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Research Article

Postmenopausal Cognitive Function and Steroid Hormone Levels

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Abstract

Introduction: Most studies on the impact of sex hormones on the postmenopausal brain have focused on the lack of estrogen, with conflicting evidence. The influence of androgens on cognitive function is not well understood. This study aimed to assess the association between steroid hormones and cognitive function in postmenopausal women.

Methods: A total of 147 postmenopausal women, aged 50-86 years, were enrolled in a cross-sectional study. Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA) test and serum levels of estradiol, Dehydroepiandrosterone (DHEA), testosterone and androstenedione were quantified by gas chromatography and tandem mass spectrometry (GC-MS/MS). The association between cognitive domains and hormone levels was assessed calculating nonparametric partial correlation coefficients, controlling for confounding variables.

Results: Negative correlations were found between estradiol and executive function (rho=-0.190, p=0.024), visuospatial abilities (rho=-0.333, p<0.001) and orientation to time and place (rho=-0.196, p=0.020). No statistically significant associations were found between DHEA, testosterone and androstenedione and cognitive domains.

Conclusion: This is the first study to correlate steroid hormones and cognitive function using GC-MS/MS, a highly sensitive bioanalytical assay. The negative correlation found between estradiol and some aspects of cognitive function suggests that in older women high levels of estrogen may be deleterious to cognition.

Keywords: Androgens; Cognitive function; Estradiol; Menopause

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Introduction

Approximately 50 million people worldwide live with dementia, with Alzheimer's disease (AD) being the most frequent cause [1]. Women are more impacted by AD than men, presenting significantly greater risk of developing AD and a greater cognitive deterioration than men at the same disease stage [2]. Women live longer than men and the average life expectancy is increasing, but despite this, there seem to be sex differences in the brain that depend on multiple social and biological factors. An age-related loss of sex steroid hormones has been associated with an increased risk of cognitive decline [3].

The majority of the studies on the impact of sex hormones on the postmenopausal brain have focused on the lack of estrogen. Estrogen is known to have an essential role in the brain: promotes neurotrophin synthesis, modulates cholinergic and dopaminergic neurotransmitter systems and protects the brain against stress and inflammation [4]. A prolonged reproductive period (indicative of a greater lifetime exposure to female sex hormones) may be associated with higher cognitive performance and delayed cognitive decline [5-8]. Nulliparity was also associated to decreased cognitive decline [9]. Bilateral oophorectomy resulting in surgical menopause, with a steep decline in estrogen production, was inversely associated with cognitive performance [10-12]. Postmenopausal women with higher remaining circulating estradiol levels have better global cognitive function [13,14], episodic memory [15,16], and better semantic memory performance [17], but other studies have revealed contradictory results [18-20].

High levels of estrogen have been associated with enhanced verbal fluency [3,4,13], but reports are not consistent [21]. The literature also reports conflicting evidence regarding the effect of Hormone Therapy (HRT): observational studies have suggested some beneficial effects of HRT on cognition, although some researchers have identified cognitive decline or an increased risk of dementia associated with HRT; interventional studies indicated detrimental effects of HRT on older women, leading to cognitive decline and a greater risk of dementia [22]. Likewise, the influence of androgens on postmenopausal cognitive function is not well understood and the scientific evidence is contradictory. Although there has been an interest in conducting studies on the effects of androgen therapy on cognitive function, there are very few studies demonstrating an association of endogenous androgen levels with cognitive function. Research studies have shown a positive association between verbal learning and memory and physiological concentrations of testosterone administered to postmenopausal women exogenously [22,23]. However, it was also reported that higher endogenous testosterone levels were associated to lower scores of cognitive function [24]. In addition, lower endogenous testosterone levels have been associated to an improvement in verbal episodic memory [17], or showed no association [20].

The aim of this study was to assess the association between steroid hormone levels and cognitive function in postmenopausal women, using a highly sensitive bioanalytical assay for steroid measurement.

Methods

From January 1, 2017 to June 30, 2019, a total of 147 postmenopausal women were recruited at a hospital Gynecology consultation and enrolled in a cross-sectional study, approved by the Ethics Committee of Hospital Amato Lusitano, a Portuguese tertiary hospital. All women had undergone natural menopause and postmenopausal status was based on 12 months of amenorrhea and serum follicle stimulating hormone levels greater than 30 mUI/mL. The exclusion criteria were: current or past users of systemic HRT or corticosteroid treatment, alcoholism, narcotic addiction and chronic hepatic or renal diseases.

Cognitive function was assessed using the 7.1 original version of the Montreal Cognitive Assessment (MoCA) test created in Canada [25] and validated for the Portuguese population [26]. The MoCA test assesses six domains: memory, visuospatial capacity, executive function, attention, language and orientation to time and space. The MoCA test was administered by only one clinician within the scope of the consultation, who also recorded personal and family anamnestic data, and referral to Neurology was prompted when the final score was less than 18 points (moderate or severe cognitive impairment). One blood sample was obtained from each woman between 8 and 10 am. Plasma samples were stored at -80°C and protected from light until analysis. The studied compounds, Dehydroepiandrosterone (DHEA), androstenedione, 17β-estradiol (E2) and testosterone were quantified by solid phase extraction (SPE) and gas chromatography and tandem mass spectrometry (GC-MS/MS). Briefly, 1mL of plasma was diluted with 1 mL of Phosphate Buffer Saline (PBS) (pH=7) and spiked with 100 µL of internal standard (DHEA-d6). SPE cartridges (Oasis® HLB 3cc, Waters, USA) were conditioned with 2 mL of methanol and 2 mL of 0.1 % acetic acid. After the sample passed through the cartridge, a washing step was performed with 2mL of deionized water. Following this step, the columns were dried under full vacuum for 30 min. Subsequently, the analytes of interest were eluted with 2 mL methanol. The resulting extracts were evaporated to dryness under a steam of nitrogen. The remaining residues were dissolved in 20 µL of methanol and vortex mixed and 3 µL was injected into the GC-MS/MS system. After this step, the remaining residue was evaporated to dryness under a gentle nitrogen stream at 36°C. The analytes under study present active moieties, and therefore derivatization is deemed necessary to the analysis of E2 and T prior to their analysis by GC-based procedures. To accomplish this, 20 µL of N, O-Bis (trimethylsilyl) trifluoroacetamide (BSTFA) was added to the dry extracts, and derivatization took place in a domestic digital microwave oven (Candy CMG 2017 M, Portugal) for 2 min at 800 W and 3 µL was injected into the GC-MS/MS system.

The statistical analysis software used was SPSS 27.0. Descriptive statistics were reported as means ± SD and range for continuous variables, and as frequencies (%) for categorical variables. In order to assess the association between cognitive domains measured by the MoCA test (global cognitive function, executive function, visuospatial abilities, short-term memory, attention, concentration and working memory, language, orientation to time and place) and hormone levels (estradiol, testosterone, DHEA and androstenedione), nonparametric partial correlation coefficients were calculated, controlling for confounding variables: age, education level, years since menopause, depression, smoking habits and BMI. Education levels were classified according to International Standard Classification of Education (ISCED). In Portugal, ISCED level 1 corresponds to basic education (the first 6 years), ISCED level 2 to basic education (the next three-year cycle), ISCED level 3 is upper secondary education and ISCED level superior to 4 corresponds to higher education. BMI was calculated as weight in kilograms divided by height in meters squared. The diagnosis of depression was assessed by the current use of antidepressants. A p value of 0.05 or less was considered statistically significant.

Results

Table 1 shows the demographic, clinical and laboratorial parameters of the participants. The majority of the participants were Caucasian and mean age was 61.7 years, ranging from 50 to 86 years. The number of years since menopause (years from menopause to date of blood collection) was on average 10.8 years. Most patients (99.3%) did not have alcoholic habits. Only 9.5% of the patients had smoking habits. Depression was present in 44 patients (29.9%). It should be noted that 48.3% of patients had only basic education ISCED level 1.

	Frequency n (%)	Mean (SD)	Range
Age (years)		61.7 (8.0)	50-86
Race (Caucasian)	146 (99,3%)		
Education level			
ISCED 1	71 (48.3%)		
ISCED 2	25 (17%)		
ISCED 3	19 (12.9%)		
ISCED 4	32 (21.8%)		
Years since menopause		10.8 (8.5)	1-38
Depression	44 (29.9%)		
Alcohol habits	1 (0.7%)		
Smoking habits	14 (9.5%)		
BMI (Kg/m^2)		28.6 (5.1)	18-46
Hormone levels			
E2 (ng/mL)		1.11(2.40)	0.05-18.00
Testosterone (ng/mL)		2.88 (6.02)	0.50-34.89
DHEA (ng/mL)		10.82 (5.77)	2.33-33.81
Androstenedione (ng/mL)		1.41 (0.96)	0.10-6.87
Cognitive domains			
Global cognitive function		24.3 (3.3)	12-30
Executive function		3.0 (0.8)	1-4
Visuospatial abilities		3.0 (0.9)	0-4
Short-term memory		2.5 (1.5)	0-5
Attention, concentration and working memory		4.8 (1.2)	1-6
Language		4.2 (0.9)	1-5
Orientation to time and place		5.9 (0.3)	3-6

Table 1: Basic descriptive parameters of the participants (n=147).

Table 2 presents the correlation coefficients for hormone levels and cognitive domains. Controlling for possible confounding variables (age, education level, years since menopause, depression, smoking habits and BMI), negative correlations were found between estradiol and the following cognitive domains: executive function (p=0.024),

visuospatial abilities (p=0.000) and orientation to time and place (p=0.020). Although a negative correlation was also found between estradiol and global cognitive function, it did not reach a statistical significance at a level of 5%. No statistically significant associations were found between DHEA, testosterone and androstenedione and cognitive domains. The variables race and alcohol habits were not considered in the analysis due to their reduced variability.

		E2	T	DHEA	A
Global cognitive function	Correlation Sig. (2-tailed)	-0.149 0.078	0.074 0.387	0.000 0.999	0.005 0.949
Executive function	Correlation Sig. (2-tailed)	-0.190 0.024*	-0.049 0.566	-0.004 0.965	0.019 0.821
Visuospatial abilities	Correlation Sig. (2-tailed)	-0.333 0.000*	-0.119 0.161	-0.041 0.634	0.006 0.941
Short-term memory	Correlation Sig. (2-tailed)	0.028 0.746	0.128 0.132	0.099 0.246	-0.006 0.944
Attention, concentration and working memory	Correlation Sig. (2-tailed)	-0.074 0.387	0.026 0.764	0.003 0.967	0.047 0.583
Language	Correlation Sig. (2-tailed)	-0.086 0.312	0.041 0.632	-0.060 0.483	0.071 0.405
Orientation to time and place	Correlation Sig. (2-tailed)	-0.196 0.020*	-0.165 0.052	0.050 0.560	0.022 0.794

Table 2: Correlation coefficients for hormone levels and cognitive domains.

*Correlation is significant at the 0.05 level

Variables controlled: age; education level; years since menopause; depression; smoking habits; BMI

Discussion

After adjustment for age and other confounding factors, an association between serum estradiol levels and executive function, visuospatial abilities and orientation to time and place was found, evidencing a tendency to obtain lower scores when evaluating these cognitive domains in patients with higher concentrations of serum estradiol. Although a negative correlation was also found between serum estradiol levels and global cognitive function, it did not reach a statistical significance at a level of 5%. Contrary to a few studies that suggested a positive association between estradiol and cognitive function [13,14], our study is in line with studies that showed a null or negative influence of estrogen [18-20,27].

Drake et al reported that E2 is associated with enhanced verbal memory but also showed negative associations with visuospatial skills [15].

The Rotterdam Study, a population-based follow-up study on chronic diseases, including dementia, in women aged 55 years or older, showed that higher levels of total estradiol were associated with an increased 6 year risk of dementia (age-adjusted hazard ratio per standard deviation increase 1.38; 95% CI 1.04-1.84) [18]. In the Rancho Bernardo Study cohort, which included 343 postmenopausal women with a median age 70 years, higher estradiol predicted a greater four year decline in performance on a category fluency test of cognitive flexibility and executive function [21]. There are many observational studies and several meta-analyses regarding the effects of systemic HRT on cognitive function, and more than half suggest benefit but nearly all long term clinical trials fail to show any benefit and the longer trials tend to show even harm [28]. Recent observational studies continue to provide conflicting results [29,30]. However, the Women's Health Initiative Memory Study (WHIMS), the largest postmenopausal estrogen trial of dementia, including a subset of 2947 women aged 65 or older, did not confirm a positive effect of HRT in aged women, and even showed a higher risk of MCI and dementia in the HRT groups [31]. In this cohort, subjects were older than in other studies. The accumulated evidence has led to the theory that there is a critical period for the beneficial effect of HRT when initiated around the age of menopause, or in the first few years after menopause. Treatment initiated many years after the menopause does not have a benefit and may even be harmful. However, the newer Early versus Late Intervention Trial with Estradiol (ELITE)-cog and Kronos Early Estrogen Prevention Study (KEEPS) trials have reported no beneficial or adverse effects of HRT on cognition among recently postmenopausal women if treatment is started within 6 years of the menopause diagnosis [32,33].

Our study showed no significant associations between serum androgen levels and cognitive function, after adjustment for possible confounding factors. Levels of testosterone were related positively to verbal fluency [15], verbal memory [16] and predicted better categorical performance on the Mini-Mental State Examination (MMSE) and the World component of the MMSE [19]. Davis et al reported in 92 postmenopausal women aged 55-65 years (on no systemic sex hormone therapy), a small but statistically significant effect of testosterone treatment on verbal learning and memory [34]. However, in line with our study, other studies showed no association between testosterone and cognitive function [20,27,35].

A prospective cohort study of 3044 women of the NHS in which women aged 70 years and older were administered the Telephone Interview of Cognitive Status, a telephone version of the MMSE, could not demonstrate that testosterone levels were associated with either objective or subjective measures of cognitive function [35]. It should be noted that in this study the blood draw was performed during the early postmenopausal stage. In another study of 402 postmenopausal women, higher testosterone concentration was associated with lower scores for neurocognition index, memory and psychomotor speed [24].

Our study is one of the few that attempt to show an association between endogenous DHEA levels and cognitive function, although there are multiple studies showing no effect of DHEA supplementation on cognitive function [36,37]. Most of the epidemiological studies focused on the role of DHEAS decline in the onset of cognitive impairment occurring with age with a large number of observations showing no association [38]. Bojar et al., reported that postmenopausal women with a high normal level of DHEA scored significantly better in verbal and visual memory [24]. Nonetheless, a recent Australian study, published in 2023, showed that in 5511 women 70 years or older, DHEA was not associated with cognitive performance [27]. There is a paucity of data regarding androstenedione and cognitive function, but a few studies reported no association between androstenedione and cognitive function [15,35].

It should be noted that the differences observed in the various studies carried out on the association between circulating levels of steroid hormones and cognitive function are probably related to the heterogeneity of the studies, with regard to the design of the study and methodology used. It is difficult to compare our results to others due to the use of different diagnostic instruments, applied to ethnically different populations, as well as differences in mean age. Most of the studies used the MMSE. The main advantage of the MoCA test when compared to MMSE is the superior sensitivity for the diagnosis of mild cognitive impairment, a transitional state between normal aging and dementia, especially Alzheimer's disease [25]. A limitation that can be pointed out to our study is the high percentage of women with a low level of education (48.3% of patients had only ISCED level 1). The MoCA test is more suitable for cognitive screening of the population with higher education [25].

Most of the previous studies used immunoassays for the measurement of steroid hormone levels, but mass spectrometry based techniques are now the gold standard for measuring steroid hormones in postmenopausal women, due to its higher accuracy. Despite the limitations of sample size and cross-sectional design, this is the first study to analyze associations between steroid hormone levels and cognitive function in postmenopausal women, using GC-MS/MS for hormone measurements and the MoCA test as a cognitive diagnostic tool. Age is the most important factor for cognitive decline. However, accumulating evidence shows that steroid hormones influence cognition, but different hormones can influence different aspects of cognition during aging, and this may also explain the different results obtained from the studies. Estrogen, known to have a beneficial association with cognitive function in pre-menopause and in the early stages of menopause, may in fact have a negative impact on some aspects of cognitive function in older women, which explains the results of studies showing that estrogen therapy has no effect or may be deleterious in older women.

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Authorship Contribution

EN and JFM were responsible for the project development. E.N. was responsible for gaining ethical approval, patient recruitment, data collection and manuscript writing. EG and SMN were responsible for data analysis. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Conflict of Interest

The authors declare that they have no competing interests.

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