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Endogenous sex hormone levels and risk of cognitive decline in an older biracial cohort

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Abstract

Background: Older women treated with conjugated estrogens may have an increased risk of dementia, but the effect of naturally occurring sex hormones on cognition is not certain.
Methods: Bioavailable estradiol and free testosterone level were obtained from 792 (55% men, 51% black) participants. We assessed cognition with the Modified Mini-Mental State Examination (3MS), Selective Reminding Test (SRT) and CLOX 1 at baseline and 2 years later.
Results: Women in the lowest estradiol tertile were more likely than those in the highest tertile to decline (≥1.0 S.D. of change) on 3MS (25% versus 9%, adjusted odds ratio [OR] = 3.9; 95% confidence interval [CI] = 1.6–9.6) and on SRT (28% versus 12%, adjusted OR [95% CI] = 3.3 [1.4–7.9]) but not CLOX 1. There was a borderline association between low estradiol tertile and decline on SRT in men (22% versus 14%, adjusted OR [95% CI] = 1.9 [0.9–3.9]). Testosterone level was not associated with decline in cognition in either men or women. Findings did not differ by race.
Conclusions: Older women with low estradiol levels were more likely to experience decline in global cognitive function and verbal memory, and a similar trend was observed for verbal memory in men. This supports the hypothesis that endogenous sex hormones may play an important role in the maintenance of cognitive function in older adults.

Keywords: Cognition; Dementia; Sex hormones; Estrogen

1. Introduction

Two major randomized, controlled trials (RCTs) have recently found that taking conjugated estrogens increases the risk of adverse cognitive outcomes including dementia in older women (Grady et al., 2002; Shumaker et al., 2003,

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2004). These findings, however, are contrary to a large body of biological (McEwen, 1999; Toran-Allerand et al., 2005) and epidemiological (Kawas et al., 1997; Tang et al., 1996; Yaffe et al., 1998b) evidence suggesting that estrogen and other sex hormones may have beneficial effects on cognitive function, especially verbal memory, in older adults.

Although it is clear that conjugated estrogens do not prevent cognitive decline or dementia in older women, it is important to conduct additional research to reconcile RCT results with other biological and epidemiological findings. Conceivably there exists an optimal biological level of sex hormones, and that levels that are either too low or too high may be detrimental to cognitive function. If so, this would raise the possibility that alternative doses or preparations of sex hormones or targeted sex hormone therapy may be beneficial.

Studies of endogenous sex hormone levels provide a unique opportunity to gain insight into the complex association between sex hormones and cognition in older adults because they are not affected by confounding related to decisions to prescribe hormone therapy. However, prior studies of endogenous sex hormones and cognition have either been cross-sectional (Almeida et al., 2005; Barrett-Connor et al., 1999; Drake et al., 2000; Hogervorst et al., 2004; Lebrun et al., 2005; Muller et al., 2005; Yaffe et al., 2002) or have focused on a single endogenous hormone or a single gender (Moffat et al., 2002, 2004; Yaffe et al., 2000), and none have included a significant number of black elders. In addition, many studies evaluated total hormone measures and total levels may not be the best measure of the biological activity of the hormones; the non-protein-bound (free) and loosely bound (bioavailable) forms cross the blood–brain barrier more readily and may be better correlated with cognitive function.

We analyzed the association between endogenous sex hormone levels (both bioavailable estradiol and free testosterone) on the risk of cognitive decline in the Health, Aging and Body Composition (Health ABC) Cognitive Vitality cohort, which includes representative samples of both white and black women and men. To focus on the role of naturally occurring sex hormones, current users of sex hormones were excluded.

2. Methods

2.1. Study population

Subjects were participants in the Health ABC study, a prospective cohort study of 3075 community-dwelling black and white elders aged 70–79 years living in the Memphis, TN and Pittsburgh, PA vicinities. Elders were recruited from a random sample of white and all black Medicare eligible adults living in designated zip codes. Sampled participants were mailed a brochure describing the study and then contacted by phone to establish functional status and to recruit eligible residents to join the study. Community-based activities were also used to enhance the recruitment of Black participants. To be eligible for the study, participants had to be age 70–79 years; report no difficulty walking a quarter of a mile, climbing 10 steps without resting, or performing activities of daily living; be free of life-threatening cancers; and plan to remain within the study area for at least 3 years. Nearly similar numbers of male and female, and black and white participants were enrolled in 1997–1998. All participants signed informed consent including consent to have blood drawn for storage at each clinic visit.

At Year 3, a subset of the Health ABC cohort was enrolled in the Cognitive Vitality Substudy, which consisted of 951 black and white women and men aged 72–81 years (mean age 75.2 years) who had additional cognitive testing. Approximately equal numbers of each sex and racial/ethnic group were included based on a random stratified sample. The subjects included in the substudy were slightly younger (75.3 years versus 75.9 years) and more likely to be black (49% versus 37%) compared to the Health ABC participants who were not part of the substudy, but did not differ on other demographics or comorbidities. Ninety-four percent of subjects ($N = 898$) had adequate levels of stored blood available for measurement of estradiol and testosterone. We excluded the 106 participants who were current users of oral androgens ($N = 6$) or estrogens ($N = 100$) for our final analytic cohort of 792 elders.

2.2. Measurements

2.2.1. Endogenous sex hormone levels

Serum and plasma from the Year 3 visit were stored at −70 °C at the Health ABC Core Laboratory (PI: Russell P. Tracy, PhD, University of Vermont). Samples were sent directly from storage to the analytical laboratories (Royal Marsden, London, England, for estradiol and Wake Forest University, NC, for testosterone) without thawing. Bioavailable plasma estradiol concentration was measured by radioimmunoassay using a highly specific rabbit antiserum raised against an estradiol-6-carboxymethyloxime-bovine serum albumin conjugate (EIR, Wurenlingen, Switzerland) and Third Generation Estradiol [I125] reagent (DSL 39120 Diagnostic Systems Laboratories Inc., TX). All samples were measured in duplicate. The lower detection limit is 0.8 pg/ml. Within assay variability, assessed in 20 assays using 4 replicates of a serum pool, gave a mean estradiol level of 7.3 pg/ml and an overall within-assay coefficient of variation of 7.6%. The between-assay coefficient of variation for the same pool was 17% ($N = 20$).

Serum concentrations of free testosterone were measured using an enzyme immunoassay (EIA) kit (sensitivity = 0.19 pg/ml, detection range = 0.25–100 pg/ml) from Diagnostic Systems Laboratories, Inc. (DSL, Webster, TX). This kit utilizes a rabbit anti-testosterone anti-serum, which has low affinity for sex hormone binding globulin (SHBG) and albumin. All samples were measured in duplicate and