding is consistent with that reported by Bahamondes et al (16) who found that changes from baseline in bone mineral density in Implanon users were not different from those in the control. Also, Bearthuisen et al (7) studied bone mineral density during long-term use of Implanon compared to a non-hormonal method of contraception at different anatomical sites with high trabecular bone contents such as lumbar spine, femur neck and distal radius. They reported no difference in bone mineral density changes in both groups and Implanon can safely be used in young women who have not yet achieved their peak bone mass. A study of ovarian function during the use of Implanon showed estradiol level was not low enough to cause osteoporosis. However, estradiol level remains far lower than with Norplant. This explains the higher BMD in Norplant users (17).

The relationship between the injectable Depo-Provera and bone mineral loss remains controversial. The first detrimental effect of Depo-Provera on bone mass was observed by Cundy et al (18) in which the spinal vertebrae of 30 women using Depo-Provera for 5 years in New Zealand proved to have 7% reduction in BMD than those of comparable non-users. Other authors observed approximately 3% loss in BMD at lumbar spine during each of the first 2 years of Depo-Provera use with a total of 6% after 2 years (19). More recent study demonstrated a decline in BMD of 6.4% over 4 years of Depo-Provera use (20). Differences between studies in the amount of bone loss among Depo-Provera

users may be attributable to variations in demographic characteristics of women.

Shaarawy et al (21) reported that long-term use of Depo-provera (> 2 years) had a significant adverse effect on BMD and induced increase in biochemical indices of bone formation and resorption. Also, El-Shafei et al. (22) reported a significant decrease in BMD at the ultradistal areas of the forearm. The present study found a significantly lower BMD in women using Depo-Provera than in those women using other contraceptives ($P \leq 0.001$). All women using Depo-Provera for 3 years experienced osteoporotic changes with a low bone mass (osteopenia). The mean lumbar spine Z-score was -2.26, placing women at increased risk of osteoporosis and fracture. Another study showed that the prevalence of low bone mass (osteopenia) at lumbar spine among women using Depo-Provera for 5 years was 41%. However, the prevalence of osteoporosis was 5% and 45% of them had already sustained one fracture (23).

Depo-Provera suppresses gonadotrophins, thus ovarian estrogen production is inhibited and the resulting estrogen deficiency has a detrimental impact on bone. Depo-Provera has been found to inhibit skeletal bone mineralization in adolescents and impede achievement of peak bone mass. Therefore, switching to a different contraceptives in this age group is recommended (23). In fact, one study demonstrated that administration of estrogen along with Depo-Provera prevents a decrease of bone mineral density. They reported an increase of 1% in BMD for Depo-Provera plus estrogen over 2 years interval as compared with 2.6% loss in Depo-Provera plus placebo. However, this would not be an option for women who have a contraindication to estrogen and would decrease the convenience of the method (24).

On the contrary to the observed low BMD among Depo-Provera users in the previous studies, many authors have failed to confirm any association and none have documented any clinical consequences (25).

Tancepanichskul et al⁽²⁶⁾ found that long term users (3 years) had no differences in mean BMD when compared with IUD users even if it reduces serum estradiol. Also, Merki et al⁽²⁷⁾ didn't find a negative impact of Depo-Provera on BMD in premenopausal women aged 30-45 years. Westhoff⁽²⁸⁾ reported that if bone density loss occurs in the presence of Depo-Provera, it is reversible and unlikely to adversely influence clinical events immediately or at a later time.

Boggs⁽²⁹⁾ showed that Depo-Provera related BMD loss occurs mostly during the first 2 years of use and slows afterwards. Over 4 years of Depo-Provera use, 75% of the hip BMD loss and 90% of the spine BMD loss occurred during the first 2 years, however, bone loss had declined to only 0.6% at hip and actually increased 0.4% at the spine during the 4th year. Other recent studies indicated that after Depo-Provera is discontinued, BMD fully recovers which appears to take about 3 years in adults and one year in adolescents⁽³⁰⁾. Cundy et al⁽³¹⁾ reported an increase of 3% in BMD at 12 months and 6.4% at 24 months at lumbar spine after discontinuation of Depo-Provera.

As a result of the adverse effect of Depo-Provera on bone mineral density in most studies, WHO (2001)⁽³²⁾ stated that Depo-Provera is relatively contraindicated in women under 18 years and over 45 years. Also, Food and Drug Administration (2004) issued a black box warning that use of Depo-Provera is associated with a significant loss of BMD that may not be completely reversible. It further stated that two years of Depo-Provera is now recommended as a maximum treatment period and calcium supplementation is highly recommended for these who use this method⁽³³⁾.

We can conclude that long-term use of Depo-Provera is associated with a significantly lower BMD at lumbar spine and should be considered a potential risk factor for osteoporosis. However, use of

combined oral contraceptives and Norplant was associated with an increase of BMD whereas Implanon did not appear to affect BMD. So we recommend that:

- Depo-Provera should not be the first choice in women above 35 years as BMD starts to decline.
- The negative effect of Depo-Provera on bone mineral density should be included as a part of counseling for women who will use it for a long period.
- Clients may be subjected to bone densitometry whenever it is available before using Depo-Provera and at two years of use.
- Advise women to practice behaviours conducive to optimal bone health.
- Any premenopausal women examined medico-legally for traumatic injury must be asked about the method of contraceptive used. If she uses Depo-Provera, the possible association of low BMD should be taken into consideration and measurement of BMD by using DEXA must be done in order to diagnose osteoporotic changes that may predispose to fractures.

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Table I: Age distribution among the studied groups.

Age in years (decade)	Group (1) O.C.	Group (2) Norp.	Group (3) Impl.	Group (4) Depo-Provera	Group (5) Control
20-30 (3 rd)	n = 4	n = 4	n = 6	n = 4	n = 4
31-40 (4 th)	n = 10	n = 12	n = 9	n = 10	n = 10
41 - 50 (5 th)	n = 4	n = 3	n = 4	n = 4	n = 3

Table II: Demographic characteristics of the studied groups.

Parameters	Group (1) O.C.	Group (2) Norp.	Group (3) Impl.	Group (4) Depo-Provera	Group (5) Control
Age (years):					
Minimum-Maximum	35 - 49	27 - 48	37 - 48	34 - 46	25 - 49
Mean \pm S.D.	42.2 \pm 2.59	38.9 \pm 6.74	41.0 \pm 3.43	40.8 \pm 4.83	40.6 \pm 8.03
Oneway Anova (F test) = 0.422, P = 0.792					
Weight (kg) :					
Minimum-Maximum	65 - 80	55-- 80	60 - 82	64 - 90	59 - 92
Mean \pm S.D.	70.9 \pm 6.61	66.7 \pm 7.72	68.9 \pm 6.82	74.3 \pm 8.45	73.7 \pm 12.53
Oneway Anova (F test) = 6.687, P = 0.0001*					
Height (cm) :					
Minimum-Maximum	146 - 162	152 - 169	152 - 166	150 - 168	150 - 165
Mean \pm S.D.	155.7 \pm 5.29	158 \pm 5.01	158.1 \pm 4.65	158.9 \pm 5.47	157.6 \pm 4.48
Oneway Anova (F test) = 0.571, P = 0.69					
BMI (kg/m ²) :					
Minimum-Maximum	26 - 35	23 - 31	25 - 31	23 - 37	24 - 36
Mean \pm S.D.	30.15 \pm 0.84	26.73 \pm 2.99	27.53 \pm 1.97	29.55 \pm 4.07	29.62 \pm 4.44
Oneway Anova (F test) = 0.452, P = 0.721					

Insignificant at P > 0.05

* Highly significant at P < 0.001

Table III: Bone mineral density (BMD) and Z-scores of women of the studied groups.

Parameters	Group (1) O.C.	Group (2) Norp.	Group (3) Impl.	Group (4) Depo-Provera	Group (5) Control
BMD (g/cm ²)					
Minimum-Maximum	35 - 49	27 - 48	37 - 48	34 - 46	25 - 49
Mean ± S.D.	42.2 ± 2.59	38.9 ± 6.74	41.0 ± 3.83	40.8 ± 4.83	40.6 ± 8.03
Oneway Anova (F test) = 198.319, P = 0.0001*					
Z scores :					
Minimum-Maximum	65 - 80	55-- 80	60 - 82	64 - 90	59 - 92
Mean ± S.D.	70.9 ± 6.61	66.7 ± 7.72	68.9 ± 6.82	74.3 ± 8.45	73.7 ± 12.53
Oneway Anova (F test) = 985.04, P = 0.0001*					

* Highly significant at P < 0.001

Table IV: Multiple comparisons by using Post-Hoc tests (Turkey HSD) as regards bone mineral density (BMD) and Z-scores of the studied groups.

Parameters	Group (1) O.C.	Group (2) Norp.	Group (3) Impl.	Group (4) Depo-Provera
BMD (g/cm ²) :				
Group 1				
Group 2	0.509			
Group 3	0.0001*	0.0001*		
Group 4	0.0001*	0.0001*	0.0001*	
Group 5	0.0001*	0.0001*	0.999*	0.0001*
Z scores :				
Group 1				
Group 2	0.925			
Group 3	0.0001*	0.0001*		
Group 4	0.0001*	0.0001*	0.0001*	
Group 5	0.0001*	0.0001*	0.999*	0.0001*

Insignificant at P > 0.05

* Highly significant at P < 0.001



Fig. 1. DEXA EQUIPMENT (DPX-IQ-Lunar)

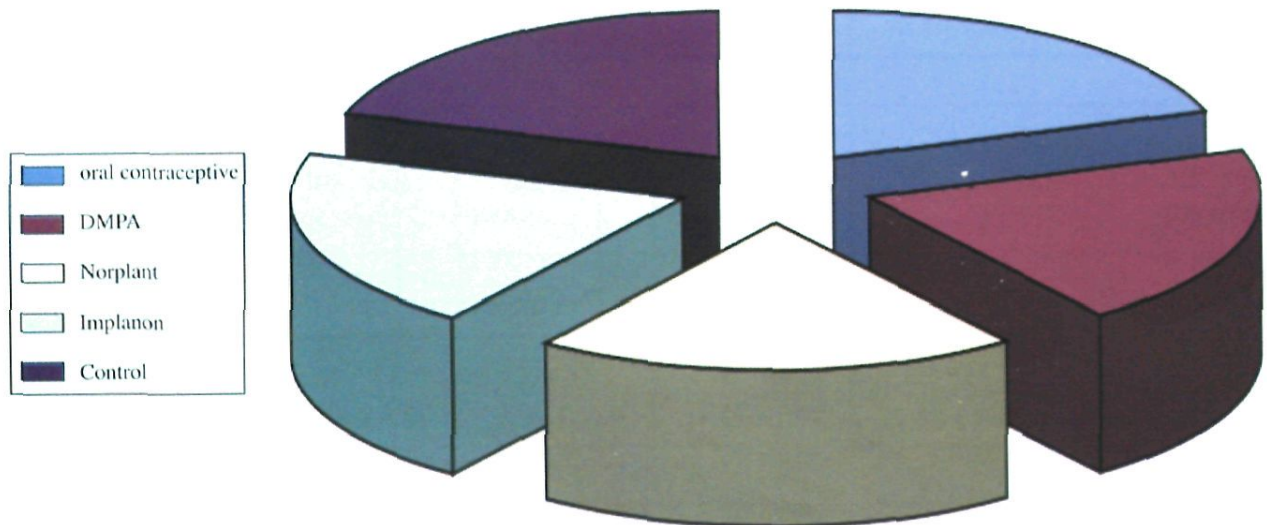


Fig. 2. BMD of the studied groups (in gm per cm²)

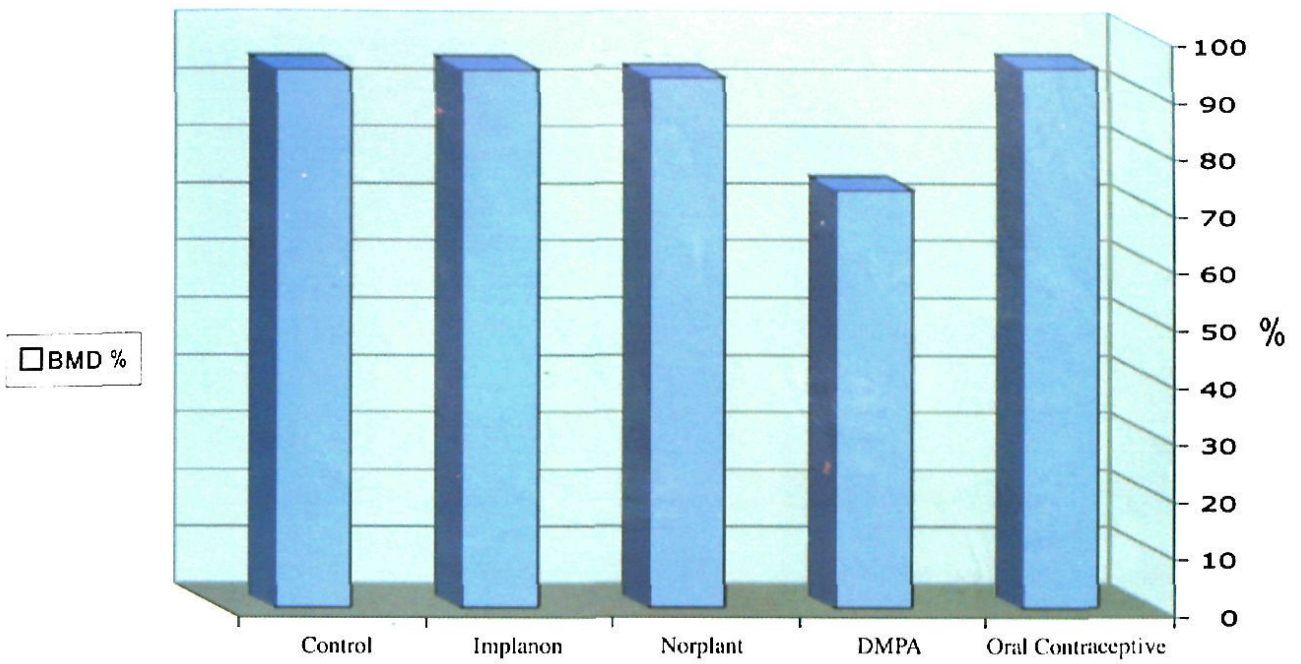


Fig. 3. BMD % of studied groups (age-matched Z scores)

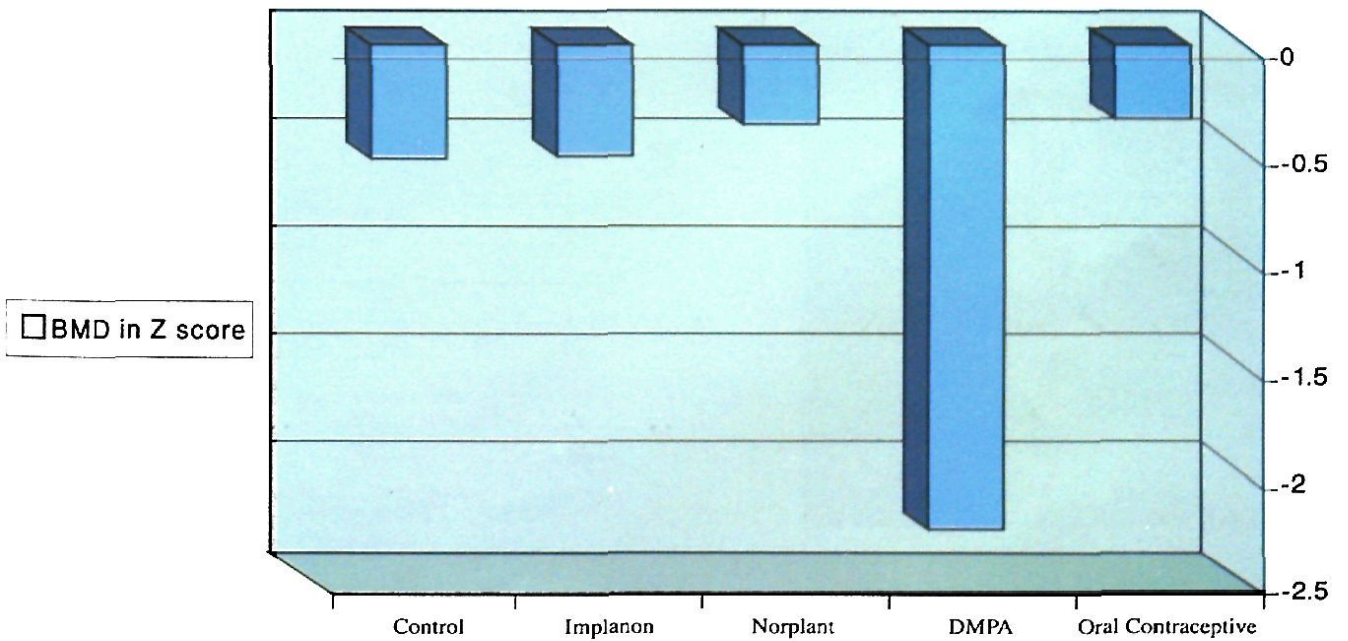


Fig. 4. Age-matched Z-scores of BMD of the studied groups

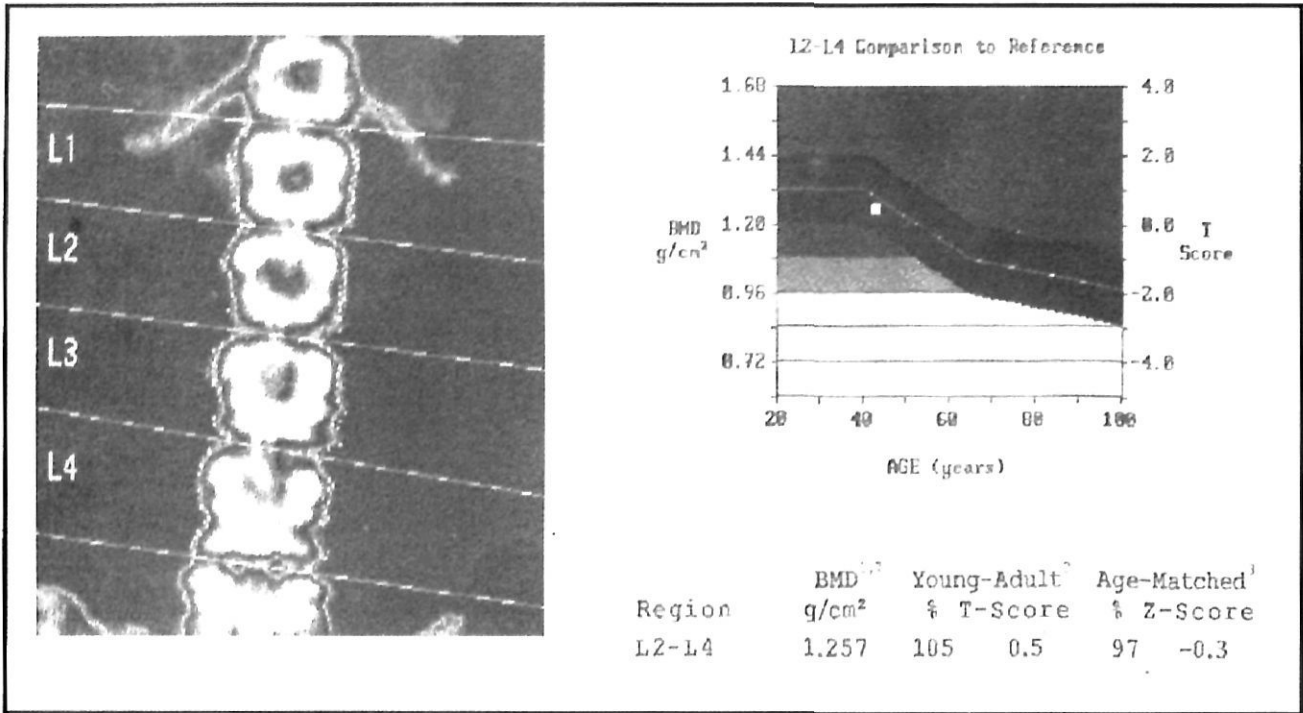


Fig. 5. Normal bone mineral density "BMD" of lumbar spine (L2-L4) in women using non hormonal contraceptive "IUD". BMD=1.257, Z-score = -0.3

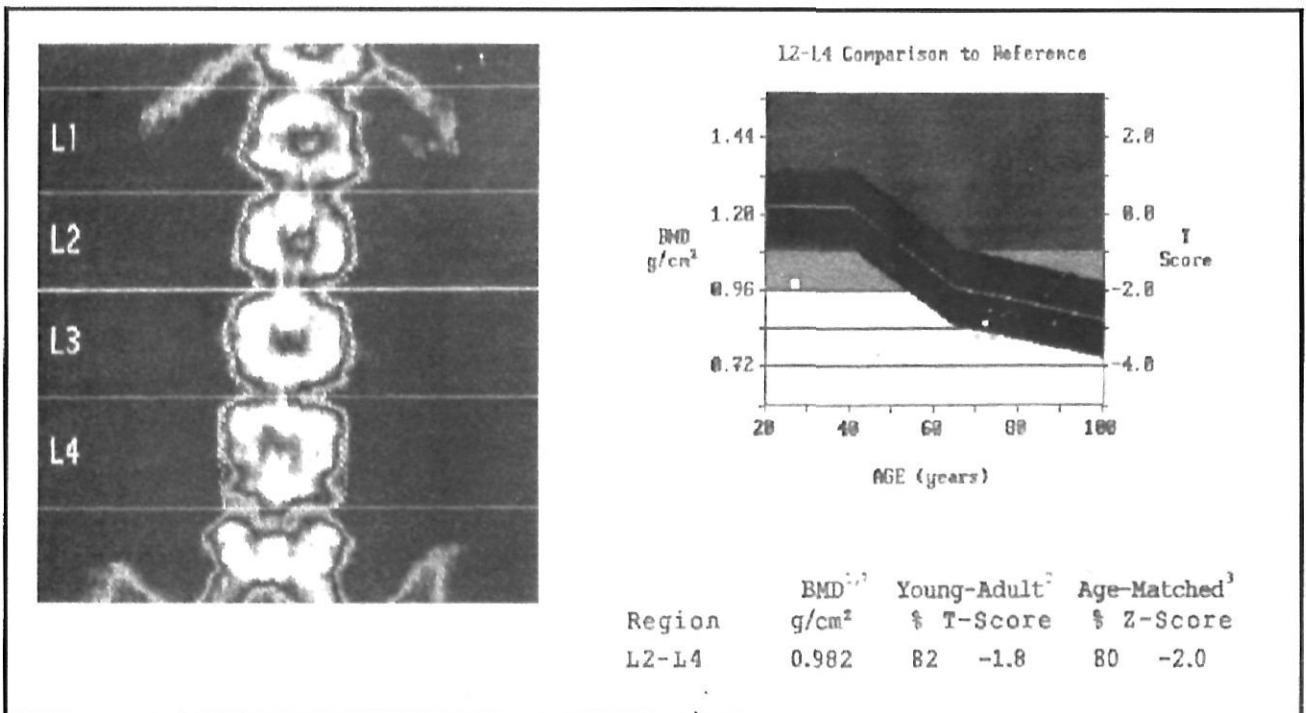


Fig. 6. Osteoporotic changes in lumbar spine (L2-L4) of women using Deop-Provera for 3 years BMD=0.982, Z-score = 2.0