Sex Differences in Sex Hormones, Carotid Atherosclerosis, and Stroke

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There are notable sex differences in cardiovascular disease. Although the cumulative incidence of cardiovascular disease in women lags behind that of men by ≈7 to 10 years, strokes comprise a larger proportion of cardiovascular events in women than in men. In terms of clinical impact, aspirin used for primary prevention is associated with a significance reduction in stroke women but not myocardial infarction in men. Differences in endogenous sex hormones have been hypothesized to underlie these substantial sex differences, but clinical data are limited on the relationship between endogenous levels and cardiovascular disease occurrence.

In this issue, Glisic et al examine the relationship of endogenous sex hormone levels and carotid plaque composition, as well as incident stroke, in >2100 older men and women in the Rotterdam Study. Notably, presence of carotid atherosclerosis (carotid intimal–medial thickness of >2.0 mm on carotid screening) was more common among men than women in the study. Among those with established atherosclerosis, the prevalence of calcified plaques was similar in men and women, whereas women were less likely to have a lipid core (36.9% of women; 49.5% of men) and less likely to have intraplaque hemorrhage than men (29.0% of women; 40.0% of men).

Endogenous hormones, specifically estradiol and testosterone, were correlated with carotid plaque composition. Higher estradiol levels were associated with increased odds of a lipid core in carotid plaque in both men and women. Women with detectable estradiol levels had a 58% increased odds of having intraplaque hemorrhage compared with women with low estradiol, whereas higher total testosterone levels were associated with decreased odds. No relationship was observed for total testosterone and carotid plaque composition features in men.

Endogenous hormones were also related to incident stroke in women. Among women with carotid plaque, those with detectable total estradiol levels had a nearly 2-fold increased risk of stroke during a median follow-up of 10 years. However, when women without evidence of carotid atherosclerosis at baseline were examined, the association was substantially attenuated; those with detectable estradiol had a nonsignificant 29% increased odds of stroke. No association between total estradiol and risk of stroke was noted in men, and no associations were observed for total testosterone with incident stroke in either men or women. Notable strengths of the study include a well-characterized, cohort-based, population study; use of magnetic resonance imaging for analysis of carotid plaque composition; and exclusion of exogenous hormone therapy users. Although testosterone levels were measured via chromatography–tandem mass spectroscopy, the gold standard, estradiol was measured by immunoassay, which has particularly low sensitivity in postmenopausal women and prevented the investigators from examining estradiol as a continuous variable in women. Additionally, relatively few incident stroke events were observed within sex strata.

Detailed examination of sex hormones and cardiovascular disease may shed light on sex differences. Postmenopausal women have markedly lower estradiol and testosterone levels than men of roughly the same age. After the cessation of estrogen production by the ovaries, estrogen biosynthesis takes place in peripheral tissues, especially adipose, through aromatase conversion of androgens in postmenopausal women. Although absolute levels of both estradiol and testosterone are lower in postmenopausal women than men, the estradiol to testosterone ratio is >6-fold higher in women than in men.

There are relatively few prospective studies of endogenous sex hormones and stroke in women. No association between estradiol and risk of cardiovascular disease, including stroke, was found in the Women’s Health Study. In the Copenhagen City Heart Study, there was no association between estradiol or testosterone levels and incidence ischemic stroke in women during almost 30-year follow-up and >500 events. Lee et al found that higher free estradiol index, but not estradiol, was associated with increased risk of stroke in older women, but this was not independent of standard cardiovascular risk factors. Higher estradiol levels were associated with a nonsignificant 34% increase in stroke among women aged >65 years in the Three City Cohort Study. In a meta-analysis of the prior 3 studies of stroke in women without evidence of pre-existing cardiovascular disease, being in the highest 10th percentile of estradiol levels was associated with a nonsignificant increased risk of ischemic stroke (hazard ratio, 1.15; 95% confidence interval, 0.91–1.45). In addition to the association with atherosclerotic features, higher endogenous estrogens may also contributed to thrombotic risk through association with lower levels of the natural anticoagulant protein S antigen. Glisic et al add to this body of evidence by showing that higher estradiol levels are associated with high-risk carotid plaque features, as well as a 2-fold increased risk of stroke in women with established carotid atherosclerosis.
Testosterone levels have been related to carotid atherosclerosis but not stroke in women. Two cross-sectional population-based studies have shown lower prevalence of carotid atherosclerosis in postmenopausal women with higher testosterone levels. In the present study, higher testosterone levels were associated with reduced odds of intraplaque hemorrhage in women, but no association was noted for incident stroke. Similarly, in a meta-analysis of the 2 prior studies of testosterone levels and risk of ischemic stroke, no association between testosterone levels and stroke in women was observed.

The timing hypothesis postulates differential effect and risk associated with estrogen exposure in women based on underlying subclinical atherosclerosis or time since menopause. The work by Glisic et al further strengthens these biological underpinnings, finding a nearly 2-fold increased risk of stroke for detectable estradiol levels among women with established carotid atherosclerosis, but a weaker, nonsignificant association for women without. This is consistent with biological studies showing that exogenous estrogen treatment in apolipoprotein E–deficient mice inhibited the development of early atherosclerosis including initiation of fatty plaques but did not inhibit intraplaque hemorrhage or progression of established lesions. Time since menopause having a differential impact based on cardiovascular disease is generally less supported for stroke than for coronary heart disease. For exogenous estrogen use, Grodstein et al found no evidence of differences in the increased risk of stroke associated with postmenopausal hormone therapy based on time since menopause or age at initiation. Similarly, in the Women’s Health Initiative, initiation of hormone therapy within 10 years of menopause was associated with a 77% significantly increased risk of stroke, even though a reduced risk of coronary heart disease was observed in this group.

In men, testosterone levels decrease with age, and lower testosterone levels have been associated with several cardiovascular risk factors. However, in cross-sectional analyses in the Atherosclerosis Risk in Communities Study, plasma testosterone levels were not associated with mean carotid intimal–medial thickness in men, consistent with the lack of association for testosterone and carotid plaque features in the current study. In contrast, several studies have observed an inverse relationship between testosterone levels and stroke in men. Among men aged 270 years, higher testosterone levels were associated with reduced risk of stroke. In the Copenhagen City Heart Study, low testosterone levels were associated with a 34% increased risk of ischemic stroke, which seemed to be partially mediated by obesity and hypertension. In a meta-analysis of 4 studies examining sex hormones and ischemic stroke in men, lower testosterone levels (<10th percentile) were associated with increased risk of ischemic stroke (hazard ratio, 1.43; 95% confidence interval, 1.21–1.70), whereas no association was observed for estradiol levels. In the current study, in contrast, no association of testosterone levels with incident stroke was observed for men with or without established carotid atherosclerosis. Further research is needed to evaluate whether low testosterone levels are a risk marker or a true effector of risk.

Sex differences in the association of endogenous hormones and carotid atherosclerosis and stroke may not be surprising, but further research is needed to understand how hormones differentially affect men and women. What are the intermediate biological mechanisms? How might risk be effectively reduced? How are endogenous hormones related to platelet function and thrombotic tendency? Further studies examining whether higher estradiol levels at baseline lead to changes in carotid plaque composition over time would add to our biological understanding. Moreover, the increased risk of stroke among women higher with established carotid atherosclerosis and higher estradiol levels, but not among those without carotid atherosclerosis, adds to the hypothesis that higher estrogen levels may have a role in preventing atherosclerosis but may aggravate progression among those with established disease, at least in women. There has been a paucity of studies of endogenous hormones and cardiovascular disease, particularly in women. A better understanding of how sex hormones influence the progression of atherosclerosis in men and women will advance our biological understanding and lead to better preventive strategies of both sexes.

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Disclosures
None.

References


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