The Effect of Short Term Estrogen Replacement Therapy on Lipoprotein (a) Levels in Surgically Induced Menopause

CERRAHİ MENOPOZDAKİ OLGULARDA KISA SÜRELİ ÖSTROJEN REPLASMAN TEDAVİSİNİN LİPOPROTEİN (a) DÜZEYİ ÜZERİNE ETKİSİ

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Summary

Objective: *To determine the effect of short term estrogen replacement therapy on lipoprotein (a) [Lp(a)] levels in women who have surgically induced menopause.*

Institution: *SSK Maternity and Women's Health Teaching Hospital, Ankara.*

Material and Methods: *Fifty-six women who had have simple hysterectomy and bilateral oophorectomy at least two months prior to recruitment and who had received no previous hormonal therapy were included in the study. Women were randomized according to restricted shuffled approach. Twenty-eight subjects served as the control group whereas twenty-eight women were included in the therapy group. Serum samples were collected for measurement of Lp(a) before and after six months of treatment with cyclic transdermal estrogen (0.05 mg/day) (Estraderm TTS® 50). The statistical analysis of the data was performed by using Mann-Whitney U test and Wilcoxon Matched-Pairs Signed -Ranks tests, where appropriate.*

Results: *The women included in the therapy group were significantly younger than the women in the control group(46.4±3.8 years versus 52.3±6.8 years, p=0.017). while the duration of menopause was found to be significantly longer in the control group (72.4 moths versus 18.9 moths, p=0.05). The mean level of Lp(a) at baseline for the control group was found to be 15.56±10.6 mg/dl. whereas it was found to be 18.23±12.8 mg/dl. at the end of six months. This elevation was not statistically significant (p=0.07). In the therapy group, the mean level of Lp(a) was found to be 25.43±21.2 mg/dl. at baseline while it was found to be decreased to 12.5±8.39 mg/dl. at the end of six months of estrogen replacement therapy. The reduction in Lp(a) levels in the therapy group was statistically significant (p=0.001).*

Conclusion: *Treatment with unopposed estrogen in women who have surgically induced menopause is associated with a 50% reduction in Lp(a) levels in short term.*

Key Words: Estrogen replacement therapy, Menopause, Lipoprotein (a)

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Özet

Amaç: *Cerrahi menopozdaki olgularda kısa süreli östrojen replasman tedavisinin lipoprotein (a) [Lp (a)] düzeyleri üzerine etkisini araştırmak.*

Çalışmanın Yapıldığı Yer: *SSK Ankara Doğumevi ve Kadın Hastalıkları Eğitim Hastanesi.*

Materyal ve Metod: *Daha önceden hormon replasman tedavisi almamış ve çalışmaya katılmadan en az iki ay önce Tip I histerektomi ve bilateral ooferektomi geçirmiş 56 olgu çalışma kapsamına alındı. Olgular kısıtlı karmaşık yaklaşım yöntemi ile randomize edildi. Yirmi sekiz olgu kontrol grubunu oluşturdu ve 28 olguya altı ay süreyle siklik transdermal östrojen tedavisi (0.05 mg/gün) (Estraderm TTS® 50) verildi. Çalışma başlangıcında ve altı ay sonra Lp(a) düzeyleri her iki grup hastada ölçüldü. Elde edilen bilgilerin istatistiki analizinde Mann-Whitney U testi ve Wilcoxon eşleştirilmiş iki örnek testi kullanıldı.*

Bulgular: *Kontrol grubuyla karşılaştırıldığında tedavi grubunda yer alan olguların daha genç oldukları belirlendi (52.3±6.8'e karşın 46.4±3.8, p=0.017). Kontrol grubundaki olgularda menopoz süresinin belirgin olarak daha uzun olduğu bulundu (72.4 aya karşın 18.9 ay, p=0.05). Kontrol grubundaki olgularda başlangıçtaki ortalama Lp(a) düzeyi 15.5±10.6 mg/dl. iken bu değerin altı ay sonunda 18.2±12.8 mg/dl'ye yükseldiği saptandı. Lp(a) düzeyindeki bu artışın istatistiki olarak anlamlı olmadığı anlaşıldı (p=0.07). Tedavi grubundaki olgularda başlangıç ortalama Lp (a) düzeyi 25.4±21.2 mg/dl olarak bulunurken bu değerin altı aylık tedavi sonunda 12.5±8.3 mg/dl.'ye düştüğü belirlendi. Tedavi grubundaki olgularda Lp(a) düzeyinde meydana gelen bu azalmanın istatiski olarak anlamlı olduğu saptandı (p=0.001).*

Sonuç: *Cerrahi menopozdaki olgularda kısa süreli östrojen replasman tedavisi Lp(a) düzeylerinde %50 oranında azalmaya yol açmaktadır.*

Anahtar Kelimeler: Östrojen replasman tedavisi, Menopoz, Lipoprotein (a).

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Evidence from many large epidemiological studies indicates that postmenopausal estrogen replacement substantially reduces the risk of cardio-

vascular disease (CVD) (1) and it has been reported that there is also protection against death from stroke (2).The protective effect on the cardiovascular system is believed to be mediated by the effect of estrogens on lipoproteins, particularly high-density lipoprotein cholesterol (3). However, changes in low and high-density lipoproteins (LDL and HDL) cannot wholly explain the reduction in risk conferred by estrogens and attention is now becoming focused on the effects of estrogens on other markers of cardiovascular risk.

Several studies have linked high levels of lipoprotein (a) [Lp(a)], a genetically determined lipoprotein variant with a lipid composition similar to that of LDL, to both cardiovascular and cerebrovascular disease (4). An increased risk of coronary atherosclerosis of at least twofold is associated with Lp(a) levels of greater than 30 mg/dl (5). Lp(a) has close homology to plasminogen and it is also present in atherosclerotic plaques where it appears to compete with plasminogen, reducing fibrinolytic activity within the clot. Therefore, as well as its strong association with diseases involving atherogenesis and thrombosis , Lp(a) may have a possible role in coagulation and fibrinolysis (4).

Although the elevation of Lp(a) levels is shown to be a risk factor for CVD in both men and women, the cardioprotective effect of low Lp(a) concentrations is not determined (6).

The purpose of this paper is to determine the effect of short term estrogen replacement therapy on Lp(a) levels in women who have surgically induced menopause.

Materials and Methods

Fifty-six women attending to Menopause Unit of SSK Maternity and Women's Health Teaching Hospital, Ankara, for treatment of climacteric symptoms were recruited for the study. All had have simple hysterectomy and bilateral oophorectomy for benign gynecological disease at least two months prior to recruitment and had received no previous hormonal therapy. Women were randomized according to "restricted shuffled approach". Twenty-eight subjects served as the control group whereas twenty-eight women were included in the therapy group. Women in the therapy group were treated with cyclic transdermal estrogen (0.05 mg/day) (Estraderm TTS® 50).

The mean age of the 56 women who completed the study was 49.4±6.2 (SD) years. The mean duration of menopause for all women included in the study was 45.6±68.5 (SD) months. None of the subjects was taking any drug known to affect lipoprotein metabolism and routine biochemical screens indicated revealed normal renal and hepatic function before and during treatment. In no case was there any contraindication to treatment with estrogen.

Fasting blood samples were obtained prior to and after six months of treatment. Serum was separated and stored at -20ºC for estimation of lipoprotein (a). Lp(a) levels were determined by using TintElize®Lp(a) (BIOPOOL) which is an enzyme immuno-assay (ELISA) for the quantitative determination of Lp(a) in human plasma. This assay utilizes affinity purified polyclonal antibodies raised against Lp(a). The statistical analysis of the data was performed by using Mann-Whitney U and Wilcoxon Matched-Pairs Signed -Ranks tests, where appropriate.

Results

The mean age of the women included in the control group was found to be 52.3±6.8 years while the mean age of the women in the therapy group was found to be 46.4±3.8 years. The women included in the therapy group were significantly younger than the women in the control group (p=0.017). The mean duration of menopause was found to be 18.9±37.1 months in the therapy group whereas it was found to be 72.4±82.7 months in the control group. The duration of menopause was significantly longer in the control group (p=0.05). The age of the subjects and duration of menopause for each group is shown in Table 1.

The mean level of Lp(a) at baseline for the control group was found to be 15.56±10.6 mg/dl. whereas it was found to be 18.23±12.8 mg/dl. at the end of six months. This arise was not statistically significant (p=0.07). In the therapy group, the mean level of Lp(a) was found to be 25.43±21.2 mg/dl. at baseline while it was found to be decreased to 12.5±8.39 mg/dl. at the end of six months of estrogen replacement therapy. The reduction in Lp(a)

Table 1. Demographic characteristics of women in the control and therapy groups*

	Age	Duration of menopause (months)
Control group (n=28)	52.3±6.8	72.4±82.7
Therapy group (n=28)	46.4±3.8	18.9±37.1
Significance	p:0.017 (S)	p:0.05 (S)

*Values are mean±SEM. S: significant

Table 2. Lp(a) levels at baseline and at the end of six months for each group*

	Control Group (n=28)	Therapy Group (n=28)
Baseline	15.56±10.6	25.43±21.2
Month 6	18.23±12.8	12.5±8.39
Significance	p:0.07 (NS)	p:0.001 (S)

*Values are mean±SEM. S: Significant. NS: Not significant

levels in the therapy group was statistically significant (p=0.001). Table 2 demonstrates Lp(a) levels for each group at baseline and at the end of six months of estrogen replacement therapy.

Discussion

Lp(a) is a risk factor for cardiovascular disease, which consists of LDL and apo A (the latter being homologous with plasminogen) and is therefore a possible risk factor for thrombosis (7). The distribution of Lp(a) levels in the population is very highly skewed and cross-sectional studies of the effects of age or therapy are difficult to interpret (7). There are, therefore, conflicting reports as to the effect of the menopause on serum Lp(a) concentrations.

The effect of estrogen on Lp(a) has not been satisfactorily investigated, as the first reports on combined hormone replacement therapy (HRT) in which Lp(a) was reduced, contained no information as to cycle phase at the time of blood sampling (7). Another study of combined HRT has confirmed an effect on Lp(a), showing a reduction of only 10 to 15% (8) ; the issue of whether the active component was the estrogen, the progesteron or the both, was not clarified.

High doses of oral synthetic (alkylated) estrogens reduce Lp(a) levels by half in men with prostatic cancer, but evidence that the lower doses of natural estrogens used in HRT affect Lp(a) is at present sparse (7). High levels of endogenous estrogen do not alter Lp(a) (9), neither do the raised levels associated with early pregnancy (10). One prospective trial of postmenopausal estrogen found a small decrease in Lp(a) , which was of borderline statistical significance (p=0.08) and perhaps reflects the low statistical power of this study because of the small numbers of patients treated (11).In the study of Lobo et al. (11), it was found out that after 6 months of treatment with conjugated equine estrogens and transdermal estradiol there was a decrease in Lp(a) levels. In that study (11), the greatest decreases in concentration were observed in women with low baseline levels. More recently, a large cross-sectional study reported a 10% decrease in Lp(a) with both estrogen/progestogen therapies (12). Durrington and Bhatnager (13) have emphasized the inappropriateness of using means, standard deviations and parametric tests for highly skewed data. Their comments can be applied to most of the mentioned studies, as well as the present one.

Farish et al. (14) found that after treatment with estradiol there was no consistent trend in lipoprotein (a) concentrations and no change in fibrinogen and tissue plasminogen activators (tPA). In the study of Farish et al.(14) Lp(a) levels remained high in five patients whose baseline levels were in the high risk category (i.e.>30 mg/dl.). This is in contrast to the effects reported for norethisterone (15) and danazol (16), both of which treatments brought all Lp(a) concentrations into the low risk irrespective of their baseline levels.

In a recent study by Andersen et al. (17), it was reported that a significant decrease in Lp(a) concentrations had been achieved in 50 healthy postmenopausal women treated with estradiol valerate 2 mg/day either continuously or cyclic, combined with cyproterone acetate 1 mg/day on days 12 to 21. In the study of Andersen et al. (17) Lp(a) levels decreased from 130 mg/l. at baseline to 75 mg/l. at the end of six months of HRT; showing approximately a 43% decrease. Although transdermal route is used in our study, our findings are similar to that of Andersen et al.(17).

Kon Koh et al. (18) reported that Lp(a) levels had decreased from 29.7±27.1 mg/dl. to 22.8±20.3 mg/dl. in 28 hypercholesterolemic postmenopausal women treated with conjugated equine estrogen (0.625 mg/day) for a period of six weeks. In a randomized, double-blind, placebo-controlled study (19), Lp(a) concentrations were reported to decrease from 10.7 mg/dl. to 6.4 mg/dl. in 46 women with surgically induced menopause who were treated with 2 mg/day of oral estradiol for a period of six months. Our findings are comparable with that of Haines et al. (19). Farish et al. (20) reported a 39% decrease in Lp(a) levels in 40 postmenopausal women going on oral estradiol (2 mg/day) combined with continuous norethisterone (1 mg/day) for 12 months.

Our findings suggest that short term treatment with unopposed estrogen is associated with a 50% reduction in Lp(a) levels in women with surgically induced menopause. Larger, longer term studies are necessary to clarify fully the effects of single or combined preparations of hormone replacement therapy on Lp(a).

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