Increased P450 aromatase levels in post-menopausal women after acute ischemic stroke

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Abstract

Background: Sex differences in stroke have been attributed to the neuroprotective effects of estrogen, yet most clinical trials of estrogen supplementation for stroke prevention have failed. The contribution of sex hormones to stroke outcome remains a subject of debate. Aromatization of testosterone to estradiol in neural tissue leads to sexual differentiation. Emerging data suggests aromatase activity increases in response to brain injury, and increased aromatase expression is seen in the ischemic penumbra in animal models. The objective of this study was to examine the levels of endogenous sex steroids after acute ischemic stroke and determine if levels of sex steroids were associated with acute stroke outcomes.

Methods: Peripheral blood from ischemic stroke patients was collected under an approved IRB within 24 hours of symptom onset. 17 β estradiol, testosterone and aromatase levels were measured in the serum of both men and women. Hormone levels were compared in men vs. women in stroke and control groups and correlated with outcomes (NIHSS and change in the modified Rankin Scale (mRS), defined as difference of premorbid and discharge mRS) using multivariate regression.

Results: We found no significant change in estradiol levels 24 hours after stroke in men ($p = 0.86$) or women ($p = 0.10$). In men, testosterone significantly decreased after stroke as compared with controls (1.83 ± 0.12 vs 2.86 ± 0.65, $p = 0.01$). Aromatase levels were significantly higher in women after stroke as compared with controls (2.27 ± 0.22 vs 0.97 ± 0.22, $p = 0.002$), but not in men ($p = 0.84$). Estradiol levels positively correlated with higher NIHSS at the time of admission, ($r = 0.62$, $p = 0.0001$) and higher change in mRS, ($r = 0.38$, $p = 0.02$) in women. Similar correlations between estradiol levels with NIHSS, ($r = 0.34$, $p = 0.02$) and change in mRS, $r = 0.3$, $p = 0.04$, was seen in men.

Conclusions: Higher estradiol levels correlated with worse acute stroke outcomes, regardless of the sex. Testosterone levels decreased after stroke in men. As seen in animal models, aromatase levels increase after acute ischemic stroke, but this was only true for older women. These indicate an active aromatization process in post-menopausal women after acute ischemic stroke. We speculate that aromatase mediated local production of estradiol may occur in the female brain after acute ischemic stroke.

Introduction

It is well established that sex differences exist in stroke incidence, prevelance and outcome in ischemic stroke (1). Elderly women bear the major brunt of stroke disability as compared to men (2, 3). Most of this sexual dichotomy in stroke has been attributed to the effects of sex hormones (4) as preclinical data has consistently shown that estrogens are neuroprotective (5). However, clinical trials of estrogen supplementation have failed. In fact, the Women's Health Initiative (WHI) and Women's Estrogen for Stroke Trial (WEST) trials showed increased mortality in elderly women supplemented with estrogen (6, 7), although there were several issues with the trial design including enrollment of older women many years past menopause (8).

P450 aromatase is the enzyme that actively converts testosterone to estradiol in the embryonic brain. During prenatal development, aromatization of testosterone to estradiol in neural tissue leads to sexual differentiation/ defeminization of male brain (9, 10). On the other hand, the female brain develops in the absence of estradiol as it is bound to α-fetoprotein, a plasma protein in the periphery (10). Interestingly, increased aromatase expression is seen in ischemic penumbra in animals (11). Administration of aromatase inhibitors or deletion of aromatase increased ischemic damage in experimental stroke models beyond what was seen in ovariectimized mice, suggesting that endogenous extragonadal estradiol production is important in females for neuroprotection (12). However, there are limited studies examining sex steroid levels in humans after ischemic stroke. The aim of this study was to assess the post stroke sex steroid milieu in men and women. Previous studies have focused on either estradiol or testosterone levels in either men or women after stroke. However, since there may be a complex dynamics of estradiol, aromatase and testosterone level after stroke, we assessed the levels of these hormones simultaneously in both men and women.

Methods

This study was conducted at Hartford Hospital, CT, a regional tertiary care facility with a Joint Commission certification as a comprehensive stroke center. Serum from patients presenting with focal neurological deficits who consent under an IRB-approved protocol to participate in a biobank study was collected within 24 hours from symptom onset. Serum samples from 102 patients (61 men and 41 women) were used for this study. Serum from patients was collected into heparinized tubes and stored at -80 °C until analysis. A blinded investigator performed serum Enzyme-linked immunoassay (ELISA) using kits for testosterone (Calbiotech, Spring Valley, CA, USA), 17β-estradiol (BQ, San Diego, CA, USA), and P450 aromatase (Cloud-Clone Corp, Houston, TX, USA), following the manufacturer's protocol.

Patients were divided into ischemic stroke and control groups. Stroke was defined as an acute-onset focal neurological deficit with confirmation by radiographic imaging (CT or MRI). Patients who presented with focal neurological deficits with subsequent resolution of symptoms and no evidence of ischemia on CT/MRI were included in the control group (most were patients with a diagnosis of transient ischemic attack, seizures, complex migraines, or hypertensive encephalopathy). Exclusion criteria were age < 56 years, hemorrhagic stroke, any malignancy, autoimmune disease, immunosuppressive, hormonal or steroid treatment including use of oral contraceptives. Demographic data including past medical history was collected from stroke patient database. Outcome measures were National Institutes of Health Stroke Scale (NIHSS; range, 0 to 42, with higher scores indicating a greater deficit) on admission and modified Rankin score (mRS, range of 0 [no symptoms] to 6 [death]). Premorbid (baseline mRS) and mRS at the time of hospital discharge were collected by patient chart review. Change in mRS (discharge-premorbid) was used for analysis.

SAS and graphpad PRISM software was used for data analysis. Two-way ANOVA was used to compare hormone levels between stroke/control and women/men groups. Post-hoc subgroup comparisons within women and men were provided and adjusted for multiple testing by Sidak method. Spearman correlation

coefficient was calculated for hormone levels with NIHSS at the time of admission and change in mRS (discharge- premorbid mRS). We performed univariate analysis for age, NIHSS, smoking, diabetes, history of cancer on each hormone. Variables with a p value less than 0.1 in the univariate analyses were included in a multivariate linear regression to control for confounders. The criterion of statistical significance in the final model was set at 0.05.

Results

Baseline characteristics of our study population are shown in Tables 1 and 2. There was no statistically significant difference in comorbidities including hypertension, hyperlipidemia, diabetes mellitus type 2 and atrial fibrillation in stroke vs. controls. Table 2 shows the stroke cohort demographics and outcomes. Women were older (79.2 ± 10.4 years) at the time of stroke as compared to men (72.8 ± 10 years), as described previously (13). Women had higher median discharge NIHSS (Men 2 ± 3 vs. Women 3 ± 9, p = 0.032) and change in mRS, (calculated as discharge- premorbid mRS), men 2 ± 3 vs. women 4 ± 2, p = 0.009, indicating worse outcomes, which has been seen in previous studies (14).

Table 1
Patient Demographics for stroke, n = 75 vs. controls, n = 27: There was no significant difference in premorbid conditions including hypertension, hyperlipidemia, Type 2 diabetes mellitus, atrial fibrillation or smoking in stroke versus controls.

Baseline characteristics	Stroke	Controls	P value
Hypertension, n (%)	57 (76.0%)	20 (74.1%)	0.842
Hyperlipidemia, n (%)	46 (61.3%)	14 (51.9%)	0.391
Heart disease, n (%)	29 (38.7%)	8 (29.6%)	0.402
Type 2 Diabetes Mellitus, n (%)	23 (30.7%)	7 (25.9%)	0.643
Atrial Fibrillation, n (%)	23 (30.7%)	5 (18.5%)	0.316
Smoking, n (%)	14 (18.7%)	2 (7.4%)	0.225

Table 2

Patient Demographics for men and women with stroke: Women were significantly older at the time of stroke as compared to men, p = 0.016. There was no significant difference in premorbid conditions including hypertension, hyperlipidemia, Type 2 diabetes mellitus, atrial fibrillation or smoking in men vs. women with stroke. Men had significantly higher heart disease history as compared to women, p = 0.036 in our patient population. Women had significantly worse outcomes as compared to men, in terms of discharge NIHSS, p = 0.032 and change in mRS, p = 0.009.

Stroke category and Outcomes	Men (n = 43)	Women(n = 32)	P value
Age (Mean ± SD)	72.8 ± 10	79.2 ± 10.4	0.016
Hypertension, n (%)	33 (76.7%)	24 (75.0%)	0.861
Hyperlipidemia, n (%)	29 (67.4%)	17 (53.1%)	0.208
Heart disease, n (%)	21 (48.8%)	8 (25.0%)	0.036
Type 2 Diabetes Mellitus, n (%)	12 (27.9%)	11 (34.4%)	0.548
Atrial Fibrillation, n (%)	11 (25.6%)	12 (37.5%)	0.268
Smoking, n (%)	11 (25.6%)	3 (9.4%)	0.132
NIHSS on admission, median (IQR)	7(12)	13(18)	0.144
NIHSS at discharge, median (IQR)	2(3)	3(9)	0.032
Cardio embolic, n (%)	21 (48.8%)	22 (68.8%)	0.085
Large Artery Atherosclerosis, n (%)	7 (16.3%)	4 (12.5%)	0.749
Small Vessel Disease, n (%)	6 (14.0%)	3 (9.4%)	0.724
Undetermined Etiology, n (%)	9 (20.9%)	3 (9.4%)	0.177
Baseline modified Rankin Score, median (IQR)	0(1)	0(3)	0.084
Change in modified Rankin Score, median (IQR) [discharge mRS- premorbid mRS]	2(3)	4(2)	0.009
Mortality	5 (11.63%)	5 (15.63%)	0.736

We first compared levels of sex hormones in stroke patients with controls. There was no significant change in estradiol levels after stroke in men (p = 0.86) or women (p = 0.10), (Fig. 1).

In men, testosterone significantly decreased after stroke as compared with controls (1.83 ± 0.12 vs 2.86 ± 0.65, p = 0.01). No change in testosterone levels was seen in women after stroke (p = 0.71), Fig. 2. There was a significant main effect of sex ($F(1, 98) = 26.27$, $p < 0.0001$) and a sex by stroke interaction ($F(1, 98) = 5.24$, $p = 0.02$).

Aromatase levels were significantly higher in women after stroke as compared with controls (2.27 ± 0.22 vs 0.97 ± 0.22, p = 0.002), but not in men (p = 0.84), Fig. 3. For aromatase, there was a significant main effect of stroke ($F(1, 98) = 9.09$, $p < 0.003$) and sex by stroke interaction ($F(1, 98) = 5.72$, $p < 0.01$).

There was a positive correlation between estradiol levels and NIHSS at the time of admission, r = 0.62, p = 0.0001. Similarly, estradiol levels positively correlated with change in mRS score, r = 0.38, p = 0.02 in women. This correlation was also seen in men, NIHSS, r = 0.34, p = 0.02 and change in mRS, r = 0.3, p = 0.04, suggesting increased levels of estradiol correlated with worse outcomes (higher mRS or NIHSS) regardless of the sex. Testosterone levels had a positive correlation with NIHSS in women, r = 0.53, p = 0.001. There was no significant correlation of testosterone level with NIHSS in men or with change in mRS score in men or women, $p > 0.05$.

No significant correlation was seen between aromatase and NIHSS (Men, r=-0.09, p = 0.5, Women = 0.2, p = 0.2,) or change in mRS score (Women r=-0.07, p = 0.6, Men, r=-0.2, p = 0.1). We used a multivariate regression model and controlled for factors like diabetes mellitus, hypertension, hyperlipidemia, age and NIHSS at time of admission, and serum levels of estradiol were still independently associated with mRS.

Discussion

Our study shows that aromatase levels are significantly higher in post-menopausal women after acute ischemic stroke when measured within 24 hours from symptom onset. Testosterone levels significantly decrease in men at this time point. No significant change in estradiol levels was seen within 24 hours post ischemic stroke in either sex, although there was a trend for higher estradiol levels in women with stroke. This may be due to lower number of patient recruitment in this study. Interestingly, higher levels of estradiol correlated with worse outcomes, higher NIHSS at presentation and mRS, regardless of sex. In intrauterine life, sexual differentiation of the brain occurs by aromatization of androgens (9). Our study suggests that this pathway may become active in the event of brain injury, as evidenced by the increased level of serum aromatase seen after stroke in women. This has been previously reported in preclinical literature. It was shown that a neurotoxic insult to the brain induced by systemic administration of kainic acid led to increased aromatase expression in astrocytes (15). In spontaneously hypertensive rats, aromatase was elevated at 24 h and at 8 days after focal cerebral ischemia in the penumbra, specifically in the astrocytic processes (11). The expression of aromatase also appears to be sex specific. Aromatase activity and expression was found to be greater in female than in male primary cultured cortical astrocytes. Arimidex, an aromatase inhibitor, abolished sex differences in astrocytic cell death induced by oxygen glucose deprivation (OGD), while addition of estradiol protected both sexes. This implies that local estradiol production by aromatase is protective (16). Studies in aromatase knock out mice (ArKO) further clarified the role of aromatase. Female ArKO mice subjected to reversible middle cerebral artery occlusion had larger infarcts compared to wild type mice. Similarly, wild type female mice treated chronically with the aromatase inhibitor, fadrozole, had more ischemic damage when compared with ovariectomized females, suggesting that extragonadal estradiol is important for neuroprotection (12). The role of aromatase in cardiovascular disease has also been highlighted by studies in breast cancer

patients who were administered aromatase inhibitors (17). A recent study demonstrated increased risks of heart failure and cardiovascular mortality in the patients taking aromatase inhibitors as compared with patients taking tamoxifen (18). Administration of the specific aromatase inhibitor, fadrozole, in male rats enhanced the neurodegenerative effects of kainic acid and this was reversed by administration of estradiol, confirming that neuroprotective effects of aromatase are mediated by estradiol (19).

The role of estradiol in stroke has long been debated. Boys have higher stroke incidence compared to girls. In fact, it has been seen that for each 1 nmol/liter increase in testosterone in young boys, there was a 1.3 fold increase in risk of stroke (20). This epidemiology reverses with advanced age, and elderly women have higher stroke incidence and worse outcomes, which is often attributed to the loss of estrogen at menopause. Preclinical studies in stroke models have shown a robust neuroprotective effect of estrogen (5), but this was not recapitulated in early clinical trials. Both the WHI and WEST trials of estrogen supplementation led to increased mortality in post-menopausal women (6, 7), although issues with trial design, including the dose, type and timing of estrogen supplementation were raised. The Kronos Early Estrogen Prevention Study (KEEPS) study found that neither oral nor transdermal estrogens affected the progression of atherosclerosis (measured as CIMT, carotid-artery intima–media thickness), when given to recently postmenopausal women (21). On the other hand, Early versus Late Intervention Trial with Estradiol (ELITE) found that oral estradiol therapy (when initiated within 6 years of menopause) was associated with less progression of subclinical atherosclerosis (measured as CIMT) (22). It appears that the type, timing of therapy and the dose response effect of estradiol on the vasculature may be important in determining the benefits of exogenous estrogen for stroke prevention.

In this study, we found a significant positive correlation between estradiol levels and the NIHSS and mRS. Higher endogenous estradiol levels were associated with higher NIHSS or mRS, suggestive of worse outcomes. This has been shown in previous studies in elderly women (23–25). We speculate that higher post stroke injury and deficits (as gauged by NIHSS) cause increased aromatase expression and that in turn increases estradiol levels in an attempt to protect the brain. However, this should be interpreted with caution, as causality cannot be determined with a correlation. Although there was a trend for increment after stroke in post-menopausal women, we did not see any significant change in estradiol levels after stroke. This may be due to a few reasons. It is possible that estradiol levels are elevated in the hyperacute phase after stroke or later than the 24 hour time period here, as we did not perform longitudinal analysis. Another possible explanation may be that the peripheral levels of estradiol in the serum are not an accurate representation of the levels in the brain. Moreover, a low patient sample size to study differences in estradiol levels was one of the limitations of this study. Future studies with hormone level assessments at multiple time points after stroke and increased sample size are needed.

We also found decreased testosterone levels in men after stroke. This has been reported previously in preclinical models of stroke (26) and also in men (27), which may be due to an acute stress response leading to lower testosterone levels. However, it is possible that decreasing androgens is a protective mechanism in men. The use of testosterone therapy has been associated with increased risk of adverse cardiovascular outcomes in some studies (28), while others have shown benefit of testosterone

replacement therapy, therefore making the role of testosterone in stroke and cardiovascular disease unclear (29). Our study did not find any correlation of testosterone levels with NIHSS or mRS but again, causality is difficult to establish at one time point after stroke, especially with small cohorts.

Perspectives And Significance:

In summary, our study demonstrated an increase in aromatase levels after stroke in post-menopausal women. This may be a protective mechanism by which estradiol is produced locally in the brain (30). We speculate that higher injury post stroke (as determined by higher NIHSS and mRS) accelerates the aromatization process, at least acutely. This is the first study to measure the milieu of sex steroids after stroke in both men and women. This study may add some value in understanding the roles of sex hormones and their contribution to sexual dimorphism in ischemic stroke.

Declarations

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Authors' contributions

PF performed the hormone ELISA. MROR, SC, were involved in patient sample collection, processing. LZ did statistical analysis. IS extracted demographics from redcap. BM and LDM designed the study, interpreted the data and wrote the manuscript. All authors read and approved the final manuscript

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Ethics approval and consent to participate

This study was approved by IRB at Hartford Hospital, IRB number: HHC-2014-0159

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests

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Figures

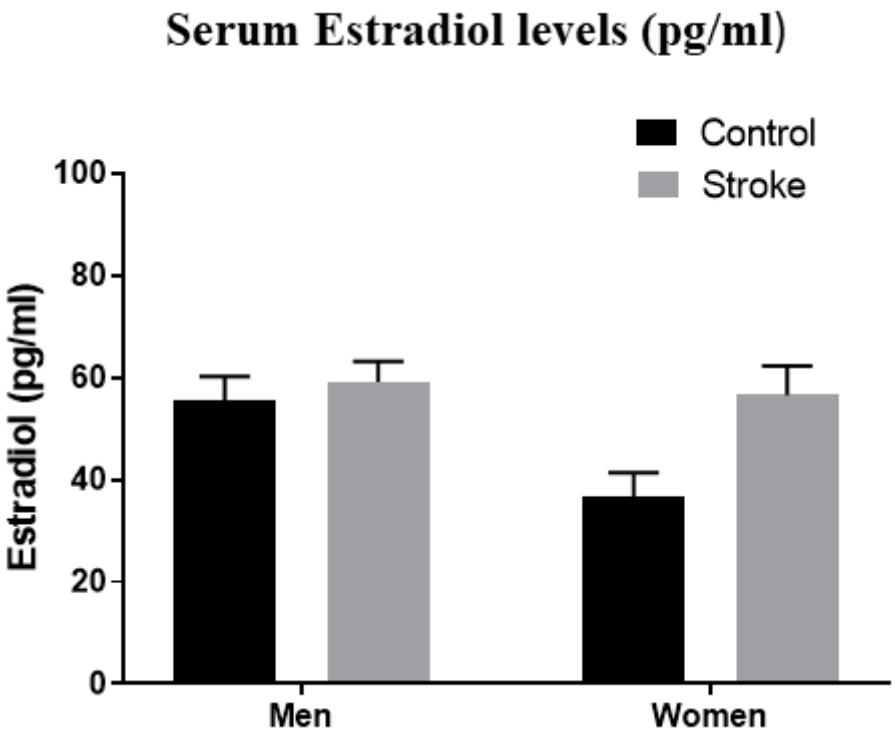

Figure 1

Serum Estradiol levels in pg/ml. There was no significant change in estradiol levels 24 hours post stroke in men or women. In women, the estradiol levels trended up after stroke but did not reach significance.

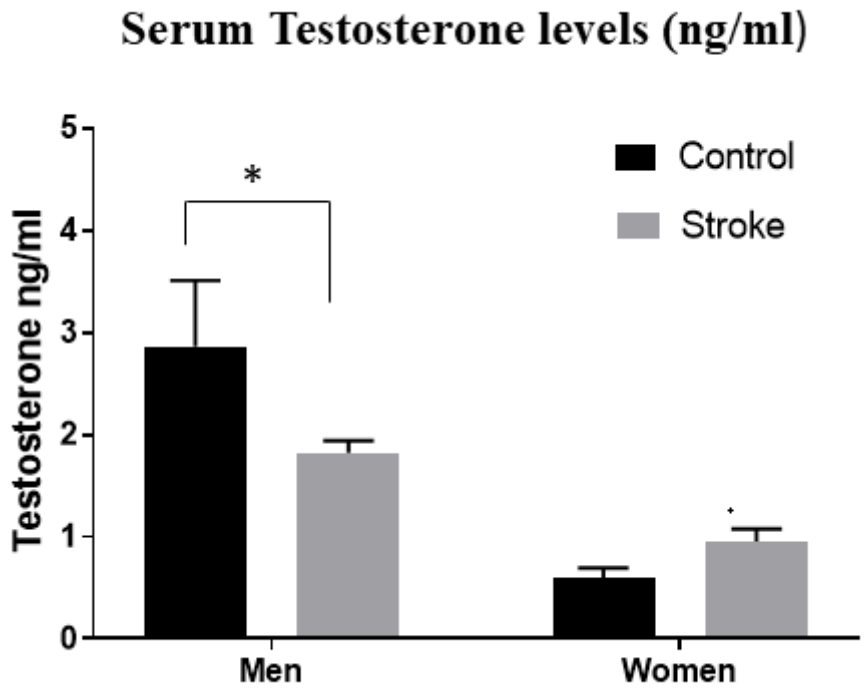

Figure 2

Serum Testosterone levels in ng/ml. The serum testosterone levels significantly decreased in men 24 hours post stroke. The serum testosterone levels are significantly higher in men as compared to women. * p=0.01

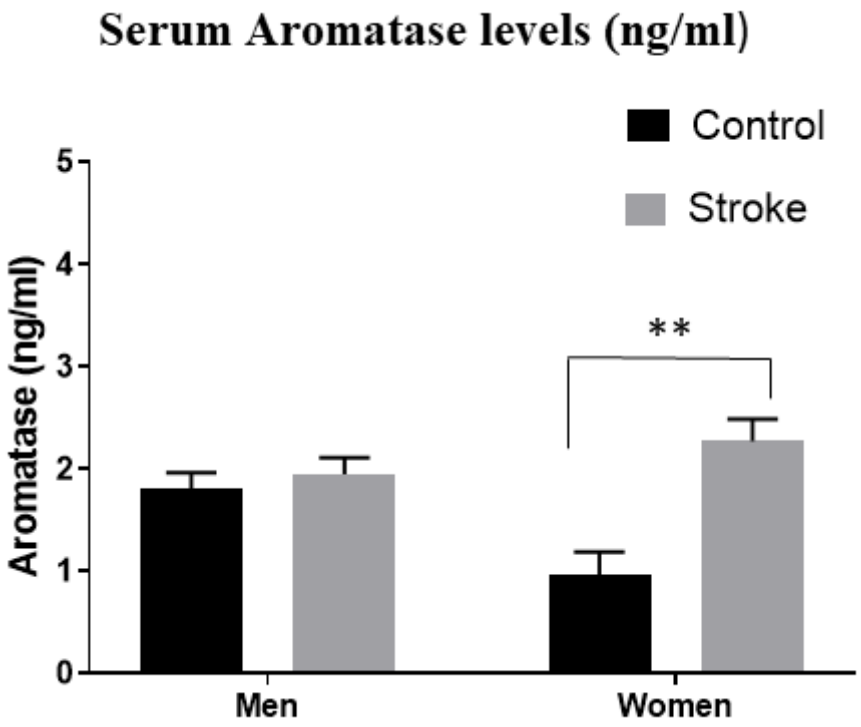

Figure 3

Serum Aromatase levels in ng/ml. The serum aromatase levels significantly increased in women after stroke. No such change was seen in men. **p=0.002