Effect of menopausal hormone therapy on methylation levels in early and late postmenopausal women

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Clin Epigenetics 2022 Jul 18;14(1):90.

doi: 10.1186/s13148-022-01311-w.

Abstract

Background: Cardiovascular disease (CVD) remains the leading cause of death among postmenopausal women but standard primary prevention strategies in women are not as effective as in men. By comparison, the Early versus Late Intervention Trial with Estradiol (ELITE) study demonstrated that hormone therapy (HT) was associated with significant reduction in atherosclerosis progression in women who were within six years of menopause compared to those who were 10 or more years from menopause. These findings are consistent with other studies showing significant reductions in all-cause mortality and CVD with HT, particularly when initiated in women younger than 60 years of age or within 10 years since menopause. To explore the biological mechanisms underlying the age-related atheroprotective effects of HT, we investigated changes in methylation of blood cells of postmenopausal women who participated in ELITE.

Results: We first validated the epigenetic data generated from blood leukocytes of ELITE participants by replicating previously known associations between smoking and methylation levels at previously identified CpG sites, such as cg05575921 at the AHRR locus. An epigenome-wide association study (EWAS) evaluating changes in methylation through interactions with time-since-menopause and HT revealed two significantly associated CpG sites on chromosomes 12 (cg19552895; $p = 1.1 \times 10\text{-}9$) and 19 (cg18515510; $p = 2.4 \times 10\text{-}8$). Specifically, HT resulted in modest, but significant, increases in methylation levels at both CpGs but only in women who were 10 or more years since menopause and randomized to HT. Changes in carotid artery intima-media thickness (CIMT) from baseline to 36 months after HT were not significantly correlated with changes in methylation levels at either cg19552895 or cg18515510. Evaluation of other previously identified CpG sites at which methylation levels in either blood or vascular tissue were associated with atherosclerosis also did not reveal any differences in methylation as a function of HT and time-since-menopause or with changes in CIMT.

Conclusions: We identified specific methylation differences in blood in response to HT among women who were 10 or more years since menopause. The functional consequence of these change with respect to atherosclerosis progression and protective effects of HT remains to be determined and will require additional studies.