Hormone Therapy and Homocysteine Levels In Postmenopausal Women: A Review of The Literature

Hakan KIRAN¹, Mustafa KAPLANOĞLU²

Homocysteine, a sulfur-containing amino acid is formed during the metabolism (remethylation or transsulfuration) of the essential amino acid methionine. An elevated homocysteine level is important and independent risk factor for cardiovascular disease in postmenopausal women. Homocysteine levels are lower in women compared with men. On the other hand, homocysteine levels is lower during pregnancy and higher during menopause. The determinants of serum homocysteine in healthy postmenopausal women are uncertain. Endogenous estrogens and not androgens are related to serum homocysteine values in postmenopausal women. The mechanism behind this observation remains unclear. The millions of postmenopausal women currently receive estrogen treatment. Estrogen replacement relieves menopausal symptoms such as hot flashes and vaginal atrophy and prevents osteoporosis. Elevations in circulating homocysteine levels also predict a significantly greater risk of coronary artery disease. The underlying mechanism for the pathogenic response is still unclear.

(Gynecol Obstet Reprod Med;13:2 127-130)

Key Words: Homocysteine, Hormone, Menopause

Homocysteine (Hcy) is a thiol-containing amino acid resulting from the demethylation of methionine. Elevated blood concentrations of Hcy are an established independent risk factor for atherosclerosis, thrombosis, and occlusive arterial disease.¹-³ Blood levels of Hcy are shown to be determined by genetic, nutritional and hormonal factors. Several hereditary enzyme disorders (e.g., methylen-tetrahydrofolate reductase thermolability) lead to increased Hcy concentrations.⁴ Deficiencies of folate, vitamin B₆, and B₁₂ are associated with elevated Hcy levels.⁵,⁶

Sex hormones have been shown to affect serum Hcy concentrations. Hcy levels are generally lower in women than in men.⁷,⁸ In pregnant women, having high estradiol concentrations, homocysteine levels were found to be lower as compared to non-pregnant women.⁹ Several investigations have reported that Hcy levels are higher in postmenopausal women than in premenopausal women.¹⁰-¹² Since Hcy promotes atherosclerosis by injuring the vascular endothelium,¹³ and it also interferes with the vasodilator and antithrombotic functions of nitric oxide,¹⁴ these observations may explain, in part, the increase in coronary heart disease in women after menopause.¹¹

The goals of menopausal hormone therapy (HT) are to reduce symptoms resulting from estrogen depletion, including hot flushes, sleeplessness, lethargy, depressed mood and treat urogenital atrophy and vaginal dryness.¹⁵ The effect of HT on Hcy levels in postmenopausal women is not yet fully understood. Therefore, in this review, we investigated related articles of that subject.

Discussion

There are two broad categories of menopausal HT: estrogen alone therapy (ET) and estrogen combined with progestogen therapy. Route of estrogen (oral vs. transdermal) also seems to influence the effect of ET on Hcy concentration. The liver is an important organ in the metabolism of Hcy,¹⁶ and the first-pass metabolism of estrogens is avoided if ET is given intranasally or transdermally. Therefore, it is possible that oral and non-oral ET have different effects on blood Hcy levels. While oral estrogen appears to decrease Hcy levels,¹⁷-¹⁹ transdermal route dose not have this effect.¹⁹,²⁰

Barnabei et al. reported that treatment with oral conjugated equine estrogens (CEE) had a modest, but transient decrease on plasma Hcy levels during 36 months of follow-up.¹⁷ However, participants in their study, who were generally healthy, had normal plasma Hcy levels at baseline. Thus, this analysis did not address the effect of ET in women with hyperhomocysteinemia. Yildirim et al. investigated the 6-month effect (s) of oral CEE therapy on plasma Hcy levels in healthy postmenopausal women. They reported that this therapy significantly lowered fasting plasma Hcy concentrations. The greatest reduction was observed in women with the highest initial fasting plasma total Hcy.¹⁸ Postmenopausal ET is not
likely to have a clinically relevant impact on plasma Hcy levels in women with normal levels prior to therapy.\textsuperscript{17}

The effect of transdermal estrogen on Hcy levels is controversial. Transdermal route appears to produce less marked changes in the Hcy levels than to oral estrogens.\textsuperscript{19,20} Smolders et al. demonstrated that treatment with oral 17β-E2, but not transdermal 17β-E2, decreases fasting plasma concentration of Hcy.\textsuperscript{19} Similarly, Marchesoni et al. reported that transdermal estrogen treatment for 12 months in postmenopausal women did not modify Hcy levels.\textsuperscript{20} But, in the other study, plasma Hcy levels were significantly reduced with the use of transdermal E2.\textsuperscript{21} Harma et al found the reduction in plasma homocysteine levels after 6 months' treatment with intranasal 17 beta-estradiol in postmenopausal women.\textsuperscript{22}

Although some studies have reported that estrogen reduces serum Hcy levels,\textsuperscript{17-19} this finding has not been confirmed by the others.\textsuperscript{23-25} Berger et al. reported that six months of estradiol treatment did not lower fasting plasma Hcy concentrations and raised Hcy concentrations following a methionine load.\textsuperscript{23} Also, high concentrations of Hcy have been found during the use of oral contraceptives (OC).\textsuperscript{24} It must be emphasized that synthetic estrogens like ethinyl-estradiol, which is the most common estrogen in OCs, may have different metabolic interactions when compared with natural estrogens.\textsuperscript{26} OCs, containing ethinyl estradiol, are known to decrease serum concentrations of vitamin B12 and folate.\textsuperscript{27,28} In the other study, intranasal 17β-E2 have not caused any change in serum Hcy level during the 3 months of treatment. But, Hcy values at 6 months of treatment were significantly elevated compared with baseline levels.\textsuperscript{25}

Investigations showed a reduction in Hcy levels during postmenopausal combined HT,\textsuperscript{17,18,29,30} but this has not been confirmed.\textsuperscript{23,31,32} Although the Hcy-reducing effect of estrogen has been reported,\textsuperscript{17-19} there is no consensus about the favorable effects of its combination with a progestin on Hcy levels. Smolders et al. demonstrated that treatment with oral 17β-E2 but not transdermal 17β-E2 decreases fasting plasma concentration of Hcy and that addition of the progestogen gestodene attenuates the reduction induced by oral E2 therapy.\textsuperscript{19} Christodoulakos et al reported that continuous CEE+MPA administration resulted in a decrease of a lesser magnitude compared with CEE.\textsuperscript{29} Mijatovic et al. detected that plasma Hcy concentrations were lowered by 17β-estradiol- dydrogesterone therapy in postmenopausal women. However, in view of their study methodology, the observed Hcy lowering cannot be attributed exclusively to either estradiol or dydrogesterone, and it may well be a combined effect.\textsuperscript{30} In the Postmenopausal Estrogen/Progestin Intervention (PEPI) trial, treatment with continuous CEE+MPA had a modest, but transient reduction on plasma Hcy levels during 36 months of follow-up. This trial indicates no additional influence of MPA. However, participants in the PEPI trial, who were generally healthy, had normal plasma Hcy levels at baseline.\textsuperscript{17} Yıldırım et al. detected that the mean Hcy concentration decreased by 24.2 % in the CEE+MPA group in postmenopausal women after 6 months of treatment. The greatest reduction was observed in women with the highest initial fasting plasma total Hcy.\textsuperscript{18} On the other hand, in the study evaluating the effect of HT on Hcy levels after a methionine load, the association of estrogens with cyclic MPA induced an elevation of post-load Hcy levels.\textsuperscript{23} Park et al reported that the mean values of Hcy levels did not change significantly after oral CEE (0.625 mg) combined with MPA (2.5 mg) therapy for 3 months.\textsuperscript{31}

Tibolone is a synthetic steroid with mixed estrogenic, progestogenic, and androgenic activity used for postmenopausal HT. Çelik et al found that Hcy levels did not change significantly after 6 months of treatment with tibolone.\textsuperscript{33} In the other study, tibolone had no effect on serum Hcy levels at least during the first 18 months of therapy.\textsuperscript{34}

Estrogenic potency of tibolone is about 1/50 that of ethinyl-estradiol, the progestogenic potency is 1/8 that of norethisterone (an androgen derivative), and the androgenic potency is about 1/3 that of norethisterone.\textsuperscript{35} Although tibolone is reported to have no effect on Hcy levels,\textsuperscript{33,34} the effect of combined estrogen-androgen derivative is controversial. Eviö et al detected that oral or transdermal combination of sequential estradiol and norethisterone acetate did not cause significant changes on Hcy levels in postmenopausal women.\textsuperscript{32} On the other hand, Ventura et al demonstrated that continuous combined oral HT with 17β-E2 plus norethisterone acetate reduced post-methionine load Hcy levels in postmenopausal women.\textsuperscript{36} In the other study, Hak et al reported a decrease in serum Hcy levels with sequential combined regimen of 17β-E2 and desogestrel or with combination of CEE and norgestrel in perimenopausal women after 6 months of therapy.\textsuperscript{37}

The data suggest that there is an association of hyperhomocysteinemia with high serum androgen levels. A sex difference in plasma Hcy levels has been found, with approximately 10-15% higher levels in men vs. women.\textsuperscript{38} It was recently shown that androgen administration in female-to-male transsexuals increased the plasma levels of Hcy by 17%.\textsuperscript{39} On the other hand, Morgante et al detected that women with polycystic ovarian syndrome (PCOS, a syndrome characterized by hyperandrogenemia) had plasma concentrations of Hcy similar to those of healthy women with normal menstrual cycles.\textsuperscript{40}

In conclusion, most of the studies have shown that the Hcy levels are reduced with using combined HT and tibolone. (Table I: Using HRT types and Homocysteine levels). Further prospective randomized controlled studies are needed for showing the effect of tibolone, transdermal and intranasal estrogen on serum Hcy levels.
Table I: Using HT types and homocysteine levels.

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HT: Hormone therapy

References


