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Featured Article

Poor cerebrovascular function is an early marker of cognitive decline in healthy postmenopausal women

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Abstract

Introduction: Impairment of cerebrovascular function becomes evident after menopause. No study has yet explored relationships between deficits in cerebrovascular function, cognitive performance, and mood in postmenopausal women.

Method: Cerebrovascular function was assessed in 80 healthy postmenopausal women by monitoring blood flow velocity (BFV) in the middle and posterior cerebral arteries using transcranial Doppler ultrasound at rest, following a hypercapnic challenge, and during performance of a cognitive test battery; the latter assessed domains of memory and executive functions. Various measures of mood (i.e., Profile of Mood States and Center for Epidemiological Studies Depression Scale) were also assessed.

Results: Cerebral artery elasticity and BFV responsiveness to cognitive tests (neurovascular coupling) correlated with cognitive performance but not with depressive symptoms or mood states. Mood deficits were related to poor cognitive performance.

Conclusion: These results highlight the importance of adequate cerebral perfusion for optimized cognitive function in healthy postmenopausal women. Preventative strategies to attenuate accelerated cognitive decline should also consider restoring cerebrovascular function.

Keywords: Menopause; Cerebrovascular function; Pulsatility index; Depression; Mood; Cognition

1. Introduction

Complaints of decreased mental clarity and mood swings are common during the menopausal transition [1]. Although these symptoms may be situational at this time of life, for example, health issues, stress of caring for aging parents, or "empty nest syndrome", we cannot ignore that the prevalence of Alzheimer's disease, most common form of dementia, is higher in elderly women than men [2]. Although the biological basis for this heightened risk in women remains to be established, basic and clinical evidence indicate that the rapid decline in estrogen at onset of menopause has adverse consequences, particularly for the brain [3,4]. Higher endogenous estrogen has been shown to be associated with better cognitive function in postmenopausal midlife women (~60 years old), particularly for semantic and verbal memory [5].

From a vascular perspective, estrogen can also bind to estrogen receptors on the endothelium of cerebral arteries, causing vasodilatation and thereby increasing perfusion of brain regions in response to need [6]. Hence, estrogen deficiency after menopause rather than aging *per se* is thought to contribute to the large reduction in cerebral vasodilator responsiveness (CVR) in postmenopausal women compared with premenopausal women and elderly men [7]. Evidence of associations between impaired CVR and cerebral arterial stiffness and severity of dementia is well established [8,9]. Impaired CVR is evident in those with major depression, suggesting that optimal cerebrovascular function may be critical for optimal brain function independent of sex

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hormones [10]. With the increased life expectancy in the aging population, extension of the postmenopausal period may result in reduced quality of life in latter years, due to prolonged cerebral hypoperfusion, thereby adversely affecting cognitive abilities and mood [11].

Recovery from depression is possible by improving cerebral perfusion [12]. However, no studies have yet explored relationships between CVR to physiological or cognitive demands and either mood states or cognitive performance in postmenopausal women. Understanding if such relationships exist can help tailor early interventions to attenuate these deficiencies so as to assist older women achieve quality of life.

We are currently investigating whether a 14-week dietary supplementation with a phytoestrogen, viz., resveratrol, can improve cerebral perfusion and thereby enhance cognitive performance and mood in postmenopausal women who are not taking HRT (Clinical Trial Registration no: ANZCTR12615000291583). Assessments of cerebrovascular function, cognitive performance in specific cognitive domains implicated in mood states, and depressive symptoms in postmenopausal women were obtained at baseline to examine the relationships between cerebrovascular function, cognitive function, and mood in this cohort.

2. Method

All potential volunteers gave written informed consent before attending the Clinical Nutrition Research Centre, University of Newcastle, for the assessments of outcomes at baseline (see [13] for details of study protocol and description of the assessments). Arriving at the center after a 1-hour fast, they undertook the Australian version of the modified Mini-Mental State Examination (3MS) to exclude those with suspected dementia (score of <78/100). Their 3MS scores were also used as a measure of global cognition as administration of this assessment does not require high level of training and frequently used in clinical settings [14]. Menopausal symptoms were quantified using the Menopausal Rating Scale [15] and used as a covariate in this exploratory analysis as they have been shown to affect mood and cognitive function [16]. The order of assessments was conducted as follows with at least a 2-minute interval between each test.

2.1. Basal cerebral hemodynamics

Transcranial Doppler ultrasound (Doppler-Box X, Singen, Germany) is a noninvasive technique to assess blood flow velocity (BFV) in the brain. Using an adjustable headpiece, the middle and posterior cerebral arteries (MCA and PCA, respectively) on both the left and right sides were isolated using the transtemporal window as this provides the least interference during insonation [17]. A 30-s continuous recording of basal BFV (maximum, mean, minimum) in the MCA and the PCA was obtained before hypercapnic provocation and before the start of each cognitive test. The Gosling pulsatility index (PI) and Pourcelot resistive index (RI) reflecting intracranial vessel stiffness and the basal mean BFV were determined by averaging the last 10 s of the 30-s basal recording. PI and RI are calculated as follows: PI = (maximum BFV − minimum BFV)/mean BFV; RI = (maximum BFV − minimum BFV)/maximum BFV. Although PI and RI are linearly correlated and reflect intracranial vascular resistance [18], RI is arguably a better reflection of resistance as it combines vascular compliance in the arterial waveform, which is modifiable by blood pressure (BP), age, and medication use [19]. The PI/mean BFV ratio (multiplied by 100 for ease of reporting) was also determined; it is a recognized index of intracranial vascular disease [20].

2.2. Cerebrovascular responsiveness

Increases in BFV in the cerebral vessels in response to physiological (i.e., hypercapnia) or cognitive stimuli are indirect measures of cerebrovascular responsiveness (CVR); they reflect the extent of vasodilator capacity in downstream vascular beds [21]. To assess CVR to hypercapnia, volunteers inhaled a carbogen gas mixture (5% CO_2, 95% O_2) through a two-way nonrebreathing mouthpiece for 180 seconds, which elicited an acute increase in BFV. The ultrasound probes were kept in position throughout the cognitive assessments to determine CVR to cognitive stimuli in the MCA during each cognitive task. CVR to hypercapnia or cognitive stimuli is calculated as the peak increase in mean BFV, expressed as a percentage of the mean BFV recorded under basal conditions.

2.3. Cognitive performance

In addition to the 3MS, we also used a neuropsychological test battery that is more sensitive to capture deficits in cognitive domains known to be negatively affected in postmenopausal women, namely semantic [22], verbal [1], and visual spatial working memory [23], as well as executive function, shown to decline with age irrespective of gender [24]. The battery consisted of the Rey Auditory Verbal Learning Test [25], the Cambridge Semantic Memory Battery [26], the Double Span [27], and the Trail Making Task [28]. Performances on each test were converted to Z scores and were summated to determine their overall cognitive performance.

2.4. Assessment of mood

Participants' mood states were assessed using two different indices, the Profile of Mood States version 2, and the Center for Epidemiological Studies Depression Scale. The Profile of Mood States questionnaire assessed how the participant was feeling over the last week (including the day of the visit) through 65 adjectives that the participant rated on a 5-point Likert scale (1 being "not at all" and 5