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Original paper

EFFECTS OF HORMONE REPLACEMENT THERAPY ON SERUM LIPIDS AND OTHER RISK FACTORS OF CORONARY DISEASES

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Summary: Our aim was to compare the effects of transdermal versus oral estrogens on mean arterial pressure, serum lipid concentrations, estradiol and body weight. The investigation includes ten postmenopausal women receiving transdermal estrogen plus cyclic oral progesterone for 6 months. Responses were compared with those of 23 women receiving oral conjugated estrogens plus cyclic progesterone also for 6 months. We concluded that both oral and transdermal estrogen significantly ($p<0.05$) decreased mean arterial pressure, total and low-density lipoprotein cholesterol level to a similar extenet. But only oral estrogen increased HDL cholesterol and triglycerides with statistical significans ($p<0.05$). Transdermal estrogen group exhibited no significant changes ($p>0.05$) in values of HDL cholesterol and triglycerides before and after the treatment. The serum estradiol level increased significantly ($p<0.05$) in oral estrogen group but in lesser extent in transdermal estrogen group ($p<0.002$). Studies in future should include multiple risk factors to allow better assessment of their impact on coronary artery health.

Key words: serum lipids, estrogen, blood pressure

Introduction

Cardiovascular risk reduction with HRT (hormone replacement therapy) in postmenopausal women has been supported by numerous epidemiological studies, the majority of which have shown 40% to 50% reduction (1–5). This benefit has been reported to occur with both estrogen alone and estrogen-progesterone combinations (2). The Nurses Health Study (2, 3) found an overall reduction in incidence of myocardial infarction, stroke, and total mortality with HRT. The beneficial effects of estrogen are multiple, beginning with the effects on lipids. Both oral and transdermal estrogens have been shown to reduce total and low-density lipoprotein (LDL) cholesterol, and comparative studies suggests that the magnitudes of these effects are similar (6). However there are contradictory findings regarding the effects of transdermal HRT on high-density lipoprotein (HDL) cholesterol. Recent studies have been reported that transdermal estrogen either does not increase HDL cholesterol or does so to a lesser extent than oral estrogen (6, 7), suggesting that the hepatic effects of estrogen absorbed through the gastrointestinal tract play an important role in regulating lipoprotein levels. Other favorable effects of estrogen include improved vasomotore tone, increased insulin sensivity and improved myocardial relaxation (5).

The primary goal of the present study was to compare changes in multiple cardiac risk factors (serum lipids and blood pressure, body weight) in healthy women receiving oral and transdermal HRT.

Material and Methods

Forty three postmenopausal women were inrolled in this 6-month investigation, which was done in the Institute of Gynecaelogy and Obstetrics Clinical Centre of Serbia. Exclusionary criteria included hysterectomy, hystory of cardiovascular disorders, or any contraindication for HRT (first degree relative with breast cancer). Menopausal status was confirmed by history (no menses for >9 months) and follicule-stimulating level>30 IU/L. First group consisted of 23

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women treated with oral conjugated estrogens (0.625 mg/d) plus cyclic progesterone (10 mg medroxiprogesteron acetat). Another group consisted of 10 postmenopausal women receiving transdermal 17 β-estradiol (0.05 mg/d) plus cyclic progesteron for 6 months. We compared the effects of transdermal estrogens versus oral estrogens on serum lipid concentrations, mean arterial pressure, body weight and serum estradiol. In fact the serum concentration of lipid parameters (total cholesterol, LDL, HDL, triglycerides, Apo A, Apo B) and estradiol before and after treatment in each group were compared, in order to see the effect of HRT therapy. We also compared the values of body weight before and after treatment to show the protective effect of hormone therapy on coronary artery health.

Triglycerides and total cholesterol concentration were determined enzymatically. HDL cholesterol was measured by the dextran sulfat precipitation method. LDL cholesterol was derived by Frieldewald equation. Estradiol was determined by radio immunoassey test (produced by INEP-Diagnostic, Yu). Apo A and Apo B were assed by nephelometry methods.

Statistical analysis. The obtained results were evaluated by parametric statistic method (11). The results were expressed by the mean value, resulting from tests of the same sample with corresponding standard error ($\bar{x} \pm$ SEM). Statistical differences between groups were tested by Student's t-test and p value of 0.05 or less was selected as the level of statistical significance.

Results

Characteristic of group before treatment

Table I shows that women in the transdermal group were older than those in estradiol oral group (F: 6.04 $p<0.05$). The oral estrogen group had significantly higher mean arterial pressure than the transdermal estradiol group ($p<0.05$). It has been shown that there was no significant differences between groups in heart rate, estradiol, body weight or any lipid parametar at the pretreatment testing session.

Table I Subject characteristics at study entery. Values are presented as mean ± SEM

	Oral estrogen (n=23)	Transdermal estradion (n=10)
Age *	52 ± 2	59 ± 2
Body mass index (kg/m^2)	27 ± 1	26 ± 2
Mean arterial pressure (mm Hg) **	95 ± 2	84 ± 3
Heart rate (beats/min)	75 ± 1	67 ± 3

* Significant group difference at pretest, oral estrogen group less than transdermal estradiol group, $p<0.05$

** Significant group difference at pretest, oral estrogen group more than transdermal estradiol group, $p<0.05$

Characteristic of group after treatment

Table II shows that significant reduction in LDL cholesterol and total cholesterol were noticed in women on transdermal HRT ($p<0.05$). Women on oral HRT produced significant decreases in LDL cholesterol ($p<0.05$) and a tred toward lower total cholesterol concentration relative to pretreatment level ($p<0.01$).

The use of oral HRT was associated with significant increased in triglycerides ($p<0.05$) and HDL cholesterol ($p<0.04$) relative to the pretreatment level. Women who received transdermal HRT exhibited no statistical significant changes ($p>0.05$) in level of cholesterol and triglycerides compare to pretreatment concentration, which is the main difference between the groups.

Table II Efect of HRT on lipids, hormones and body weight. Values are presented as mean ± SEM

	Oral estrogen (n=23)	Transdermal estradion (n=10)
Total cholesterol (nmol/L)		
Before treatment	5.79 ± 0.23	5.83 ± 0.33
After treatment	5.45 ± 0.18*	4.96 ± 0.28**
LDL cholesterol (nmol/L)		
Before treatment	3.83 ± 0.20	3.46 ± 0.31
After treatment	3.36 ± 0.18**	3.07 ± 0.25**
HDL cholesterol (nmol/L)		
Before treatment	1.21 ± 0.07	1.31 ± 0.10
After treatment	1.31 ± 0.07***	1.24 ± 0.10
Triglycerides (nmol/L)		
Before treatment	1.63 ± 0.19	1.33 ± 0.28
After treatment	1.83 ± 0.18**	1.43 ± 0.27
Estradiol (pg/mL)		
Before treatment	16.7 ± 4.2	8.3 ± 6.1
After treatment	47.3 ± 3.7**	27.1 ± 5.3****
Apo-A1 (nmol/L)		
Before treatment	1.51 ± 0.28	1.57 ± 0.3
After treatment	1.59 ± 0.21	1.56 ± 0.4
Apo-B		
Before treatment	0.87 ± 0.27	0.81 ± 0.22
After treatment	0.71 ± 0.25	0.80 ± 0.22
Weight (kg)		
Before treatment	76 ± 2	75 ± 3
After treatment	76 ± 2	76 ± 3

* Significant change relative to pretreatment level, $p<0.01$

** Significant change relative to pretreatment level, $p<0.05$

*** Significant change relative to pretreatment level, $p<0.04$

**** Significant change relative to pretreatment level, $p<0.002$

The serum estradiol level increased significantly ($p<0.05$) in the oral HRT and in the transdermal estrogen group only (F 7.25 $p<0.002$). There were no significant changes ($p>0.05$) in body weight and body mass index after treatment in the both groups. There was also no statistical significant ($p> 0.05$) in values of Apo-B and Apo-A before and after treatment, in the both groups.

Discussion

In this study we confirmed the view that hormone replacement therapy provides cardioprotective effects via multiple mechanisms including reductions in atherogenic lipids and vascular constriction. In fact we observed equivalent reduction in blood pressure, LDL and total cholesterol, in healthy women taking oral and transdermal estrogens.

The effect of estrogen on serum lipids is related to the increased catabolism of LDL cholesterol, which up-regulates LDL receptors in the liver, increases production of bile acids and reduces catabolism of HDL cholesterol. Estrogen therapy in postmenopausal women leads to decreased concentrations of total serum cholesterol, LDL cholesterol, lipoprotein A, apolipoprotein B, as well as increased levels of serum HDL cholesterol and triglycerides (7). The form of estrogen administration affects the magnitude of the metabolic responce. The lipid lowering effects of transdermal estrogen are much less significant than those of oral preparations. In keeping with several previous studies (6, 7) we hypothesis that both forms reduce total cholesterol and LDL, and only oral estrogen would increase HDL cholesterol and triglycerides concentrations. In fact HDL cholesterol concentration increased by 9% ($p<0.05$) with oral HRT, whereas transdermal estrogen produces no significant changes in this important lipids. Our finding of an HDL increase with oral estrogen therapy is in general agreement with the findings of the other studies using fasting lipids and with one investigation of postprandial lipid metabolisms (9). Oral administration delivers significantly higher dose of estradiol to the hepatic circulation and this may explain its unique effects on the lipid profile (8).

Lipid effects appear to account for only 20% to 30% of the cardiovascular benefit noted in the numerous epidemiological studies (6). Other effect of estrogen includes its relaxant effects on vascular smooth muscle. There is a considerable evidences that both formulations of pharmaceutical estrogen promote nitric oxide activity and decreased calcium influx into vascular smooth muscle cells (8, 10). The vasodilatative actions of estrogens do not appear to be attenuated by additional use of micronized progesteron (8). Estrogen also appears to inhibit formation of oxidized LDL cholesterol, an accelerator of early atherogenesis (5). Estrogen may also attenuate the inflamatory process associated with development of atherosclerosis.

Combination HRT including cyclic progestin and either oral or transdermal estrogen significantly reduced mean arterial pressure, total and LDL cholesterol in postmenopausal women. It is important to note that our patients were healthy women without a history of coronar disease and that changes in risk factors, not incidences of disease, were the dependent measures. Further studies should address the dose sufficient to achieve cardioprotective effects and should evaluate the contribution of estrogen and progestin relative to the changes observed.

EFEKTI HORMONSKE SUPSTICIONE TERAPIJE NA SERUMSKE LIPIDE I OSTALE FAKTORE RIZIKA KORONARNE BOLESTI

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Kratak sadržaj: Cilj ovog istraživanja bio je poređenje efekta između transdermalne i oralne upotrebe estrogena na arterijski pritisak, serumske lipide, nivo estradiola i telesnu težinu. Istraživanje je obuhvatilo deset pacijentkinja koje su dobijale transdermalno estrogen sa progesteronom 6 meseci. Rezultati su komparirani sa rezultatima kod 23 pacijentkinje koje su dobijale oralno kojnugovani estrogen sa progesteronom. Oralna i transdermalna upotreba estrogena dovodi do statistički značajnog smanjenja ($p<0,05$) ukupnog holesterola i LDL holesterola, kao i smanjenja arterijskog pritiska. Međutim samo oralno primenjeni estrogen dovodi do statistički značajnog povećanja ($p<0,04$) HDL holesterola i statistički značajnog povećanja ($p<0,05$) triglicerida. Kod pacijentkinja sa transdermalnom upotrebom estrogena nema statistički značajne promene vrednosti ovih parametara ($p>0,05$). Serumske vrednosti estradiola su značajno povišene ($p<0,05$) nakon upotrebe bilo oralne bilo transdermalne ($p<0,002$) forme estrogena. Buduće studije bi uključile mnoge faktore rizika radi što bolje procene njihovog uticaja na stanje koronarnih arterija.

Ključne reči: serumski lipidi, krvni pritisak i estrogen

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