Hormone replacement therapy among postmenopausal women: Effects on the haemostatic system

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This Ph.D. dissertation, consisting of five papers and a review, is based on research carried out during employment at the Department of Clinical Biochemistry, Odense University Hospital, and was made possible due to collaboration with the Department of Endocrinology, Odense University Hospital and the Institute for Thrombosis Research, Esbjerg.

The aim of the project was to investigate long-term effects of postmenopausal hormone replacement therapy (HRT) on selected variables within the haemostatic system.

An investigation of mechanisms by which HRT may influence risk of coronary heart disease (CHD) seem of major importance as most women, today, spend at least one-third of their lives after menopause, and postmenopausal health, thus, has assumed greater importance than ever before.

The study included 719 women from three centres in The Danish Osteoporosis Prevention Study, randomised to a HRT or no substitution 5 years prior to investigation. Throughout, both an intention-to-treat and a per-protocol analysis were performed.

HRT was associated with lower levels of fibrinogen, homocystein (Hcy), tissue factor pathway coagulation inhibitor (TFPI) and a beneficial fibrinolytic profile. All these effects were equal with opposed and unopposed therapy. Coagulation factor VII (FVII) was not affected by opposed HRT whereas un-opposed therapy was associated with higher levels. No effect of HRT on thrombin activatable fibrinolysis inhibitor (TAFI) was found. The effects of HRT were similar within all genotypes of the methylenetetrahydrofolate reductase –677T/C, PAI-1 –675(4G/5G), t-PA intron8ins311 and TFPI –287T/C polymorphisms. The fibrinogen lowering effect of HRT was restricted to the GG genotype of the fibrinogen β –455G/A polymorphism and the effect of un-opposed HRT on FVII was solely found in women homozygous for the common P0 allele of the FVII –323ins10, the R535 allele of the R/Q353polymorphism or the H6H6 genotype of the FVII intron7$(37bp)_n$ polymorphism. HRT was associated with lower TAFI levels in homozygotes for the rare TAFI –438A allele. Smoking counteracted the effect of HRT on fibrinogen and FVII.

Based on the effects on risk factors/markers for CHD, HRT was associated with beneficial effects on fibrinolytic profile, fibrinogen and homocysteine concentrations, whereas the decrease in TFPI and increase in FVII (only un-opposed HRT) was potential deleterious. Some of the effects were genotype-specific, and smoking counteracted the effect of HRT on fibrinogen and FVII. The combined clinical impact of these effects is uncertain, and may not serve as a guide towards clinical decision-making, but may help us further in understanding aspects of vascular biology.

This Ph.D. dissertation was accepted by the Faculty of Health Science of the University of Southern Denmark, and defended on September 22, 2004.
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