นิพนธ์ต้นฉบับ

Effect of hormonal replacement therapy on bone changes in Thai menopausal women: a preliminary reports.

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Objective : *To study the effect of hormonal replacement therapy on bone changes*

Design : *Prospective, randomised study*

Setting : *Menopause clinic Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University.*

Subjects : *One hundred and thirty seven premenopausal and postmenopausal women with age range of 40–62 (mean ± SD = 48.67 ± 7.65) years were recruited into the study. Women in the study group (77/137) used estrogen replacement therapy either with or without progestogen. The control group (60/137) did not use any hormonal regimens.*

Main outcome measure : *Bone mass density was measured at both lumbar spines and hips in each clients with Dual Energy x-ray Absorptiometry (DEXA) at O and 6 month*

Results : *There were no significant difference in bone changes between the study group (Lumbar spines : 0.48 ± 0.70%; Hips : 0.56 ± 1.76%) and the control group (Lumbar spines : -2.97 ± 1.29%; Hip : 1.37 ± 1.43%) in the first six-month of bone monitoring. Nevertheless, when considered into the surgical menopausal women, it showed that there was tendency of greater bone loss in the non-hormonal group (Lumbar spines : -9.08 ± 4.37%; Hip : -5.62 ± 5.67%) than in the hormonal treated group (Lumbar : -1.70 ± 0.78%; Hip -2.48 ± 0.56%), though, there was no statistically significant difference.*

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Conclusion : *The preliminary results showed some beneficial effects of hormonal replacement therapy (HRT) in slowing bone loss especially in the group of surgical menopause, any further long term effect ofHRT in other group of menopausal women will be followed.*

Key words : *Hormonal replacement therapy, Bone changes.*

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กอบจิตต์ ลิมปพยอม, นิมิต เตชไกรชนะ, มาคุ้มครอง โปษยะจินดา, อรรณพ ใจสำราญ. ผลของฮอร์โมนทดแทนต่อการเปลี่ยนแปลงของกระดูกในสตรีไทยวัยหมดระดู : รายงานเบื้องต้น. จุฬาลงกรณ์เวชสาร 2537 พฤศจิกายน; 38(11): 679-687

วัตถุประสงค์ *เพื่อศึกษาถึงผลของฮอร์โมนทดแทนต่อการเปลี่ยนแปลงของกระดูก*

รูปแบบการวิจัย *การศึกษาไปข้างหน้า แบบแรนดอมไมส์*

สถานที่ *คลินิคสตรีวัยหมดระดู ภาควิชาสูติศาสตร์-นรีเวชวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์ มหาวิทยาลัย*

ผู้เข้าร่วมการศึกษา *การศึกษานี้ได้คัดเลือกสตรีก่อนและหลังวัยหมดระดู อายุระหว่าง 40-62 ปี (ค่าเฉลี่ย ± ค่าเบี่ยงเบนมาตรฐานของอายุ =48.67 ± 7.65) จำนวน 137 ราย โดยเป็นกลุ่มศึกษาคือ สตรีที่ได้รับฮอร์โมนทดแทน (ได้รับเอสโตรเจนอย่างเดียว หรือร่วมกับโปรเจสเตอโรน) 60 ราย และกลุ่มควบคุม ซึ่งไม่ได้รับฮอร์โมนทดแทน 77 ราย*

การวัดผล *ทำการตรวจวัดความหนาแน่นของกระดูกที่บริเวณสันหลังลัมบาร์ และกระดูกสะโพกโดยเครื่อง Dual Energy X-ray Absorptiometry (DEXA) ที่ 0 และ 6 เดือน*

ผลการศึกษา *ภายหลัง 6 เดือน พบมีความแตกต่างในการเปลี่ยนแปลงของความหนาแน่นของกระดูกในกลุ่มศึกษาและกลุ่มควบคุมอย่างไม่มีนัยสำคัญทางสถิติ (กลุ่มศึกษา : การเปลี่ยนแปลงของกระดูกสันหลังลัมบาร์ = 0.48 ± 0.70% กระดูกสะโพก = 0.56 ± 1.76%; กลุ่มควบคุม : การเปลี่ยนแปลงของกระดูกสันหลังลัมบาร์ = 2.97 ± 1.29%; กระดูกสะโพก = 1.37 ± 1.43%) อย่างไรก็ตามเมื่อพิจารณาในกลุ่มสตรีหมดระดูจากการตัดมดลูกและรังไข่ทั้งสองข้าง พบว่าในกลุ่มที่ไม่ได้รับฮอร์โมนทดแทนมีการสูญเสียเนื้อกระดูกมากกว่ากลุ่มที่ได้รับฮอร์โมนทดแทนอย่างชัดเจนถึงแม้จะไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติก็ตาม (กลุ่มศึกษา : การเปลี่ยนแปลงของกระดูกสันหลังลัมบาร์ = -1.70 ± 0.78%; กระดูกสะโพก = -2.48 ± 0.56%; กลุ่มควบคุม : การเปลี่ยนแปลงของกระดูกสันหลังลัมบาร์ = -9.8 ± 4.37%; กระดูกสะโพก = -5.62 ± 5.67%)*

วิจารณ์และสรุป *ผลการศึกษาในเบื้องต้นแสดงแนวโน้มของประโยชน์ในการใช้ฮอร์โมนทดแทนเพื่อป้องกันการสูญเสียเนื้อกระดูก โดยเฉพาะในสตรีที่ได้รับการตัดมดลูกและรังไข่ทั้งสองข้าง สำหรับผลในระยะยาวโดยเฉพาะสตรีวัยหมดระดูตามธรรมชาติ คณะผู้วิจัยจะได้ทำการติดตามและศึกษาต่อไป*

Loss of ovarian function at menopause results in changes in many organ systems such as vasomotor instability, urogenital atrophy, cardiovascular changes, bone changes, etc. Osteoporosis is one of the most common diseases and affects most women by the end of their lives. About 50% of those affected sustain some form of osteoporotic fracture.[1] At present, osteoporosis is a major public health peoblem. For example, in the United States it affects more than 25 million people. Predisposes to more than 1.3 million fractures annually, including more than 500,000, 250,000 and 240,000 fractures of the spine, hip and wrist, respectively and costs the nation in excess of $10 billion[2,3] Hip fracture is a devastating manifestation of osteoporosis; 5-20 of hip fracture victims will die within one year of the fracture event and over 50% of the survivors will be incapacitated, many of them permanently.[2] Osteoporosis is worldwide-occurring in every population and peopraphic area studied thus far. Nevertheless, fracture incidence differs markedly among different populations and ethnic groups. It is greatest in whites and Asians and being least in black.[2,3] With urbanization, the incidence of hip fracture increased dramatically in the 1980's in some Asian countries, such as Hong Kong, Singapore, Japan, etc.[4,5] Since the elderly are at greatest risk for osteoporotic fractures, the progressive aging of the world's population predicts a substantial increase in the global burden of osteoporosis.[2] According to a United Nation definition[6], a population is said to be aging if the proportion aged 65 years and over 1s 7%. Using this criteria, Thailand will have an aged population (9.1%) by the year 2025.

Among the risk factors for osteoporosis other than falls, age and existing fractures which are predictors of fracture incidence, bone mass is the major measurable determinant of osteoporotic fractures.[2] The major factors that determine whether a person develops osteoporosis are the peak bone mass and subsequent bone loss,[7] particularly at the menopausal period. Strong evidence indicates that genetic and life style factors are important determinants of peak bone mass.[2] Concerning subsequent bone loss, bone density in women appears to fall exponentially, commencing just before menopause[8,9] when ovarian function begins to decline. The loss is even greater after oophorectomy.[10] The 1993 Consensus Development Coference on osteoporosis concluded that[2] estrogen is the agent of choice in preventing postmenopausal bone loss, because it is the only treatment which unequivocally reduces fractures. Estrogens are also effective in reducing bone loss among women long after menopause. However, the use of estrogen alone increases the risk of uterine cancer with some studies estimating that women who use estrogen for at least 8 years have a relative risk for endometrial cancer of 8.2.[11] There has also been about the possible risk of breast cancer in estrogen treated women. Though many studies have failed to show an increased incidence of breast cancer, some have shown a small increase after prolonged therapy for ten years or longer.[2]

In Thailand, there is no concrete conclusion concerning the risks and benefits of hormonal replacement therapy, especially on the effect on bone changes in menopausal women. And with the different life style and nutritional status of Thai people as compared to modernized western countries, the objective of this study is to determine the effect of HRT on bone changes among Thai menopausal women.

Materials and Methods

Healthy premenopausal and postemenopausal women attending the Menopausal Clinic at the Department of Obstetrics and Gynecology, Chulalongkorn University Hospital were eligible for this prospective, ramdomised study if the postmenopausal women had had amenorrhea for at least 6 months and a serum follicle stimulating hormone (FSH) level above 35 IU per liter and a serum estradiol level below 100 pmol per liter or the premenopausal women who still had their periods or who had had amenorrhea for less than 6 months but complained of climacteric symptoms such as hot flushes and had serum FSH and estradiol levels as mentioned above. To eliminate factors influencing lipid metabolism, we included only women who were nonsmokers, did not consume alcohol regularly, were not on steroid hormones or medications that affect lipid metabolism, and did not have any endocrinologic disorders or any chronic illnesses.

One hundred and thirty seven premenopausal and postmenopausalsubjects who were recruited in this study as the above criterias, were randomly allocated into two groups. The first study group comprised of 77 natural and surgical menopausal women, were given hormonal replacement therapy and the second group, comprised of 60 natural and surgically menopause women, were given only calcium supplements with or without parasympatholytic agents as whown in Table 1.

Table 1. Intervention.

Group	Type of menopause	Type of hormone used
HRT	1. Natural	1. Cyclic : EV (2mg) + Norgestrel (500 ug)
		2. Cyclic : CEE (0.625 mg) + Medrogestone (5 mg)
		3. Combined continued regimen : CEE (0.625 mg) + MPA (2.5 mg)
	2. Surgical	1. Cyclic : (CEE 0.625 mg)
		2. Cyclic : E2 gel
		3. Cyclic : E2 transdermal patch
Non-HRT		**Calcium + Parasympatholytics**

*EV = Estradiol valerate, CEE = Conjugated equine estrogen
MPA = Medroxy progesterone acetate, E2 = Estradiol

Bone mass density (BMD) measurement at both lumbar spines (L1-L4) and hip using Dual Energy X-ray Absorptiometry (DEXA), Hologic QDR-2000 were obtained from each subject before entering the study. Subsequently, measurements were performed at 0 and 6 month. The treatment effect was defined as percent changes of BMD after the first six month interval. Com-

parison between the HRT and non-HRT groups, and determination of statistical significance, was evaluated using the unpaired t=test and analysis of variance (ANOVA). The data are presented as mean ± standard error (S.E.).

Results

One hundred and thirty seven women were recruited in the study. The characteristics of the hormone use and nonusers groups did not show significant differences as in table 2.

Table 2. Clinical characteristics of the study population.

Characteristic	Hormone use** (N = 77)	Non users** (N = 60)	P-value* (p < 0.01)
1. Age (yr)#	49.16 ± 0.59	49.68 ± 0.60	NS
2. Height (cm)	154.50 ± 0.59	154.35 ± 0.62	NS
3. Weight (kg)	55.36 ± 0.72	59.33 ± 1.51	NS
4. Postmenopausal period (yr)	2.89 ± 0.33	2.54 ± 0.51	NS

Age range = 40-62 (mean ± SD = 48.67 ± 7.65) years

* Unpaired t-test

** Mean ± standard error

When comparing the mean baseline BMD before entering the study among the three different age groups, (the premenopausal group, the early postmenopausal age group which was within 5 years since cessation of menstruation, and the late postmenopausal age group which was more than 5 years after menopause) the ANOVA, results showed that mean baseline value decreased with advancing age with a was statistically significant difference among the groups. Table 3.

Table 3. Mean baseline BMD in various premenopausal and postmenopausal groups.

Site of measurement	Premenopause** (N-44) (gm/cm^2)	Postmenopause** (<5yrs) (N=73) (gm/cm^2)	Postmenopause** (>5yrs) (N=14) (gm/cm^2)	P-value* (p<0.001)
1. Lumbar spines	0.97 ± 0.02	0.91 ± 0.01	0.75 ± 0.02	P<0.001
2. Hips	0.85 ± 0.02	0.82 ± 0.02	0.71 ± 0.02	P<0.01

NB There're still some results of measurements unavailable at the time of this preliminary report.

*ANOVA

** Mean ± standard error

Of the 95 women who completed the first two measurements at 6 month-interval apart at the time of this preliminary report, there were 81 naturally menopausal women, of these 47 in the hormone use and 34 were in the nonusers group. Of the 14 surgically menopausal women, there were 7 each in the hormone and nonusers groups.

When considering the percent changes of BMD after the first 6 month interval among the hormone use and nonusers groups there were no statistically significant differences between both groups, though the results showed negative changes of lumbar spines in the nonusers group. Table 4.

Table 4. Percent changes of BMD in HRT group in the first 6-month interval.

Site of bone measurement	Hormone use** (N = 54) (%)	Non users** (N = 41) (%)	P-value* (p<0.001)
1. Lumbar spines	0.48 ± 0.70	-2.97 ± 1.29	NS
2. Hips	0.56 ± 1.76	1.37 ± 1.43	NS

* Unpaired t-test

** Mean ± stamdard error

Comparing the natural with the surgical menopausal groups, we found a significant reduction in percent changes in the nonuser of the surgical group over the natural group. Nevertheless, there were no statistically significant difference in percent changes between the hormone use and nonusers groups both in the natural and surgical menopausal women. Table 5 and 6.

Table 5. Percent change of BMD in hormone use and nonusers, natural menopausal group in the first 6-month interval.

Site of measurement	Hormone use** (N = 47) (%)	Non users** (N = 34) (%)	P-value* (p<0.001)
1. Lumbar spines	0.59 ± 0.70	-1.72 ± 1.29	NS
2. Hips	0.43 ± 1.76	2.81 ± 1.43	NS

*Unpaired t-test

**Mean ± standard error

Table 6. Precent change of BMDin hormone use and nonusers, surgical menopausal group in the first 6-month interval.

Site of measurement	Hormone use** (N = 47) (%)	Non users** (N = 34) (%)	P-value* (p<0.001)
1. Lumbar spines	-1.70 ± 0.78	-9.08 ± 4.37	NS
2. Hips	-2.48 ± 0.56	-5.62 ± 5.67	NS

* Unpaired t-test

** mean ± standard error

Discussion

Bone loss after menopause is believed to be hormonally controlled[12,13] and is therefore susceptible to medical intervention. Although one study suggested that integral spinal bone density declines in a linear fashion throughout life,[14] and another that at least 50% of trabecular bone in women is lost before menopause[15] most authorities would agree that bone density declines slowly in women until just before menopause and that the loss increases considerably thereafter.[12] Our analysis, when comparing mean baseline BMD in the three different age groups as shown in Table 2 revealed significant decreases in BMD with advancing age. But after the first 6 month we found no statistically significant differences in percent changes between the hormone use group and the nonusers group, though there was a stricking negative percent change in the BMD of the lumbar spines of the nonusers group (Table 3). This is probably due to the slow change in bone density, the decline of which is approximately 0.5% per year.[7] The bone densitometer used in our study is a Dual-Energy x-ray Abdorptiometry (DEXA) which has a precision error of 2-2.5%.[16] This report is a preliminary result of the first 6 month interval, so changes might not yet be noticable in this short time interval.

However, when looking at only the surgically menopausal group, our study showed a significant decrease in percent change of BMD, particularly in the monusers group (Table 5). Nevertheless, there was no statistically significant difference in percent changes of BMD among the hormone use and nonusers of the both natural and surgically menopausal groups. Hence, a long term study using more subjects should be conducted to arrive at a firm conclusion in the effect of HRT on bone changs in Thai menopausal women.

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