Genes may determine the side effects of menopausal hormone therapy, study suggests

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A woman's genes may influence whether hormone therapy after menopause will provide her some protection against heart disease.

Risk of cardiovascular disease in women increases after menopause and is associated with the drop in estrogen levels. Although replacing estrogen with menopausal hormone therapy could slow the progression of cardiovascular disease, the oral formulations also increase the risk of blood clots. A new study published in Physiological Genomics reports that genes may influence whether a woman will obtain cardiovascular benefits from some types of hormone therapy.

The findings are the results of the Kronos Early Estrogen Prevention Study (KEEPS), a multi-institutional study tracking the progression of cardiovascular disease in menopausal women in the U.S. who are receiving hormone therapy. While each person has the same genes, every individual is unique because genes can have different forms called genetic variants. The KEEPS study examined whether the cardiovascular effects of menopausal hormone therapy were influenced by a woman's particular genetic variants.
512 healthy participants received conjugated equine estrogen orally via a pill, 17β-estradiol through the skin via patch or a placebo. Both hormone treatment groups received progesterone. Blood samples were collected for gene analysis. Cardiovascular and genetic changes were evaluated four years after treatment started. According to lead investigator Virginia Miller, PhD, the main findings of the study are:

- Genetic variants influenced the cardiovascular effects of menopausal hormone therapy
- Genetic effects differ with the formulation of estrogen (oral conjugated equine estrogens or transdermal 17β-estradiol), and
- Genes with the greatest influence were ones involved in immune response. This observation also further supports evidence suggesting that infection and inflammation contribute to the development of vascular disease, including in healthy women, says Miller.

"Whether use of menopausal hormone treatments reduces the risk of cardiovascular disease is a controversial topic, and hormones are not recommended for primary prevention of cardiovascular disease," says Miller. "Our findings help explain the variability in responses to menopausal hormones specifically in the progression of atherosclerosis. As we move toward personalized management of menopause, these results are another small piece of the puzzle needed to direct therapy. We aren't there yet, but to our knowledge, this is the first paper that has addressed the pharmacogenomics of menopausal hormone therapy relative to the progression of asymptomatic cardiovascular disease."

More information: Virginia M. Miller et al. Pharmacogenomics of estrogens on changes in carotid artery intima-medial thickness and coronary arterial calcification - Kronos Early Estrogen Prevention Study, *Physiological Genomics* (2015). DOI: 10.1152/physiolgenomics.00029.2015

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