2005; Cilt: 2 Sayı: 4 Sayfa: 332-336

THE EFFECTS OF THE COMBINED ORAL CONTRACEPTIVES ON THE BONE MINERAL DENSITY OF REPRODUCTIVE AGE WOMEN

Gökçen YÜCER* , Aykan YÜCEL, Volkan NOYAN **, M. Sühha BOSTANCI *, Nevin SAĞSÖZ *****

*Kırıkkale University Department of Obstetrics and Gynecology
**Kırıkkale University Department of Obstetrics and Gynecology
***Kırıkkale University Department of Obstetrics and Gynecology

SUMMARY

Objective: *To determine the effects of combined oral contraceptives (COC's) on bone mineral density of women after 12 month treatment.*
Design: *Comparison of the Bone Mineral Density (BMD) and serum Ca+2, osteocalcin, alkaline phosphatase, Vitamin D3 and urinary OH-proline levels.*
Setting: *Kırıkkale University Medical Faculty Hospital.*
Patients: *Fifty patients of ages < 40 years who took combined oral contraceptive for 12 months.*
Intervention: *Bone Mineral Density Measurements and comparison of these values at the beginning and after 12 month of COC treatment.*
Results: *The serum level of Ca+2 significantly increased [p<0.05] at the time of observation in comparison to the basal level. The urinary excretion of OH-proline over 12 months significantly decreased [p<0.05] at the end of study. At 12th month, no significant difference was detected in lumbar, femur, and distal ulna-radius BMD values in comparison with basal values. The BMD of proximal ulna-radius significantly increased [p<0.05] at the end of twelve months in comparison to basal content.*
Conclusions: *The contraceptive pill containing 20 µg Ethinyl estradiol + 100 µg Levonorgestrel has beneficial effects on the bone turnover and bone mineral density at proximal ulna-radius.*

Key words: *combined oral contraceptive, bone mineral density, OH-proline, proximal ulna-radius.*

ÖZET

Kombine Oral Kontraseptif Tedavisinin Kemik Mineral Yoğunluğu Üzerine Etkisi

Objektif: *Kadınlarda 12 ay kombine oral kontraseptif tedavisinin kemik mineral yoğunluğu üzerine etkisi.*
Planlama: *Kemik mineral yoğunluğu, serum Ca+2, osteokalsin, alkaline fosfotaz, Vitamin D3 ve uriner OH-prolin seviyelerinin karşılaştırılması.*
Ortam: *Kırıkkale Üniversitesi Tıp Fakültesi Hastanesi.*
Hastalar: *Oniki ay süresince kombine oral kontraseptif kullanan 40 yaşaltı 50 hasta.*
Girişim: *Kombine oral kontraseptif tedavisi başlangıcında ve 12. ayındaki kemik mineral yoğunluğu ölçümlerinin karşılaştırılması.*
Sonuçlar: *Serum Ca+2 seviyesi bazal seviye ile karşılaştırıldığında 12. ayda anlamlı olarak artmıştır [p<0.05]. Çalışmanın sonunda uriner OH-proline atılımı anlamlı oranda azalmıştır. Onikinci ayda ilk değerler ile karşılaştırıldığın da lumbar, femur, ve distal ulna kemik mineral yoğunluğu seviyeleri arasında anlamlı fark gözlenmemiştir. Proksimal ulna-radius kemik mineral yoğunluğu, ilk değerler ile karşılaştırıldığında 12. ay sonunda anlamlı olarak artmıştır [p<0.05].*
Yorum: *20 µg Ethinyl estradiol + 100 µg Levonorgestrel içeren oral kontraseptifler kemik mineral yoğunluğu ve kemik dönüşümü üzerinde yararlı etkilere sahiptir.*

Anahtar kelimeler: *kombine oral kontrazeptif, kemik mineral dasitometrezi, OH-prolin, proksimel ulna radiur*

Correspondence Address: Aykan YÜCEL. Kırıkkale Üniversitesi Tıp Fakültesi Hastanesi Kadın Hastalıkları ve Doğum Anabilim Dalı, KIRIKKALE
Tel: (0318) 225 24 85 (181) e.mail:aykanyucel@gmail.com
Alındığı tarih: 07. 11. 2005, kabul tarihi:23.11. 2005

INTRODUCTİON

The peak bone mass and its progressive loss are thought to be the determinants of bone mass in later life and are, therefore, major determinants of fracture risks[1]. Bone mass increases quickly during childhood and reaches a peak at about 30 years of age[2]. This stage is followed by transient stability period through 35 years of age[3] when the bone mass begins to decline, it accelerates again at the perimenopausal years[2,4]. Cross-sectional studies indicate that approximately 80% of peak bone mass is controlled by genetic factors, with hormonal status, body weight changes, physical activity, and diet as potentially modifiable determinants [5, 6].

During treatment with low-dose (<50 μg) combined oral contraceptives (COC's), plasma 17 _ – estradiol levels are similar to those found in early follicular phase[7] and increased levels of sex hormone-binding globulin are observed[8], resulting in diminished concentrations of free testosterone, an inhibition of gonadotropin secretion, and further decrease in ovarian androgen secretion[9], suggesting the presence of an estrogenic environment. COC's could potentially have a greater effect on bone mineral density due to a decreased concentration of circulating sex steroids. As estrogen and testosterone can profoundly affect bone metabolism[10], both premenopausal and postmenopausal women with low estrogen concentrations are at increased risk for osteoporosis[11]. The potential effect of COC's over bone in premenopausal women is a current topic of interest.

Relatively there are few studies concerning the association between COC's use and changes in bone mineral density in women under age 40 and the results have been inconsistent[12, 15]. Conflicting results may be due in large part to the age of participants, the estrogen/progestin doses in COC preparations, and the duration of the studies.

MATERİALS AND METHODS

Fifty healthy women between 18 and 34 years of age were enrolled for the study. All the subjects were given their written informed consent according to the protocol approved by the local ethics committee. All women had normal menstrual cycles and age of menarche between 12 and 14 years old. The criteria for inclusion in our study were no evidence of pregnancy, absence of menstrual abnormalities, presence of an ovulatory cycle just prior to the study (assessed by basal temperature and a progesterone assay), and no history oral contraceptive use. The criteria for exclusion were the presence of endocrinological pathology (thyroid, parathyroid, renal dysfunction of hypothalamus-hypophysis-ovary axis), cigarette smoking, hepatic pathological history and dysfunctions of glucose, lipid or coagulation metabolism. Before the study, all the subjects underwent gynecological examination and a complete hematochemical evaluation. The systolic and diastolic pressures were evaluated, and body mass indexes (BMI) were calculated. All women enrolled, did not suffer from bone diseases or disorder of bone metabolism. All of them followed a normal diet without low or high caloric ingestion.

After confirming inclusion in the study, 50 women were assigned to a 12-month oral treatment with a pill containing 20μg Ethinyl estradiol + 100 μg Levonorgestrel; (Miranova®;Schering, Istanbul, Turkey). No additional treatment was given. The serum FSH, LH, E2, PTH, Collagen, and C-peptide were measured using Olympus AY 92 (Roche), bone alkaline phosphates by EIA (Metra BAP, Merck), Ca +2 , osteocalchine, and Vitamin D3 by Olympus AU 800 (Roche). The urine OH-proline was measured using by DPD EIA (Roche).

Blood and urine samples were collected upon awaking between 8:00-9:00 a.m. after a 12-h fast. Blood samples collected in tubes with clot-activating factor were immediately centrifuged in a refrigerated centrifuge. Sera were stored at -80 °C until assayed. Urine samples were stored at -20°C until biochemical analysis. All samples from the same women were analyzed in the same assay and were analyzed in laboratory blinded to the treatment. Baseline urinary and serum samplings were thus repeated 12 –month, during the 3rd to 7th day after the onset of spontaneous or pill-induced menstrual bleeding.

Bone Mineral Densitometry (BMD) was determined by dual-energy X-ray absorptiometry (DEXA, Norland XR-36 Corporation, Wisconsin, USA) of posterior-anterior lumbar spine (L1-L4), proximal femur (total hip), distal radius-ulna and proximal ulna-radius of the forearm at the beginning of the study and after 12 months of treatment. Each woman received all of her

scans on the same densitometer and operated by the same technician.

RESULTS

All of the patients completed the study. Irregular bleedings or side effects did not occur.

The mean age was (23.3 ± 5.4). The demographic, and obstetric characteristics of the patients studied are shown in Table I.

Table I: *Demographic, obstetric characteristics of the patients*

	n=50
Age	25.30 ± 5.44
BMI (kg/cm^2)	21.10 ± 2.37
Number of deliveries	2.12 ± 1.80
Number of pregnancies	3.20 ± 2.60

The serum levels of PTH, Collagen C peptide, Osteocalcin, vitamin D3 over 12 months did not show any significant difference in comparison with basal levels (Table II). Similarly, alkaline phosphatase levels did not reveal any significant modifications in comparison with baseline. The serum level of Ca+2 significantly increased [p<0.05] at the time of observation in comparison to the basal level (Table II). The urinary excretion of OH-proline over 12 months significantly decreased [p<0.05] at the end of the time of observation in comparison to basal level (Table II). Though, no significant difference was detected in lumbar, femur, and distal ulna-radius BMD values at twelve months in comparison with basal values (Table III), the BMD of proximal ulna-radius significantly increased [p<0.05] at the end of twelve month in comparison to basal content (Table III).

Table II: *Serum values of bone determinants at the beginning and at 12 months treatment.*

	Mean ± Standard Deviation		
	Baseline	After 12 months	p value
Ca^{+2}	9.38±0.58	9.62±1.48	0.002
PTH	39.9± 1.58	43.0±4.49	NS
Collagen C peptide	0.38±0.19	0.38±0.17	NS
Osteocalcin	9.38± 4.19	9.44±5.06	NS
Vitamin D3	27.8±2.52	34.4±3.74	NS
Alkaline phosphatase	26.4 ±8.07	28.5±3.45	NS
OH proline	9.53± 2.97	7.84±2.56	0.002

NS: non-significant

Table III: *The bone mineral density values at the beginning and at 12 months treatment.*

	Mean ± Standard Deviation		
	Baseline	After 12 months	p value
Femur (g/cm^2)	0,7724±0,609	0,6700 ±0,615	NS
Lumbar vertebra (g/cm^2)	0,6350±0,489	0,5476 ±0,461	NS
Distal ulna-radius (gr/cm^2)	0,7110±0,662	0,6394 ±0,642	NS
Proximal ulna-radius (gr/cm^2)	0,9798 ±0,677	1,1018 ±0,681	0,01

NS: non-significant

DISCUSSION

Cross-sectional studies indicate that approximately 80% of peak bone mass is controlled by genetic factors, with hormonal status, body weight changes, physical activity, and diet as potentially modifiable determinants [5, 6].

COC's use has been associated with increased cortical and trabecular bone mass and higher BMD in both premenopausal and postmenopausal women in some studies[4, 8, 13, 16, 17], however, other studies did not find a positive effect of COC's on bone mass[4, 18, 19].

Estrogen increases calcium absorption and decreases the concentrations of minerals in serum and urine, indicating reduced bone resorption[20]. We found an increased serum Ca+2 level after 12 months of COC treatment. An inverse relationship between serum osteocalcin and estradiol concentration has been described in pregnancy and lactation[21], and after menopause[22], suggesting that physiological changes in estradiol levels may affect bone turnover rate. Since estradiol production changes during menstrual cycle, with highest concentrations before ovulation, the levels of bone markers may also vary depending on the sampling day. However, studies on bone turnover have yielded conflicting results; some authors have reported no changes in osteocalcin[23], alkaline phosphatase, and urinary OH-proline levels[24]. Though there are reports describing elevated osteocalcin levels during the luteal phase[25]. We found no significant difference between the levels of osteocalcin, alkaline phosphatase, vitamin D3, and collagen C peptide at the beginning and after 12 months of the treatment. These results contrast with previous findings of Rodin et al.[26] who found no significant difference in serum alkaline phosphatase and osteocalcin.

Indeed, consistent with the finding of Rodin et al.,[26] we found no significant difference in total alkaline

phosphatase activity, a non-bone specific marker. Although the bone turnover rate was decreased by oral contraceptive use, no difference in bone mineral density measured at various sites including lumbar spine, femur, and distal ulna-radius occured at the beginning and after 12 months of COC use. But we found a significant increase in bone mineral density at the proximal ulna- radius. Owing to its nature, the scan of the lumbar spine includes mainly the metabolically active trabecular bone of the vertebral body but also a substantial amount of cortical bone, particularly in the posterior elements[27]. But proximal ulna-radius region occurs mainly by the cortical bone and the increase of bone mineral density may be due to this reason. This is probably due to the low Ethinyl estradiol content (20 μg) which is able to prevent bone mass loss but is ineffective in achieving the peak bone mass [28].

Our data showed a positive effect of COC's containing 20 μg Ethinyl estradiol + 100 μg Levonorgestrel on bone turnover. Indeed, a significant decrease of urinary OH-proline was observed with 12 month treatment with COC in comparison to basal values. In conclusion, the present study suggests that the contraceptive pill containing 20 μg Ethinyl estradiol + 100 μg Levonorgestrel has beneficial effect on the bone turnover and bone mineral density at the proximal ulna-radius region.

REFERENCES

1. Riggs BL, Melton LJ III. The prevention and treatment of osteoporosis. N Engl J Med 1992;327:620-627.
2. Recker RR, Davies KM, Hinders SM, Heaney RP, Stegman MR, Kimmel DB. Bone gain in young adult women. JAMA 1992;17:2403-248.
3. Buchwalter JA, Glimcher MJ, Cooper RR, Recker R. Bone biology formation, modeling, remodeling and regulation of all function. J Bone Joint Surg 1995;77:1276-1289.
4. Mazess RB, Barden HS. Bone density in premenopausal women: effect of age, dietary intake, physical activity, smoking, and birth-control pills. Am J Clin Nutr 1991;53:132-142.
5. Barr SI, Mckay HA. Nutrition, exercise, and bone status in youth. Int J Sport Nutr 1998;8:124-142.
6. Rubin LA, Hawker GA, Peltekova VD, Feielding LI, Ridout R, Cole DEC. Determinants of peak bone mass: clinical and genetic analyses in young female Canadian cohort. J. Bone Miner Res 1999;14:633-643.
7. Ludicke F, Sullivan H, Spana J, Elstein M. Dose Finding in a low dose 21-days combined oral contraceptive containing gestodone. Contraception 2001;64:243-248.
8. Paoletti AM, Orr_ M, Floris S, et al. Evidence that treatment with monophasic oral contraceptive formulations containing ethinyestradiol plus gestodone reduces bone resorption in young women. Contraception 2000;61:259-263.
9. Burkman RT. The role of oral contraceptives in the treatment of hyperandrogenic disorders. Am J Med 1995; 98 (Suppl1A): 1305-1365.
10. Hoshimo S, Inove S, Hosoi T, et al. Demonstration of isoforms of the estrogen receptor in the bone tissues and in osteoblastic cells. Calcif Tissue Int 1995;57:466-468.
11. Consensus Development Conference. Diagnosis, prophylaxis, and treatment of osteoporosis, Am J Med 1993;94:646-650.
12. Lloyd T, Buchanan JR, Ursino GR, Myers C. Woodward G, Halbert DR. Long-term oral contraceptive use does not affect trabecular bone density. Am J Obstet Gynecol 1989;160:402-404.
13. Perrotti M, Bahamondes L, Petta C, Castrol S. Forearm bone density in long term users of oral combined contraceptives and depot medroxyprogesteron acetate. Fertil Steril 2001;76: 469-473.
14. Berenson AB, Radecki CM, Grady JJ, Rickert VI, Thomas A. A prospective, controlled study of the effects of hormonal contraception on bone mineral density. Obstet Gynecol 2001; 98:576-582.
15. Cromer BA. Effects of hormonal contraceptives on bone mineral density. Drug Saf 1999;20:213-222.
16. Volpe A, Amram a, Cagnacci A, Battaglia C. Biochemical aspects of hormonal contraception: effects on bone metabolism. Eur J Contracept Reprod Health Care 1997;2:123-126.
17. Massaryk P, Lunt M, Benevolenskaya L, et al. Effects of menstrual history and use of medications on bone mineral density: the EVOS Study. Calcif Tissue Int 1998;63:271-276.
18. Tuppurainen M, Kroger H, Saarikoski S, Honkanen R, Alhava E. The effect of previous oral contraceptive use on bone mineral density in perimenopausal women. Osteopor Int 1994;4:93-98.
19. Murphy S, Khaw KT, Compston JE. Lack of relationship between hip and spine bone mineral density and oral contraceptive use. Eur J Clin Invest 1993,23:108-111.
20. Aitken JM, Hart DM, Lindsay R. Oestrogen replacement theraphy for prevention of osteoporosis after oophorectomy. Br. Med J 1973;3:515-518.
21. Cole DEC, Gundberg C. M. , and Stirk L. , et al. Changing osteocalcin concentrations during pregnancy and lactation:

Implications for maternal mineral metabolism. J Clin Endocrinol Metabol 1987;65:290.

22. Slemenda C, Hui S, Logcope C, Johnston C. sex steroids and bone mass. A study of changes about the time of menopause. J Clin Invest 1987;80:1261-1269.
23. Gundberg CM, Markowitz ME, Mizruchi M, Rosen JF. Osteocalcin in human serum. A circadian, rhythm. J Clin Endocrinol Metabol. 1985;60:736.
24. Tjellesen L, Christiansen C, Hummer L, Larsen NE. Unchanged biochemical indices of bone turnover despite fluctuations in 1,25-dihydroxyvitamin D during menstrual cycle. Acta Endocrinol 1983;102:476.
25. Nielsen HK, Brixen K, Bouillon R, Mosekilde L. Changes in biochemical markers of osteoblastic activity during menstrual cycle. J Clin Endocrinol Metabol 1990;70:1431-1437.
26. Rodins SP, Black D, Paterson CR, Reid DM, Duncan A, Seibel MJ. Evaluation of hydroxypyridium cross link measurements as resorption markers in metabolic bone diseases. Eur J Cin Invest 1991;21:310-315.
27. Jergas M, Genant HK. Lateral dual X-ray absorptiometry of the lumbar spine: current status. Bone 1997;4:311-314.
28. Polatti F, Perotto F, Filippa N, Gallina D, and Nappi ER. Bone Mass and Long-Term monophasic oral contraceptive treatment in young women. Contraception 1995;51:221-224.