An Effect of Hormone Replacement Therapy on Skin Thickness in Early Postmenopausal Women

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Abstract

Background: It is well known that dermal thickness, the major component of skin thickness, will decrease progressively after menopause. Bone and dermis share a similar organic constituent (collagen type I). The effect of hormone replacement therapy on bone has been established, whereas, its effects on skin are less well-described. This study was performed to determine the effect of combined estrogen-progestin replacement therapy in a sequential regimen on skin thickness in women during the early postmenopausal period.

Method: One hundred early postmenopausal women who met the eligibility criteria and had already signed a consent form were non-randomly allocated in two groups. Group A; sixty women who received cyclic hormone replacement therapy in each 28-day cycle for 6 cycles. Group B; forty women who received 1,000 mg of calcium carbonate daily. Skin thickness was measured by ultrasonography before and after treatment and the Student's *t*-test was used to compare the results.

Results: A statistically significant increase in skin thickness over baseline was noted after combined estrogen-progestin replacement therapy had been administered for 24 weeks compared to the control and baseline groups. The skin thickness was also significantly decreased after calcium had been administered for 24 weeks when compared to baseline.

Conclusion: Skin thickness was increased in early postmenopausal women subjected to hormone replacement therapy with an alternating dose of estrogen and progestin.

Key word : Hormone Replacement Therapy, Skin, Menopause, Estrogen, Progestin

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The menopause is a major event in a woman's life. During the postmenopausal period, there are deleterious changes in several organs, especially the urogenital tract, bones and the cardiovascular system. In addition, the skin shows significant changes during menopause. The skin has a tendency to dry and to eventually form wrinkles, as the dermis becomes atrophic[1].

During the last few decades, several studies have demonstrated that estrogen replacement therapy increases the thickness of the skin[2] and augments the skin collagen content[3,4]. However, the reported effects of combined estrogen-progestin replacement therapy on skin are conflicting[5,6]. In addition, the effect of sequential estrogen-progestin replacement therapy on skin thickness has never been explored. This study was undertaken to assess the effect of combined estrogen-progestin replacement therapy in a sequential regimen on the skin thickness in women during the postmenopausal period.

MATERIAL AND METHOD

One hundred early postmenopausal women between 40-55 years of age, attending the menopause clinic, King Chulalongkorn Memorial Hospital, were enrolled in this study. Early postmenopause was defined as a natural cessation of menstruation of between one and five years' duration. All subjects had no previous history of unilateral oophorectomy and no evidence of endometrial premalignant or malignant lesions. The body mass index (BMI) was between 19 and 30 kg/m^2.

Exclusion criteria were skin disorders such as psoriasis, extensive burns or scars; scleroderma; lupus erythematosus; diabetes mellitus; diastolic blood pressure > 95 mmHg; corticosteroid treatment and a past or present history of taking any hormone replacement treatment.

Women meeting the eligibility criteria were non-randomly allocated to two groups. Counseling about the benefit and risk of hormone replacement therapy was given. Subjects then made their own choice of therapy and completed a consent form which had been approved by the institute ethics committee. Group A; 60 women received a twenty-eight-day sequential regimen of estradiol valerate-cyproterone acetate (Climen®) (2 mg of estradiol valerate from day 1 to day 21 plus 1 mg of cyproterone acetate on day 12-21, followed by a one-week hormone free interval). The indications for hormone replacement therapy in this group were menopausal symptoms (15 cases), osteoporosis (1 case) and prevention of osteoporosis (44 cases). Group B; 40 women received 1000 mg of calcium carbonate daily. All subjects in this group had no indication for treatment with hormone. Compliance was checked for each participant by pill counting during the entire study.

All subjects had assessment of bone mineral density of the lumbar spine (L_1-L_4) and left femur at baseline by dual-photon absorptiometry (Hologic QDR 2000, Hologic Inc.; Massachusetts, USA). The long-term precision was 1.5 per cent. Skin thickness was measured by ultrasonography with an Acuson 128 (ACUSON corporarion; California, USA) with a linear 7.5 MHz probe adjusted for thyroid resolution as described by Maheux et al[7] at the right great trochanter (Fig. 1). Ultrasonography was performed at baseline and 24 weeks after treatment by the same radiologist who was not informed about the status of the participants throughout the study.

Results were presented as mean, standard deviation or standard error of mean and a 95 per cent confidence interval. The Student's *t*-test was used to compare the readings from before and after 24 weeks of treatment within each group and between group A and group B at baseline and 24 weeks after treatment. The SPSS for Windows® statistical package program (Release 9.0, SPSS Inc.; Chicago, IL) was used to analyze the data. An intention-to-treat basis was applied to this study. The level of significance was considered to be 0.05.

RESULTS

The baseline characteristics of the participants in this study are shown in Table 1. The median time since menopause in both groups was 2 years. After 24 weeks of treatment, 91 subjects had completed the study (55 subjects in group A and 36 subjects in group B). Six subjects were loss-to-follow-up (2 cases in group A and 4 cases in group B). Three subjects, all in group A, withdrew from the study because of bleeding per vagina. As shown in Fig. 2, baseline skin thickness between the two groups was not significantly different. A statistically significant increase in skin thickness at the right great trochanter was observed after 24 weeks of combined estrogen-progestin treatment (Fig. 2). Skin thickness also decreased significantly when calcium carbonate was given alone for 24 weeks

Table 1. Baseline characteristics of the population.

Characteristics	Group A (n = 60)		Group B (n = 40)	
Age (years)	49.7	(48.6, 50.8)	49.2	(48.0, 50.4)
Body weight (kg)	56.0	(53.9, 58.2)	56.6	(54.2, 59.0)
Height (cm)	155.8	(154.6, 157.1)	156.2	(154.6, 157.8)
BMI (kg/m^2)	23.1	(22.3, 23.9)	22.9	(22.2, 23.6)
T score of BMD				
L_1-L_4	-1.18	(-1.57, -0.80)	-1.39	(-1.81, -0.96)
Total hip	-1.25	(-1.57, -0.92)	-1.25	(-1.67, -0.83)
Femoral neck	-1.53	(-1.90, -1.15)	-1.70	(-2.14, -1.27)

Note : values shown are mean and 95% confidence interval
BMD = bone mineral density
BMI = body mass index
L_1 = the first lumbar spine
L_4 = the fourth lumbar spine

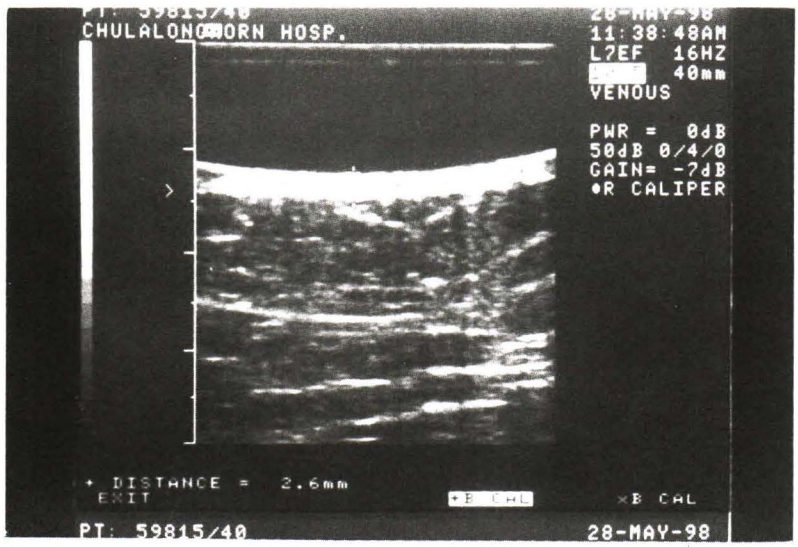
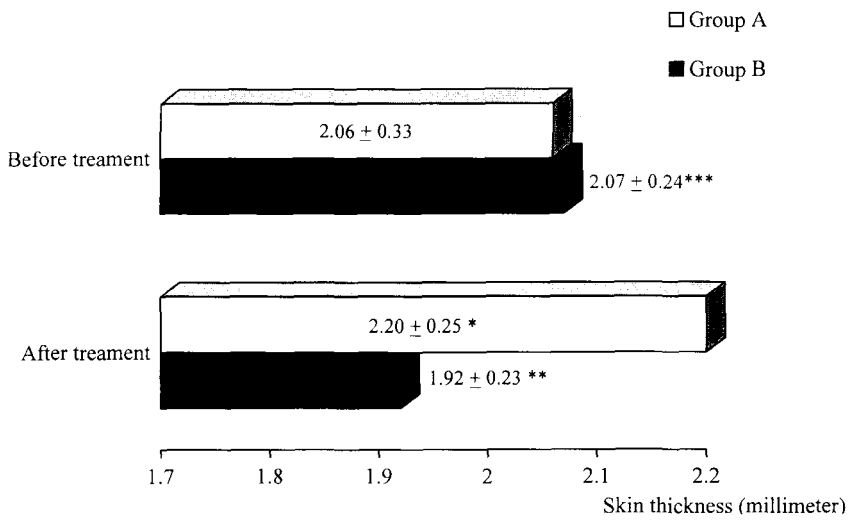


Fig. 1. Ultrasonography of the skin. The thickness is measured between two calipers.

(Fig. 2). After 24 weeks of treatment, there was a statistically significant difference in skin thickness at the right great trocanter between group A and B (Fig. 2).

DISCUSSION

Over 90 per cent of the thickness of the skin is due to the dermis, which is mainly composed of type I collagen[8]. With increasing age after menopause, the skin collagen content tends to decrease[1,9] and the skin becomes thinner[10]. These effects are shown in our study which demonstrated that skin thickness decreased when calcium carbonate was given alone for 24 weeks. Nevertheless, the thickness of the skin declined more rapidly than expected in this group. This might be due to the collagen in the skin, like in the bone, decreasing rapidly (approximately 30%) in the first five years after menopause[3]. Another explanation is that the decrement of the thickness of the skin



Note : values shown are mean and standard error of mean

* $p < 0.001$ for group A VS group B after 24 weeks of treatment and $p < 0.01$ for baseline VS 24 weeks after treatment within group A

** $p < 0.05$ for baseline VS 24-weeks after treatment within group B

*** $p > 0.05$ for group A VS group B at baseline

Fig. 2. Skin thickness at right great trochanter at baseline and after 24-weeks of treatment.

was aggravated by calcium. However, the effect of calcium on skin has never been shown.

This study also demonstrated that skin thickness was significantly increased after combined estrogen-progestin therapy in a sequential regimen compared to calcium and baseline groups. Several studies have demonstrated that estrogen replacement therapy increases the thickness of the skin[1, 2,11], including in a randomized controlled study[7]. However, the effect of progestin alone has not yet been evaluated. Progestin may have a synergistic effect with estrogen on the skin collagen, resulting in increased skin thickness.

Schmidt et al[12] found that progesterone receptors in the skin of postmenopausal women were approximately fifty per cent lower than in premenopausal women. It is possible, therefore, that the antagonistic effect of progestin is less significant in the postmenopausal woman.

Haapasaari et al[5] showed that estrogen combined with progestin did not affect skin thickness or the amount and rate of collagen synthesis in early postmenopausal women. It should be noted that the number of cases in the estrogen-progestin treatment group was quite small (15 cases) and various types of hormone were given in the treatment group. Furthermore, norethisterone acetate, which has been classified in the 19-nortestosterone group, might have a more antagonistic action on the skin than cyproterone acetate.

Sauerbronn et al[6] demonstrated that skin collagen content, which is a major component of the skin, was increased after six months of treatment with combined estradiol valerate plus cyproterone acetate. Although the age of the subjects was not shown, this study supports our results that the thickness of the skin improved after combined estrogen-progestin treatment for 6 months. Nevertheless, the

increment of skin thickness during therapy might partly be due to the enhancement of hyaluronic acid[13] or water in the dermis[14].

This is the largest study yet performed to evaluate the effects of combined oral estrogen-progestin replacement therapy on the skin. However, we faced a number of limitations. This study was open label and lacked randomization. It was difficult to blind investigators and subjects because bleeding per vagina almost always presented at the end of each cycle of sequential combined estrogen-progestin therapy in early postmenopausal women. Also, subjects made their own choice of treatment. However, the baseline data between the two groups were not significantly different and we attempted to blind the group assignment of patients to the radiologist.

No histopathological examination of the skin was obtained in this study. However, the validity of ultrasonographic examination for the measurement of skin thickness has been shown in several clinical studies[7,15], and this method has now become routine. The precision of the location measured by ultrasound was another consideration. The right great trochanter is a site that it is easy to locate accurately and is subjected to fewer environmental influences, especially ultraviolet radiation. Finally, the effects of these treatments on other skin properties were not explored in this study.

Our results support the existence of hormonal skin aging. Hormone replacement therapy can improve skin elasticity[16] and dermal atrophy, which contributes to skin fragility and erosion. From the evidence that skin thickness correlated with bone mineral density[17] and our results that skin thickness was increased after hormone replacement therapy, it may extrapolate to use the skin thickness to predict the response of hormone replacement therapy.

In conclusion, skin thickness increased significantly in early postmenopausal women receiving six-cycles of combined estrogen-progestin treatment.

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ผลของการใช้ฮอร์โมนทดแทนต่อความหนาของผิวหนังในสตรีวัยหมดระดูระยะต้น

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วัตถุประสงค์: เพื่อศึกษาถึงผลของการใช้ฮอร์โมนทดแทน ต่อความหนาของผิวหนังในสตรีวัยหมดระดูระยะต้น

วัสดุและวิธีการ: สตรีที่มารับบริการที่คลินิกวัยหมดระดู โรงพยาบาลจุฬาลงกรณ์ จำนวน 100 รายแบ่งเป็น 2 กลุ่ม กลุ่มที่ 1 สตรีจำนวน 60 ราย ได้รับฮอร์โมนทดแทนชนิดเป็นรอบจำนวน 6 รอบ กลุ่มที่ 2 สตรีจำนวน 40 ราย ได้รับแคลเซียม คาร์บอเนต 1,000 มิลลิกรัมทุกวัน สตรีที่ได้รับคัดเลือกจะได้รับการตรวจความหนาของผิวหนังด้วยคลื่นเสียงความถี่สูง ที่ Great trochanter ข้างขวา โดยรังสีแพทย์ หลังจากนั้นจะได้รับฮอร์โมนทดแทนชนิดเป็นรอบ จำนวน 6 รอบ แล้วทำการตรวจซ้ำที่ตำแหน่งเดิมเมื่อได้รับฮอร์โมนทดแทนครบ 24 สัปดาห์ โดยรังสีแพทย์คนเดิม

ผลการศึกษา: มีสตรีจำนวน 55 ราย ที่ได้รับฮอร์โมนทดแทนครบ 24 สัปดาห์ ผิวหนังมีความหนาเพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติเมื่อได้รับฮอร์โมนทดแทนเป็นเวลา 24 สัปดาห์ อีกทั้งยังพบว่าผิวหนังมีความหนาลดลงอย่างมีนัยสำคัญทางสถิติเมื่อได้รับแคลเซียม

สรุป: สตรีวัยหมดระดูระยะต้นที่รับประทานฮอร์โมนทดแทนเอสโตรเจนและโปรเจสโตเจนชนิดเป็นรอบ มีผิวหนังบริเวณ Great trochanter หนาขึ้นอย่างมีนัยสำคัญทางสถิติ

คำสำคัญ : ฮอร์โมนทดแทน, ผิวหนัง, สตรีวัยหมดระดู, เอสโตรเจน, โปรเจสติน

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