

Estrogen and cerebral small vessel disease

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To the Editor: Cerebral small vessel disease (CSVD) refers to a wide spectrum of pathological processes, which affects the small arteries, arterioles, venous, and capillaries in the brain. This disease causes cognitive, psychological, and physical disabilities and is responsible for up to 45% of vascular dementia in the elderly. With the prolongation of human life expectancy, the medical expense and family burden of cognitive disorders in the elderly increasingly aggravate, and the early identification and effective treatment of CSVD are receiving increasing attention.

Other studies suggest that the incidence of cerebral large vessel disease and histological damage is less in female patients.^[1] As estrogen replacement therapy (ERT) has been shown to provide neuroprotective effects in stroke cases, those of the female gender that produce estrogen may exhibit reduced incidence and severity of cerebrovascular diseases. However, few studies had evaluated how CSVD affects those of different genders, which is of particular concern as the clinical efficacy of estrogen in patients with CSVD remains unclear. Estrogen-based postmenopausal hormone therapy is effective for alleviating menopausal symptoms. Here, we aim to provide clinicians and researchers with an overview of the relationship between estrogen and CSVD to benefit the development of effective therapeutic interventions in CSVD.

Estrogen not only acts on the reproductive axis in the central nervous system but also regulates the function of the brain, an important target organ for estrogen (estrogen receptor α and β), in various ways. Menopause, a period where estrogen production is ceased, affects emotion, cognitive processes, and can cause changes to cerebral hemodynamic and cortical structures. Although the Melbourne Women's Midlife Health Project (MWMHP) demonstrates that verbal memory is not affected during the menopausal transition or in the years immediately after natural menopause,^[2] the mainstream view believes that

menopause is associated with cognitive decline and that perimenopausal ERT can improve cognitive functions to varying degrees.

Human epidemiological evidence and experimental animal studies provide evidence that ERT protects against cerebrovascular diseases, such as dementia and stroke,^[3] and that estrogen benefits cerebral vasculature by reducing vascular reactivity and increasing blood flow through endothelial NOS- and cyclooxygenase (COX)-dependent mechanisms. There are also studies suggesting that estrogen protects against Alzheimer's disease (AD) in a dose- and time-dependent manner and that prolonged ERT lowers the risk for AD.^[4]

Few have investigated the effects of estrogen on cerebral small vessels. Thurston *et al*^[5] first described the correlation between menopause and women's midlife health. It was later suggested that the effects of estrogen on cerebrovascular function may be changeable and that there are age-dependent shifts from beneficial to detrimental effects on the small cerebral arteries.^[6] The possible mechanisms for this are that age alters the specific COX isoform leading to constrictor/dilator prostanoid production, with this effect potentially enhanced by estrogen. In addition, estrogen can enhance vasopressin-stimulated prostacyclin and thromboxane production in both middle- and old-age, although, in advanced age, lack of estrogen may decrease vasopressin-stimulated prostacyclin production, and increased thromboxane production can only be obtained with estrogen replacement.^[6] Later studies revealed that menopause, and therefore, lack of estrogen, was strongly associated with the development of leukoarteriosclerosis.^[7] In addition, early menopause appears to increase the risk of silent brain infarction in the elderly population. Therefore, the female hormone may be beneficial in lowering the risk of CSVD or delaying the progression of CSVD.

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Moreover, estrogen is an essential component in the modulation of the entire bioenergetic system, including glucose transport, glucose metabolism, mitochondrial (Mito) respiration, and ATP production, as well as the lipid metabolism in the white brain matter. ERT has been shown to alter the regional cerebral metabolism and brain activation patterns in post-menopausal women within specific brain regions, such as the inferior frontal cortex, the temporal cortex, the inferior parietal lobule, and the right superior frontal gyrus,^[8] a change which may be related to alteration of the small blood vessels.

However, two large-scale randomized controlled trial (RCT) studies have failed to confirm the protective effect of estrogen on brain structures. The cross-sectional Women's Health Initiative Memory Study Magnetic Resonance Imaging Study (WHIMS-MRI) investigated whether menopausal hormone therapy (mHT) affects the hippocampal and prefrontal cortex. The Kronos Early Estrogen Prevention Study ancillary MRI study (KEEPS-MRI) included 95 women aged 42 to 59 years who were 5 to 36 months past menopause.^[9] These women were randomly assigned to either conjugated equine estrogens, 17 β -estradiol transcutaneous therapy, or a placebo treatment. This study found that white matter hyperintensities (WMH) volume in the oral estrogen group increased faster than the control treatment and the whole brain volume declined during the 48 months of the mHT phase. This trend was reversed after mHT ended, such that the decline in whole brain volume was less than in the control group and, by 84 months post-treatment, there was no difference in whole-brain volumes decline between oral estrogen and control groups. On the other hand, there was no difference in WMH volume increase or in the volume of dorsolateral prefrontal lobe decline between the transcutaneous estrogen group and the control group. Furthermore, deposition of the amyloid- β protein was significantly reduced in the transcutaneous estrogen group, especially in APOE ϵ 4 carriers.^[10]

However, these studies have some intrinsic limitations. For example, the average age of patients in the WHIMS-MRI study when they began mHT was 63 years old, which was beyond the "optimal time-window". The purpose of the KEEPS was to assess whether early initiation of hormone therapy could reduce subclinical atherosclerosis in healthy women. However, MRIs were not routinely examined nor were they grouped according to the brain image and genetic background of the patients. As a result, there were more APOE ϵ 4 carriers in the transdermal estrogen group (48% vs. 16%, $P < 0.03$), confounding the result that the volume of WMH was significantly higher in this population than that in the control group. Additionally, the medication courses were short in all the above RCTs; however, as the retrospective study by Cache County found that MHT for more than 10 years improved cognitive function. In addition, the synthetic progesterone used in the Women's Health Initiative (WHI)-Memory Study has been discouraged in later studies because of an increase in the incidence of breast cancer. Therefore, several variables affect the beneficial effects of ERT for the emotional and cognitive processes, such as genetic factors, the time between estrogen loss and replacement, extent and

types of pathology, and other environmental and health factors.

At present, the positive effects of estrogen on neuro, cerebrovascular, and brain networks have been extensively studied and explored. Studies from animal models suggest that estrogen facilitates neuroprotection by regulating the expression of the anti-apoptotic gene (bcl-2) in the ischemic penumbra. Estrogen also induces an increase in the Mito calcium load by collapsing the Mito membrane potential and thereby preventing Mito Ca^{2+} transport and by reducing the translocation of cytochrome C, caspase-3 (a key apoptotic protein) activation, and DNA fragmentation [Figure 1]. All these mechanisms suggest that estrogen acts in an anti-apoptotic manner in cerebral ischemia. Estrogen additionally possesses potent antioxidative properties that enhance the bioavailability of NO. Estrogen can regulate glucose metabolism and enhance Mito function, as well as incite an inflammatory response by activating microglia cells. These pathways may result in a beneficial therapeutic opportunity for post-menopausal symptoms or CSVD. Moreover, our current knowledge suggests that estrogen is an important regulator of vasoconstriction by enhancing the action of COX-1- and COX-2-dependent prostanoid pathways in vasopressin reactivity-induced cerebrovascular vasoconstriction. Estrogen enhances the production and/or the sensitivity of cerebral arteries to vasodilatory factors, including NO and PGI₂, shifting the balance of prostanoid production toward greater production of vasodilator forms. There is substantial evidence that estrogen contributes to structural neuroplasticity and changes in the brain network in women, such as inducing neuroplasticity in the central nervous system by modulating dendritic spine and synapse density in the hippocampus, hypothalamus, amygdala, and nucleus accumbens, eventually leading to changes in white matter volume. The positive effects of estrogen include neurotrophic (for hippocampus) and neuroprotective effects, balancing neurotransmitters, regulating vasoconstriction, and improving brain network. Each component in the vasculo-glio-neuronal unit, such as endothelial cells, pericytes, astrocytes, oligodendrocytes, neurons, and the extracellular matrix, plays a key role in all of these complex processes and each is a potential therapeutic target. At present, the treatment of CSVD is still very limited, with most trials still in the research stage. Future CSVD clinical trials require a more definite diagnosis, which depends on further exploration of the CSVD mechanism and requires more large-sample clinical trials. In addition, a more complete multi-dimensional CSVD prognostic evaluation system needs to be established that considers the recurrence of stroke and changes of cognitive function, and abnormal gait and blood vessel function and structure, among other factors.

This review provides a brief overview of what we currently know regarding the correlation between estrogen, menopause, and hormone replacement therapy and CSVD, and relevant cognitive dysfunctions. The diversity of findings among experimental and clinical results could be due to several factors:

1. *Population age*: Most of the research population is approximately 60 years old, which is quite different

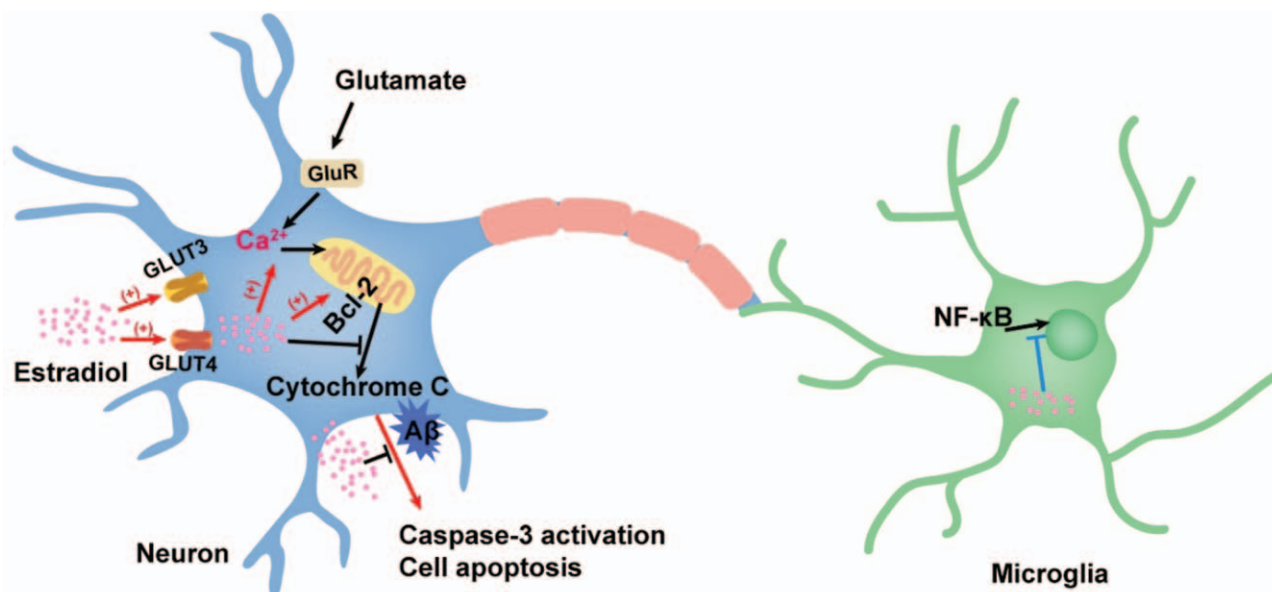


Figure 1: Neuroprotective effects of estrogen. Estrogen promotes the transfer of Ca^{2+} to Mito and maintaining the normal level of Ca^{2+} . It also inhibits the transfer of cytochrome C from Mito to cytoplasm induced by ischemia, increases the expression of Bcl-2, and increases the tolerance of Mito to Ca^{2+} . Estrogen helps cells resist apoptosis, inhibits the activation of caspase-3 and apoptosis induced by $\text{A}\beta$, and increases the expression of GluT3 and GluT4, which are beneficial to neuronal energy metabolism. Finally, estrogen can inhibit the transfer of NF- κ B into the nucleus of microglia induced by $\text{A}\beta$ and the production of inflammatory factors and inflammatory response. GluR: Glutamate receptors; Mito: Mitochondrial; Bcl-2: B-cell lymphoma 2; GluT3: Glucose transporter 3; GluT4: Glucose transporter 4; NF- κ B: Nuclear factor kappa light chain enhancer of activated B cells.

from the time of menopause. After the administration of exogenous estrogen through ERT, the hormone levels in the body remain low and are unable to play their protective effect.

2. *Administration of estrogen:* There is no consistent protocol for hormone therapy at present and, as such, administration route and dosage differ across treatments, potentially confounding the treatments' effectiveness.
3. *The cause of menopause:* While most women undergo menopause naturally, there are a small number of women who experience surgical menopause brought on by certain diseases. As these individuals are not excluded from these studies, this may have a certain impact on the research results.

Fortunately, our correspondence suggests that ERT is a promising avenue for preventing the development and progression of CSVD.

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Conflicts of interest

None.

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