

Free testosterone and risk for Alzheimer disease in older men

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Abstract—Objective: To investigate the relationships between age-associated decreases in endogenous serum total testosterone (T) and a free T index (FTI) in men and the subsequent development of Alzheimer disease (AD). **Method:** The authors used a prospective, longitudinal design with follow-up in men since 1958. Participants were from the Baltimore Longitudinal Study of Aging, a community-dwelling volunteer sample with baseline ages of 32 to 87 years. All subjects were free of AD at baseline T assessment. Five hundred seventy-four men assessed at multiple time points were followed for a mean of 19.1 years (range, 4 to 37 years). Diagnoses of AD were based on biennial physical, neurologic, and neuropsychological evaluations. **Results:** Diagnosis of AD was associated inversely with FTI by itself and after adjustments for age, education, smoking status, body mass index, diabetes, any cancer diagnoses, and hormone supplements. In separate analyses, total T and sex hormone binding globulin were not significant predictors after adjustment with covariates. Increases in the FTI were associated with decreased risk of AD (hazard ratio = 0.74; 95% CI = 0.57 to 0.96), a 26% decrease for each 10-nmol/nmol FTI increase. **Conclusions:** Calculated free testosterone concentrations were lower in men who developed Alzheimer disease, and this difference occurred before diagnosis. Future research may determine whether higher endogenous free testosterone levels offer protection against a diagnosis of Alzheimer disease in older men.

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A sizable literature now exists relating age-related alterations in the endocrine environment to cognitive changes^{1–3} and the onset of Alzheimer disease (AD) in women.^{4–7} The comparative dearth of similar research in men may be attributable primarily to the fact that testosterone replacement therapy (TRT) has been used much less commonly in men than hormone therapy in women. Moreover, TRT has not been administered for time periods that are sufficiently long to establish linkages to AD. Nevertheless, androgen levels in men decrease substantially with age, raising the question of whether this decrease may contribute to the development of AD.^{8,9} Although numerous studies have demonstrated contributions of testosterone (T) to selected cognitive functions in young^{10–12} and old men,^{13–15} to date there have been no studies assessing prospectively the risk for AD associated with the so-called “andropause.”

Decreased total T levels have been reported in men with AD compared with age-matched control subjects.¹⁶ However, these data are ambiguous because the depleted T levels may be a consequence

rather than a cause of the disease. To assess the impact of T decline in the subsequent manifestation of AD, it is essential to obtain measures of T that precede the development of the disease.

In the present study, we followed 574 men whose ages at baseline T assessment ranged from 32 to 87 years for a mean duration of 19.1 years. We collected multiple serum samples for determination of total T, sex hormone binding globulin (SHBG), and the calculated free T index (FTI) and evaluated presence or absence of a diagnosis of AD as the principal outcome variable. We report here the first prospective longitudinal study assessing the impact of long-term total and estimated free T levels on the development of AD.

Methods. Subjects. Subjects were men who volunteered to participate in the Baltimore Longitudinal Study of Aging (BLSA), a study performed by the National Institute on Aging (NIA).¹⁷ Participants were community dwelling and returned every 2 years to the Gerontology Research Center of the NIA for comprehensive medical and neuropsychological evaluations. Androgen data were available for a large number of BLSA men whose blood samples were assayed as part of a study of prostate health and disease.

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