นิพนธ์ต้นฉบับ

Hormonal replacement therapy and lipid metabolism in Thai menopausal women

Nimit Taechakraichana*
Kobchitt Limpaphayom* Unnop Jaisamrarn*

Taechakraichana N, Limpaphayom K, Jaisamrarn U. Hormonal replacement therapy and lipid metabolism in Thai menopausal women. Chula Med J 1995 Feb;39(2): 97-105

Objective : *To study the effect of hormonal replacement therapy (HRT) on lipid metabolism*

Design : *Prospective, randomised study*

Setting : *Menopause Clinic, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn Hospital.*

Patients : *One hundred and twenty three 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 used estrogen replacement therapy either with or without progestin. The control group did not use any hormonal regimen.*

Main outcome measure : *Total serum cholesterol, triglycerides, low density lipoprotein (LDL), high density lipoprotein (HDL), Apolipoprotein A-1 (Apo-A) and Apolipoprotein B (Apo-B) were measured before and 6 month after starting the treatment.*

Results : *After 6 month, 60 cases completed the two measurements by the time of this report. The results showed that, total cholesterol (TC), LDL and HDL increased in the control (27/60) more than in the study group (33/60). (Control group : TC = +5.12 ± 5.34%, LDL = +8.78*

*Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University.

±9.43%, HDL = +10.44± 4.64% vs Study group : TC = +0.83 ± 2.88%, LDL = +3.58 ± 4.40%, HDL = -3.17 ± 3.56%). However, triglyceride, Apo-A and Apo-B decreased in the study more than in the control group. (Study group : Triglyceride -5.47 ± 6.62%, Apo-A = -10.99 ± 2.59%, Apo-B = -7.26 ± 3.13% vs Control group : Triglyceride = -1.12 ± 6.73%, Apo-A = -5.32 ± 2.70%, Apo-B = -2.14 ± 3.77%). Nevertheless, there was no statistical signigicant difference of changing lipid values between the two group, except HDL.

Conclusions : *Most of the lipid values changed in the beneficial way in the HRT group. Anyway, the negative changes of HDL in the HRT group might be due to the effect of progestins used in this study.*

Key words : *Hormonal replacement therapy, Lipid metabolism.*

Reprint request: Taechakraichana N. Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

Received for publication. December 1,1994.

นิมิต เตชไกรชนะ, กอบจิตต์ ลิมปพยอม, อรรณพ ใจสำราญ. ฮอร์โมนทดแทนกับการเปลี่ยนแปลงไขมันในสตรีไทยวัยหมดระดู. จุฬาลงกรณ์เวชสาร 2538 กุมภาพันธ์; 39(2): 97-105

วัตถุประสงค์ *เพื่อศึกษาถึงผลของฮอร์โมนทดแทนต่อเมตาบอลิซึมส์ของไขมัน*

รูปแบบการวิจัย *การศึกษาไปข้างหน้า แบบแรนดอมไมส์*

สถานที่ *คลินิกสตรีวัยหมดระดู ภาควิชาสูติศาสตร์-นรีเวชวิทยา คณะแพทยศาสตร์ โรงพยาบาลจุฬาลงกรณ์*

ผู้เข้าร่วมการศึกษา *การศึกษานี้ได้คัดเลือกสตรีก่อนและหลังวัยหมดระดู อายุระหว่าง 40-62 ปี (ค่าเฉลี่ย ± ค่าเบี่ยงเบนมาตรฐานของอายุ = 48.67 ± 7.65) จำนวน 123 ราย โดยเป็นกลุ่มศึกษาคือ สตรีที่ได้รับฮอร์โมนทดแทน (โดยได้รับเอสโตรเจนอย่างเดียวหรือร่วมกับโปรเจสติน) และกลุ่มควบคุมซึ่งไม่ได้รับฮอร์โมนทดแทนใด ๆ*

การวัดผล *ทำการตรวจหาระดับ Total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), Apolipoprotein A-1 (Apo-A) และ Apolipoprotein B (Apo-B) ก่อนและหลังการรักษา 6 เดือน*

ผลการศึกษา *ภายหลัง 6 เดือน มีสตรีที่ได้รับการตรวจระดับไขมันครบ 2 ครั้งจำนวน 60 ราย ผลการศึกษาพบว่าระดับ Total cholesterol (TC), LDL และ HDL ในกลุ่มควบคุม (27/60) เพิ่มขึ้นมากกว่ากลุ่มศึกษา (33/60) (กลุ่มควบคุม : TC = +5.12 ± 5.34%, LDL = +8.78 ± 9.43%, HDL = +10.44 ± 4.64%; กลุ่มศึกษา : TC +0.83 ± 2.88%, LDL = +3.58 ± 4.40%, HDL =-3.17 ± 3.56%) สำหรับระดับของ Triglyceride, Apo-A และ Apo-B ในกลุ่มศึกษาลดลงมากกว่าในกลุ่มควบคุม (กลุ่มศึกษา : Triglyceride = -5.47 ± 6.62%, Apo-A = -10.99 ±2.59%, Apo-B = -7.26 ± 3.13%; กลุ่มควบคุม : Triglyceride = -1.12 ± 6.73%, Apo-A = -5.32 ± 2.70%, Apo-B = -2.14 ± 3.77%) อย่างไรก็ตามไม่พบว่ามีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติยกเว้นค่าของ HDL*

สรุป *กลุ่มที่ได้รับฮอร์โมนทดแทนมีการเปลี่ยนแปลงของระดับไขมันส่วนใหญ่ไปในทางที่ช่วยการป้องกันโรคหัวใจและหลอดเลือด การลดลงของ HDL ในกลุ่มที่ได้รับฮอร์โมนทดแทนอาจเป็นผลจากฮอร์โมนโปรเจสตินที่ใช้ร่วมด้วย*

Cardiovascular disease (CVD) is the leading cause of death among women in industrialized countries; more than 50% of postmenopausal women will die of CVD.[1] Dyslipidemia is one of the three major risk factors for coronary artery disease other than hypertension and smoking.[2] Estrogens have been hypothesized to protect against atherosclerosis because the incidence of CVD is low before menopause. Premenopausal women have approximately one-fifth the CVD mortality of men, but after menopause, their mortality rate exponentially rises to approach that of men.[3] Many studies have shown that postmenopausal estrogen use may reduce the incidence of cardiovascular disease by 40% or more.[4] The possible mechanisms of action of estrogen on the cardiovascular system may be explained by lipoprotein hypothesis in which numerous clinical studies have revealed that exogeneous estrogens can produce beneficial effects on lipid changes.[5] Epidemiologic data from the Lipid Research Clinics[6] have indicated that the increase in total cholesterol had a "2 to 1" impact on the incidence of myocardial infarction; that is every 1% increase in total cholesterol, there is a 2% increase in the risk of myocardial infarction. Low density lipoprotein (LDL) is the major deleterious cholesterol moieties. It has specific apolipoproteins. The most important is apolipoprotein B which is important for receptor attachment. At the level of the vessel wall, the LDL particles contribute to atherogenesis through a complex series of events.[7] LDL receptor is critical for removal of cholesterol from the circulation.[8,9] Therefore, if the LDL receptors are diminished in number, severe atherosclerosis results. There is some evidence that estrogen may induce the formation of LDL receptors.[7]

High-density lipoprotein (HDL), which associated apolipoproteins are apolipoprotein A1 and A2,[7] plays a major role in the collection of excessive cholesterol and transport back to the liver for degradation and reformation of other lipoproteins. There are several forms of HDL but the one that is most active in reverse cholesterol transport is HDL_2[10], which is also the moiety to which apolipoprotein A1 is specific. In the liver, hepatic lipase destroys HDL. Estrogen degrades hepatic lipase, and this fact may partly explain the increase in HDL levels with estrogen administration and the inverse relationship between the incidence of cardiovascular disease in women and the HDL level. Concerning triglycerides, it make up the overwhelming proportion of dietary fat. Its elevations are highly significant independent risk factor for coronary heart disease in women.[11]

The other explanation of action of estrogen on the cardiovascular system is the direct effects of estrogen on blood vessels, because estrogen receptors have been found in various types of blood vessels, including coronary arteries[12] and estrogens could also interact with the prostaglandin metabolism in the vessels wall, resulting in vasodilatation and increased blood flow.[13] Thailand is a developing, agricultural country but going to be an industrialized nation. The lifestyle and nutritional status of the Thai people are different from those in Western world. Hence, the objective of this study is to determine the effect of hormonal replacement therapy (HRT) on each lipid and lipoprotein profiles in Thai menopausal women.

Materials and Methods

Healthy premenopausal and postmenopausal women attending the Menopausal Clinic at the Department of Obstetrics and Gynecology, Chulalongkorn University Hospital were eligible for this prospective, randomised study, if the postmenopausal women had experienced amenorrhea for at least 6 months and a serum follicle stimulating hormone (FSH) levels above 35 IU per liter and had a serum estradiol level below 100 pmol per liter or the premenopausal women who still experienced periods or had experienced amenorrhea for less than 6 months but complained of climacteric symptoms such as hot flushes and had a serum FSH and estradiol 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,were not taking medications that affect lipid metabolism, and did not have any endocrinologic disorders or any chronic illnesses.

The subjects were randomly allocated into two groups. The first studygroup, including natural and surgical menopausal women,were given hormonal replacement therapy. The second group included natural and surgical menopause, were given only calcium supplements, with or without parasym-patholytic agents as shown in Table 1.

Table 1. Intervention (Total number = 60)*

Group	Type of menopause	Type of hormone used	N
HRT (N=33)	1. Natural (N = 27)	1. Cyclic : EV (2 mg) + Norgestrel (500 ug)	14
		2. Cyclic : CEE (0.625 mg) + Medrogestone (5 mg)	8
		3. Combine continue regimen : CEE (0.625 mg) + MPA (2.5 mg)	5
	2. Surgical (N = 6)	1. Cyclic : (CEE 0.625 mg)	4
		2. Cyclic : E_2 gel	2
Non-HRT (N=27)		Calcium ± Parasympatholytics	

EV = Estradiol valerate, CEE = Conjugated equine estrogen
MPA = Medroxy progesterone acetate, E_2 = Estradiol
ug = microgram
Cyclic = Estrogens on days 1-21 and progestin on days 12-21
Combined = Estrogen and progestin daily
* Total number of patients who completed the two measurements of lipid profiles by the time of this report

Blood for fasting lipid and lipoprotein measurments were obtained from each subject before entering the study, then the measurements were performed 6 month later. The measurements included total serum cholesterol, triglycerides, low density lipoprotein (LDL), high density lipoprotein (HDL), Apolipoprotein A (Apo-A) and Apolipoprotein B (Apo-B) using enzymatic method (Automatic COBAS-S).

The treatment effect was defined as percent changes of each serum lipid and lipoprotein profile after six month interval, comparison between HRT and non-HRT groups, and the 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

Of all 123 women recruited in this study, we compared the baseline value of lipid and lipoprotein profiles before entering the study among the three different age groups, which are the premenopausal group, the early postmenopausal age group which was within 5 years since menopause and the late postmenopausal age group which was more than 5 years, the results revealed no statistically significant difference among the three groups (Table 2). However when compared in pair of age groups by unpaired t-test there was statistically significant difference of serum total cholesterol between the premenopausal and early postmenopausal group and between the early and late postmenopausal age groups. ($P < 0.05$)

Table 2. Mean baseline value of lipid profiles in various pre-and postmenopausal age groups (N = 123).

Characteristic	Premenopausal** group (N=36) (mg/dl)	Postmenopausal** group (<5 yr) (N=73) (mg/dl)	Postmenopausal group (>5yr) (N=14) (mg/dl)	P-value* (p < 0.05)
1. Total cholesterol	231.07 ± 6.65	252.87 ± 5.81	249.48 ± 7.83	NS
2. Triglyceride	105.50 ± 8.30	111.83 ± 7.38	127.94 ± 10.88	NS
3. LDL	162.60 ± 6.61	173.07 ± 4.94	176.04 ± 12.75	NS
4. HDL	50.31 ± 1.61	52.21 ± 1.68	52.35 ± 2.56	NS
5. Apo-A	159.62 ± 4.05	160.71 ± 3.19	151.00 ± 0.72	NS
6. Apo-B	112.65 ± 5.64	122.54 ± 5.16	131.50 ± 5.42	NS

N.B. * ANOVA
** Mean + standard error

Of all the women enrolled in this study, 60 cases completed the two measurements by the time of this report. There were 49 natural menopausal women, of these 27 in the hormone use and 22 in the nonusers group. Of the 11 surgical menopausal women, 6 were in the hormone use and 5 were in the nonusers group. The population characteristics of the hormone use and non users groups did not show significant differences as in Table 3.

Table 3. Clinical characteristics of the study population@

Characteristic	Hormone use ** (N = 33)	Non users ** (N = 27)	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

@ There were 60 cases completed the two measurements of lipid profiles by the time of this report
# Age range = 40-62 (Mean ± SD = 48.67 ± 7.65) years
* Unpaired t-test
** Mean ± standard error

When considered the percent changes of these lipid profiles after 6 month interval in hormone use and nonusers groups there were no statistically significant difference between both groups except for HDL which decreased in hormone use group but increasd in nonuser group and the difference was also statistically significance as shown in Table 4. However, the results showed tendency of greater increment in serum total cholesterol, LDL and HDL and less decrement in triglyceride, Apolipoprotein A and Apolipoprotein-B in the nonusers group than in the hormone use group.

Table 4. Percent changes in lipid levels in HRT and non-HRT group during the first 6-month interval.

Lipid profiles	Hormone use ** (N = 33) (%)	Non users ** (N = 27) (%)	P-value* (p < 0.05)
1. Total cholesterol	0.83 ± 2.88	5.12 ± 5.34	NS
2. Triglyceride	-5.47 ± 6.62	-1.12 ± 6.73	NS
3. LDL	3.58 ± 4.40	8.78 ± 9.43	NS
4. HDL	-3.17 ± 3.56	10.44 ± 4.64	P = 0.024
5. Apolipoprotein-A	-10.99 ± 2.59	-5.32 ± 2.70	NS
6. Apolipoprotein-B	-7.26 ± 3.13	-2.14 ± 3.77	NS

* Unpaired t-test

** Mean ± standard error

Discussion

This study did not show statistically significant difference of baseline lipid profiles among the three age groups (Table 2). Several studies[14] revealed that while total cholesterol increases with age, the rise is more marked with the onset of menopause. Triglyceride levels, on the other hand, are relatively independent of age but may increase after menopause. Various cholesterol fractions do not change in the same direction. LDL rises after menopause, whereas total HDL falls. Anyway, there is dissociation between different HDL subfractions. HDL_2 falls while HDL_3 rises after menopause. In our study, when considered in particular pairs of age group, total cholesterol was significantly higher in the early postmenopausal women (<5 years) than in the premenopausal age group. Nevertheless, the cholesterol level was significantly lower in the late postmenopausal women (> 5 years) than in the early postmenopausal women (< 5 years). This might be because the studied population in the late postmenopausal women was in the low risk group and then survived from cardiovascular disease. Beside this, there was an upward trend of triglyceride, LDL and Apo-B with increasing age. Nevertheless, large scale clinical, population based studies and more detailed studies into HDL subfraction may give a clearer information in these aspects.

Considering the percent changes of lipid and lipoprotein level in HRT and non-HRT group during 6 month interval, we found that serum total cholesterol, and LDL increased more in the non-HRT than in the HRT group, while triglyceride, Apo-A and Apo-B decrease more in HRT group, anyhow there was no statistically significant difference. When considered the "2 to 1" impact of percent changes of total cholesterol on the incidence of myocardial infarction[6] as mentioned before, in our study the percent changes of total cholesterol in non HRT and HRT group were 5.12% and 0.83% (Table 4). Hence, the incidence of myocardial infarction in both groups may increase to 10.2 and

1.6% respectively. This figure make a substantial difference in the clinical aspect. However, HDL decreased significantly in the HRT group when compared to the non-HRT. Previous clinical trials in postmenopausal women have generally reported that the addition of a progestin opposes many beneficial effects of estrogen by lowering the level of HDL cholesterol, mainly the level of HDL_2[15-17] without changing that of HDL_3.[18] Progestins appear to increase hepatic lipase activity, thus increasing the catabolism of HDL_2 and lowering the levels of both HDL_2 and HDL-cholesterol.[18] Progestins do not appear to change the levels of LDL significantly. However, there is one study which revealed similar levels of HDL, HDL_2 and HDL_3, apolipoprotein A-1, LDL, apolipoprotein B, and lipoprotein (a).in both users of estrogen with progestin and users of estrogen alone.[19]

Nevertheless, the study mentioned above used medroxyprogesterone acetate, a progestin with low levels of androgenic activity, which has slight effect[18,20] or no effect[21] on lipoprotein levels when used alone[20] or in combination with estrogen.[18] It also has less influence on hepatic lipase activity than most other progestins, as suggested by a clinical trial in premenopausal women 40 to 50 years old.[22] Our analysis revealed the effects of HRT in broad perspectives. Further scrutiny in the effects of HRT, with or without progestins or the effects of different progestins on lipid and lipoprotein changes may clearify this problem.

Acknowledgement

This study was financially supported by a research grant from Rachadapiseksomphot fund, Faculty of Medicine, Chulalongkorn University.

We are indebted to Assist. Prof. Yupa Ontaum for assistance with the statistical analysis, to Assoc. Prof. Witaya Sreedama for expert clinical assistance in the lipid laboratory. We would like to thank Mrs.Montatip Jetaporn for preparing this manuscript and most of all to the dedicated patients in this study.

References

1. Walsh BW. Estrogen replacement and heart disease. Clin Obstet Gynecol 1992 Dec; 35(4) : 894-900
2. Farmer JA, Gotto AM. Risk factors for coronary artery disease. In : Braunwald E,editor. Heart disease : A textbook of cardiovascular medicine, 4th edition. Philadelphia, WB Saunders. 1992:1125-60
3. Lerner DJ, Kannel WB. Patterns of coronary disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. Am Heart J 1986 Feb; 111(2) : 383 - 90
4. Ross RK, Pike MC, Mack TM. Oestrogen replacement therapy and cardiovascular disease, In : Drife JO, Studd JWW, eds. HRT and Osteoporosis. London: Springer-Verlag, 1990; 299-22
5. Persson I, Falkeborn M, Lithell H. The risk of acute myocardial infarction and stroke in women taking HRT. Proceedings of the Novo Nordisk International Symposium. Copenhagen, Denmark. September 4th - 5th, 1992: 109-17
6. The Lipid Research Clinic Program. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. JAMA 1984 Jan 20; 251(3): 351-64
7. Lobo RA. Cardiovascular implications of estrogen replacement therapy. Obstet Gynecol 1990 Apr; 75(4 Suppl) : 18S-25S
8. Brown MS, Goldstein JL. Lipoprotein receptors in the liver. Control signals for plasma cholesterol traffic. J Clin Invest 1983 Sep; 72(3) : 743-7
9. Goldstein JL, Kita T, Brown MS. Defective lipoprotein receptors and atherosclerosis. Lessons from an animal counterpart of familial hypercholesterolemia. N Engl J Med 1983 Aug 4; 309(5): 288-96
10. Krauss RM, Perlman JA, Ray R, Petitti D. Effects of estrogen dose and smoking on lipid

and lipoprotein levels in postmenopausal women. Am J Obstet Gynecol 1988 Jun; 158(6 pt 2) : 1606-11

11. Castelli WP. The triglyceride issue : A view from Framingham. Am Heart J 1986 Aug; 112(2) : 432-7
12. McGill HC Jr. Sex steroid hormone receptors in the cardiovascular system. Postgrad Med 1989 Apr;Spec No: 64-8
13. Harder DR, Coulson PB. Estrogen receptors and effects of estrogen on membrane electrical properties of coronary vascular smooth muscle. J Cell Physiol, 1979 Aug; 100(2) : 375-82
14. Ginsburg J. The menopause, hormonal reg-placement therapy and the cardiovascular system. In : Burger H, Boulet M, eds. A Portrait of the Menopause. Carnforth: The Parthenon Publishing Group, 1990 : 45-66
15. Lobo RA. Estrogen and cardiovascular disease. Ann N Y Acad Sci 1990; 592 : 286-95, 334-45
16. Sacks FM, Walsh BW. The effects of reproductive hormones on serum lipoproteins : unresolved issues in biology and clinical practce. Ann N Y Acad Sci 1990; 592 : 272-85, 334-45
17. Tikkanen MJ, Kuusi T, Nikkila EA, Sipinen S. Postmenopausal hormone replacement therapy : effects of progestogens on serum lipids and lipoproteins : a review. Maturitas 1986 Mar; 8(1): 7-17
18. Tikkanen MJ, Nikkila EA, Kuusi T, Sipinen SU. High density lipoprotein-2 and hepatic lipase : reciprocal changes produced by estrogen and norgestrel. J Clin Endocrinol Metab 1982 Jun; 54(6) : 1113-7
19. Nabulsi AA, Folsom AR, white A, Patsch W, Heiss G, Wu KK, Szklo M. Association of hormone-replacement therapy with various cardiovascular risk factors in postmenopausal women. N Engl J Med 1993 Apr 15; 328(15) : 1069-75
20. Silfverstolpe G, Gustafson A, Samsioe G, Svamborg A. Lipid metabolic studies in oophorectomised women : effects on serum lipids and lipoproteins of three synthetic progestogens. Maturitas 1982 Aug; 4(2) : 103-11
21. Weinstein L. Efficacy of a continuous estrogen-progestin regimen in the menopausal patient. Obstet Gynecol 1987 Jun; 69(6) : 929-32
22. Tikkanen MJ, Nikkila EA, Kuusi T, Sipinen S. Different effects of two progestins on plasma high density lipoprotein (HDL_2) and postheparin plasma hepatic lipase activity. Atherosclerosis 1981 Nov-Dec; 40(3-4) : 365-9