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Low testosterone and the risk of dementia in elderly men: Impact of age and education

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Abstract

Objective: The objective of this study was to examine the association of plasma estradiol and testosterone with risk for dementia in elderly men.

Methods: Within the population based Three-City study, including 3650 men age 65 years and older, a case–cohort design was set up after 4-years of follow-up. Baseline plasma levels of total 17-β estradiol (Total-E2), total testosterone (total-T) and bioavailable testosterone (bio-T) were measured for all cases of incident dementia (n = 105) and for a random sample of the cohort (n = 413). Cox regression models were used to estimate multivariate steroid sex hormone-associated hazard ratios (HR) and 95% confidence intervals of dementia.

Results: There was a reverse J-shaped relationship between total-T and risk for dementia ($P = .007$). Compared with the median tertile, the HRs associated with total-T in the lower and upper tertile were increased (HR, 2.33; $P = .026$; HR, 1.9, $P = .126$; respectively). Low bio-T was associated with a greater risk for dementia (HR for one standard deviation of decreasing log(bio-T), 1.29; 95% confidence interval, 1.03–1.62). An interaction was found between bio-T and age ($P < .0001$), and bio-T and education ($P = .044$). Risk for dementia associated with low bio-T was greater in older men (80 years or older) than in younger men (younger than 80 years; HR, 3.11; $P = .011$ vs. HR, 1.07, $P = .715$, respectively) and in men with high level of education compared with those with low level of education (HR, 2.32; $P = .0002$ vs. HR, 0.95; $P = .790$, respectively). No significant association was found between Total-E2 and dementia.

Conclusions: Low levels of testosterone are associated with a risk for dementia in elderly men. The association between low bio-T and dementia may be more relevant to men 80 years or older and men with a high level of education.

Keywords: Testosterone; Estradiol; Dementia; Elderly men; Cohort study

1. Introduction

Advancing age is associated with an overall increased risk for cognitive decline and dementia. However, beyond well-identified risk factors such as age, apolipoprotein E ε4 allele (*APOE* ε4), and education, the contribution of age-related changes in the immune, endocrine, and vascular systems to the development of dementia are far from being understood.

In men, the progressive decline in testosterone levels with age [1,2] could play a role in the pathogenesis of dementia

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through various mechanisms. Testosterone may have neuroprotective properties, especially in brain region's susceptible to Alzheimer's disease (AD) [3,4]. In addition, low testosterone may be involved in adverse vascular mechanisms also associated with the risk of dementia. Low testosterone has been associated consistently with cardiovascular risk factors [5], and recent prospective data showed an increased risk of coronary heart disease [6] and stroke [7] among men with low testosterone levels.

Despite a wide number of studies evaluating the association of endogenous testosterone with cognitive decline [8], only a few longitudinal studies have examined its relationship with incident dementia [9–13], of which three pertain to a white population. Results from these studies are conflicting, with two reporting a decreased risk of AD in men with high free or bioavailable testosterone (bio-T) levels [9,11] and two others reporting no association of testosterone (total or free) with either AD or vascular dementia (VaD) [10,12]. Besides having direct neuroprotective effects, testosterone may act through its conversion to 17-β estradiol (E2) by aromatase in adipose tissue. Few studies have investigated the association of endogenous E2 with risk for dementia. Although higher E2 levels were found to be associated with increased risk for cognitive decline and AD in men from the Honolulu-Asia Aging Study [10], two other studies failed to find any significant association [12,14].

In the current study, we examined the association of total testosterone (total-T), bio-T, and total E2 (Total-E2) levels with the 4-year incidence of all-cause dementia, AD, and VaD in a large cohort of French elderly men (the Three-City Study [3C]). In addition, in a post hoc analysis, we assessed whether major dementia or vascular risk factors modified the association of steroid sex hormones (SSH) levels with dementia.

2. Methods

2.1. Population study

We used data from the 3C, a French prospective cohort study with the aim of evaluating the role of cardiovascular risk factors and disease in the development of dementia in the elderly [15]. Briefly, 3650 men and 5644 women older than 65 years who were registered on electoral rolls and not institutionalized were recruited in three French cities (Bordeaux, Dijon, and Montpellier) between 1999 and 2001. Baseline data were collected by trained psychologists or nurses during a face-to-face interview using standardized questionnaires at home or at the study center. Information on sociodemographic characteristics, medical history, medication use, food consumption, and alcohol and tobacco use was acquired. In addition, blood pressure and anthropometric measures were assessed during a physical examination. Subjects were monitored approximately every 2 years for the incidence of cardiovascular disease and dementia. For our analysis, we used data up to and including the second evaluation. This protocol was approved by the Consultative Committee for Protection of Persons Participating in Biomedical Research of the University Hospital of Kremlin-Bicêtre (Paris), and all subjects signed a legal consent form.

After the second evaluation, a case–cohort design was set up for biological investigations. This study design consisted of the selection of all incident cases of dementia and a random sample of the initial population used as a control group. The full methodology used in the 3C has been described previously [16]. During our analysis, we used data from men from whom we had acquired a blood sample. In total, 495 men were eligible for the random sample (Fig. 1). After the exclusion of 17 men with a prostate cancer, five men who were undergoing hormonal treatment possibly affected endogenous SSHs levels, 11 men with prevalent dementia (see the next section Dementia Evaluation), and 49 men who had not undergone a dementia examination during the two follow-up visits, the final random sample included 413 men, of whom 15 developed

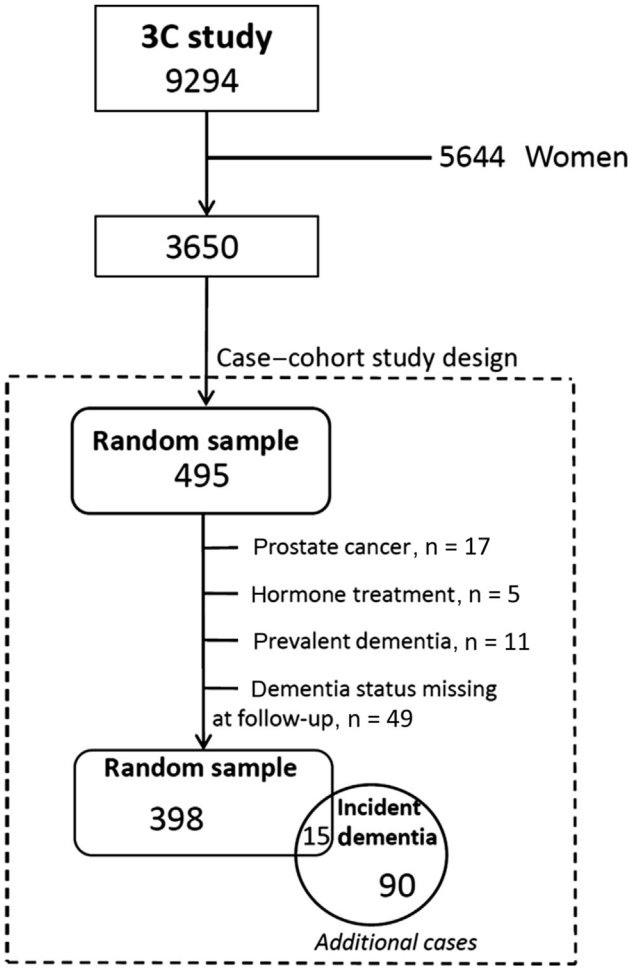

Fig. 1. Flow chart of the sample selection. 3C, Three-City Study.