Oral versus Transdermal Estrogen: Contrasting Effects on C-Reactive Protein

C-reactive protein (CRP) is one of the main independent predictors of cardiovascular events. Oral post-menopausal estrogen replacement therapy (ERT) increase CRP levels by a first-pass hepatic effect. These elevated levels of CRP may be responsible for the early increased cardiovascular risk that has been reported shortly after women begin oral combined hormone replacement therapy (HRT) using NON bio-identical synthetic hormones. However, transdermal 17beta-estradiol has shown no significant effect on CRP in either short-term or long-term use.

The incidence of ischemic heart disease shows a sharp rise after menopause. However, the effects of HRT on cardiovascular disease are still controversial. Kawano et al. compared the effects of HRT on endothelial function, cellular antioxidant system and inflammation between oral and transdermal administration in mild hypercholesterolemic postmenopausal women. Transdermal bio-identical estradiol replacement was administered to 12 patients for 12 weeks, and oral conjugated equine estrogen was administered to 12 patients for 12 weeks. The vasodilation of the brachial artery increased with HRT, and thioredoxin levels (a marker of the cytoprotective antioxidant system) decreased with HRT. CRP levels increased with oral HRT while transdermal HRT did not elicit any changes. Both oral and transdermal HRT improved endothelial function and decreased oxidative stress through affecting the cellular redox state.

Abbas et al. of the University of Texas, found that synthetic oral conjugated estrogens significantly increased levels of serum amyloid A (SAA), HDL, and HDL-SAA, whereas transdermal estradiol reduced both SAA and HDL-SAA but had no effect on HDL in the same women. They concluded that the effect was due to first-pass hepatic mechanism on oral estrogens.

At the University of Connecticut Health Center, a randomized, double-blind, placebo-controlled study evaluated the effect if 3 doses (0.25 mg/day, 0.5 mg/day, and 1 mg/day) of micronized 17beta-estradiol (E2) on CRP, interleukin-6, and lipids, compared with placebo, in healthy older women participating in an osteoporosis study, and found that after 12 weeks of treatment, CRP decreased 59% in the o.25 mg/day E2 group and increased 65% in the 1 mg/day E2 group, compared with placebo. The CRP level continued to be elevated 12 weeks after treatment was discontinued in the 1 mg/day E2 group. HDL and HDL2 cholesterol increased and LDL decreased at 12 weeks in the 1 mg/day E2 group, with a significant dose-response effect. Therefore, low-dose E2 decreased CRP, but did not affect lipid parameters, whereas the highest dose increased CRP and had a beneficial effect on lipid parameters. This study indicates that estradiol dose should be considered when risk:benefit ratios are evaluated for individual women before ERT is initiated.

A Finnish study reported that oral but not transdermal estradiol combined with cyclic NETA (synthetic progestin) increased hs-CRP levels. A placebo-controlled study of 27 healthy postmenopausal women showed that 12 weeks of oral but not transdermal estradiol (unopposed by progestin) was associated with an increase in CRP.

In another placebo-controlled study in healthy women using oral conjugated equine estrogens and transdermal estradiol (both with oral sequential medroxyprogesterone acetate), only oral treatment with NON-bio-identical hormones increased CRP during 6 and 12 months of therapy.

No published studies describe the effects on CRP produced by bio-identical estriol or a balanced of bio-identical hormones. In conclusion, our review underscores the importance of customized HRT, using the hormones and route of administration that are most appropriate for each patient, while considering medical history and treatment goals.

Arterioscler Thromb Vasc Biol. 2004 Oct;24(10):e164-7
Int J Clin Pharmacol Ther. 2003 Aug;41(8):346-53
Maturitas. 2003 Dec 10;46(4):245-53Hum Reprod. 2003 Apr;18(4):866-70
Thromb Haemost. 2003 Jul;90(1):124-31Am J Cardiol. 2003 Jul 15;92(2):212-4
Thromb Haemost. 2001 Apr;85(4):619-25