# Plasma testosterone levels in Alzheimer and Parkinson diseases

M.S. Okun, MD; M.R. DeLong, MD; J. Hanfelt, PhD; M. Gearing, PhD; and A. Levey, MD, PhD

**Abstract—***Background:* Testosterone deficiency, a treatable condition commonly seen in aging men, has been linked to Parkinson disease (PD) and Alzheimer disease (AD). In normal subjects, low testosterone levels are associated with cognitive and neuropsychiatric symptoms, yet the relationship between testosterone levels and cognitive function in PD and AD remains unclear. *Objective:* To examine the relationship of testosterone levels to age and cognitive function in PD and AD. *Methods:* Plasma testosterone levels were determined in men enrolled in a clinical registry of subjects with PD and AD, and neuropsychological testing was performed on subjects who consented. Testosterone levels in men with PD were compared with those in men with AD. In both groups, the relationship between testosterone levels and neuropsychological test scores was analyzed, adjusting for age and education. *Results:* Linear regression analysis revealed that testosterone levels decreased with age in male PD patients ($p < 0.03$) and male AD patients ($p < 0.07$). The rate of decline was similar for the two groups. In PD patients, lower testosterone levels were associated with poorer performance on Trails B Seconds ($p < 0.02$). *Conclusions:* There is a similar age-related decline in plasma testosterone levels in men with either PD or AD. Previously described associations between low testosterone levels and frontal lobe dysfunction in normal aged men, together with these results, suggest that the hormonal deficiency may act as a "second hit" to impair cognitive function in neurodegenerative disease.

NEUROLOGY 2004;62:411–413

Recent studies have revealed a link between testosterone and neurodegenerative diseases,[1,2] yet hormonal influences on dementia risk and neurodegenerative disease treatment and progression are still poorly understood. Estrogen has received the most attention, based on reports of increased Alzheimer disease (AD) risk in estrogen-deficient postmenopausal women.[3-7] However, emerging evidence has linked testosterone deficiency to Parkinson disease (PD) and AD,[1,2,7-11] and it has been shown that some nonmotor symptoms of PD may respond to testosterone replacement therapy. Moreover, testosterone deficiency, which in normal subjects is associated with cognitive and neuropsychiatric symptoms, might act as a "second hit" and exacerbate symptoms when superimposed in PD, AD, and other neurodegenerative disorders. As testosterone deficiency is common in aging men, despite the availability of hormone replacement,[12] clarification of the relationship between testosterone and cognition in neurodegenerative disorders is critical to address this potentially important and treatable risk factor.

**Methods.** Men with symptoms of cognitive, behavioral, or motor dysfunction were referred to the Emory University Department of Neurology for evaluation. Patients (and guardians) who agreed and signed an informed consent were entered into an institutional review board–approved Clinical Registry in Neurology and Alzheimer's Disease Center Registry involving subjects recruited from the Movement Disorders and Cognitive Disorders Clinics. Sixty-eight male PD and 50 male AD patients were studied. The diagnosis of PD was made by neurologic examination as well as by adherence to standard criteria for the diagnosis of idiopathic PD, including the presence of two of three cardinal symptoms of PD in the absence of relevant exclusion criteria.[13] The diagnosis of AD was made by adhering to Diagnostic and Statistical Manual of Mental Disorders (3rd. rev. ed.) criteria and by consensus conference among the behavioral neurologists and neuropsychologists. Diagnosis of dementia in PD patients was made by neurologic and neuropsychological examination in addition to appropriate laboratory and imaging studies. Eight of the 68 PD patients had evidence of dementia. Plasma samples were drawn from all 118 patients, and selective cognitive testing was performed on those patients who agreed. Plasma free and total testosterone levels were determined at a commercial laboratory (Quest Diagnostics). Neuropsychological measures included Boston Naming (alternate items), Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Naming, CERAD Word List Learning and Delayed Recall Memory Savings, Clinical Dementia Rating (Total) (CDR), Mattis Dementia Rating Scale (DRS) Total Score, Mattis Dementia Rating Scale Memory Subscale, Geriatric Depression Scale, Letter Fluency, Mini-Mental State Examination (MMSE), Wechsler Memory Scale III (WMS-III) Backward Digit Span, WMS-III Forward Digit Span, WMS revised (WMS-R) Backward Digit Span, WMS-R Forward Digit Span, and Trail Making A and B.

Testosterone levels in men with PD were compared with those in men with AD, and a multiple linear regression model was utilized to examine whether testosterone levels in PD and AD patients varied with age. The relationship between testosterone levels and neuropsychological test scores was also analyzed in both patient groups.

**Results.** Testosterone levels did not differ significantly between the PD and AD patient groups (table 1). Linear regression analysis indicated that testosterone levels decreased with age in male PD patients ($p = 0.03$) and male AD patients ($p = 0.07$) (figure; table 2). In men with PD, testosterone levels declined by an estimated 65.9 ng/mL (95% CI, 7.5 to 124.3 ng/mL) per every 10 years of age. In

From the Department of Neurology (Dr. Okun), University of Florida, Gainesville; and Departments of Neurology (Drs. DeLong and Levey), Biostatistics (Dr. Hanfelt), and Pathology and Laboratory Medicine (Dr. Gearing), Emory University, Atlanta, GA.

Received February 20, 2003. Accepted in final form October 13, 2003.

Address correspondence and reprint requests to Dr. M.S. Okun, Movement Disorders Program, University of Florida McKnight Brain Institute, Rm. L3-100, Department of Neurology, 100 S. Newell Dr., 3rd fl., PO Box 100236, Gainesville, FL 32610; e-mail: okun@neurology.ufl.edu

 

***Table 1*** *Characteristics of 118 male patients with a diagnosis of PD or AD*

| Characteristics | PD, mean ± SD (range) | AD, mean ± SD (range) | Unadjusted *p* value |
|---|---|---|---|
| n | 68 | 50 | — |
| Age at T measurement, y | 66 ± 10 (38–85) | 75 ± 8 (56–89) | <0.001 |
| Education, y | 16 ± 3 (7–22) | 14 ± 4 (3–20) | <0.001 |
| Duration of disease, y | 11 ± 7 (0–30) | 4 ± 3 (0–16) | <0.001 |
| T level, ng/mL | 417 ± 210 (4–1,114) | 392 ± 194 (3–833) | 0.51 |
| Proportion with T <325 ng/mL, % | 35 | 38 | — |

PD = Parkinson disease; AD = Alzheimer disease; T = testosterone.

male AD patients, testosterone levels dropped by 60.1 ng/mL (95% CI, −4 to 124.6 ng/mL) per every 10 years of age. The rate of decline of testosterone was not different in PD and AD patients ($p = 0.42$). Comparison with the Baltimore Longitudinal Study of elderly community-dwelling men[14] revealed that the rate of decline in testosterone levels in our PD (65.9 ng/mL) and AD (60.1 ng/mL) groups was somewhat greater than that seen in the Baltimore aging study where there was an estimated drop of 35 ng/mL per every 10 years of age (PD vs community; $p = 0.30$; AD vs community; $p = 0.45$).

To determine the effects of testosterone deficiency on cognition in subjects with neurodegenerative disease, we analyzed the relationship between testosterone levels and performance on several neuropsychological measures (table 3). Neither MMSE ($p = 0.14$), DRS Total score ($p = 0.14$), nor DRS Memory Subscale ($p = 0.21$) was related to testosterone level in PD or AD patients. However, PD patients with lower testosterone levels performed more poorly on Trails B Seconds ($p = 0.02$), after adjusting for age and education. None of the *p* values reported above were adjusted for multiple comparisons. Hence, the above results should be interpreted with caution, and larger studies will be needed to confirm our observations.

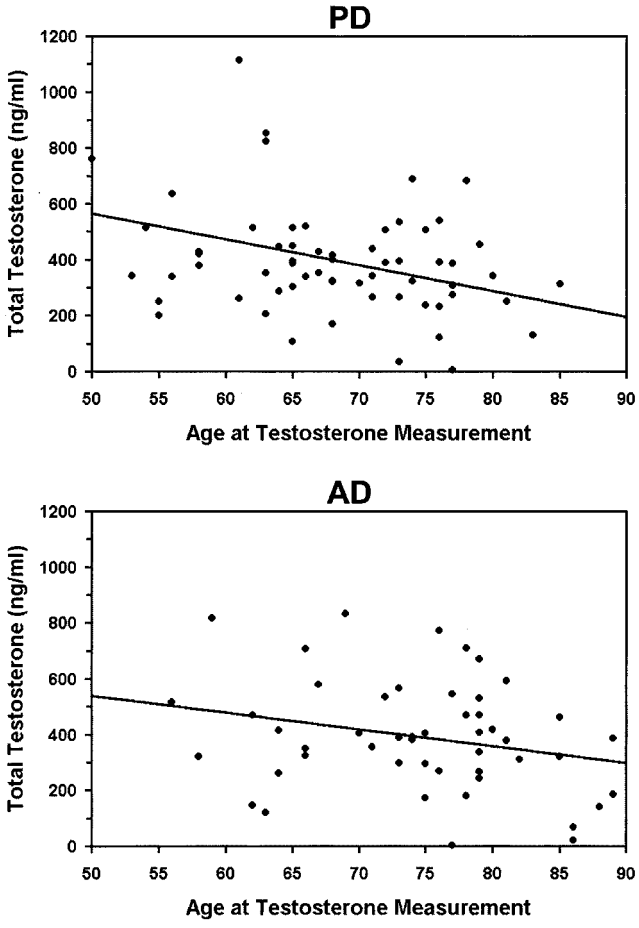


*Figure. Linear regression analysis indicated that testosterone levels decreased with age in men with Parkinson disease (PD) (*p *= 0.03). A similar tendency was noted in male Alzheimer disease (AD) patients (*p *= 0.07).*

**Discussion.** There is little information about testosterone's relationship to PD, AD, and other neurodegenerative disorders in humans.[1,2,7-11] In the current study, we found no significant difference in the rate of decline of testosterone levels in our PD and AD patients compared with that in an elderly population without neurodegenerative diseases or dementia.[14] A larger sample size will be needed to confirm this observation.

Symptoms of testosterone deficiency overlap with those of PD, AD, and other neurodegenerative disorders and include memory loss, depression, anxiety, irritability, insomnia, and sexual dysfunction.[1,11,15,16]

***Table 2*** *Relationship between age and testosterone levels (T) in men with PD or AD*

| Age at time of T measurement, y | Male PD patients n | Male PD patients Mean T (SD) | Male PD patients % low T | Male AD patients n | Male AD patients Mean T (SD) | Male AD patients % low T |
|---|---|---|---|---|---|---|
| <50 | 6 | 691 (194) | 0 | 0 | N/A | N/A |
| 50–59 | 10 | 427 (171) | 20 | 3 | 551 (249) | 33 |
| 60–69 | 24 | 428 (224) | 33 | 10 | 420 (232) | 40 |
| 70–79 | 24 | 360 (173) | 46 | 26 | 402 (173) | 31 |
| 80+ | 4 | 259 (94) | 75 | 11 | 298 (176) | 55 |

T levels are expressed in ng/mL, with "% low T" indicating the proportion of patients with T <325 ng/mL.

PD = Parkinson disease; AD = Alzheimer disease.

***Table 3*** *Relationship between testosterone levels and cognitive function, adjusted for age and education*

| | Male PD | | Male AD | |
|---|---|---|---|---|
| Neuropsychological test | n | *p* value | n | *p* value |
| BNT 30 | 37 | 0.15 | 4 | N/A |
| CERAD BNT | 22 | 0.06 | 13 | 0.02 |
| CDR total | 23 | 0.98 | 12 | 0.62 |
| CERAD word list 1 | 22 | 0.09 | 13 | 0.04 |
| CERAD word list 2 | 22 | 0.70 | 13 | 0.77 |
| CERAD word list 3 | 22 | 0.42 | 13 | 0.66 |
| Delay recall | 22 | 0.07 | 13 | 0.41 |
| DRS memory | 24 | 0.36 | 39 | 0.08 |
| DRS total | 24 | 0.55 | 39 | 0.11 |
| GDS 30 | 22 | 0.65 | 10 | 0.70 |
| Letter fluency total | 22 | 0.42 | 7 | 0.19 |
| Letter fluency A | 20 | 0.74 | 7 | 0.16 |
| Letter fluency F | 20 | 0.51 | 7 | 0.09 |
| Letter fluency S | 20 | 0.98 | 7 | 0.39 |
| MMSE | 27 | 0.28 | 43 | 0.09 |
| Savings | 22 | 0.06 | 13 | 0.60 |
| Trail A errors | 17 | 0.11 | 8 | 0.76 |
| Trail A seconds | 17 | 0.19 | 8 | 0.72 |
| Trail B errors | 11 | 0.36 | 3 | N/A |
| Trail B seconds | 11 | 0.02 | 3 | N/A |
| W3 digits backward | 20 | 0.43 | 6 | 0.85 |
| W3 digits forward | 20 | 0.15 | 6 | 0.88 |
| WR digits backward | 14 | 0.36 | 2 | N/A |
| WR digits forward | 14 | 0.70 | 2 | N/A |

PD = Parkinson disease; AD = Alzheimer disease; BNT 30 = Boston Naming Test 30; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CDR = Clinical Dementia Rating Scale; DRS = Mattis Dementia Rating Scale; GDS = Geriatric Depression Scale; MMSE = Mini-Mental State Examination; W3 = Wechsler Memory Scale-III; WR = Wechsler Memory Scale revised.

However, there is little information about the role of testosterone on cognition and other symptoms in PD and AD patients. In the current study, there was no correlation between neuropsychological test scores and testosterone levels. Two small studies on PD showed lower levels of testosterone in men with PD as well as responsiveness of nonmotor and some cognitive symptoms to treatment with testosterone.[1,2] We are aware of a single case report[11] and one small cross-sectional study of 39 men with AD.[16] In the latter study, the AD patients had lower levels of total serum testosterone than control subjects, independent of potential confounds such as age and other risk factors. Thus, low testosterone levels may be a co-morbid feature of PD and AD in men. A larger prospective longitudinal study is needed to confirm our results and to clarify the role of testosterone in neurodegenerative diseases.

## References


1. Okun MS, McDonald WM, DeLong MR. Refractory nonmotor symptoms in male patients with Parkinson disease due to testosterone deficiency: a common unrecognized comorbidity. Arch Neurol 2002;59:807–811.
2. Okun M, Walter BL, McDonald WM, et al. Beneficial effects of testosterone replacement for the nonmotor symptoms of Parkinson disease. Arch Neurol 2002;59:1750–1753.
3. Kawas C, Resnick S, Morrison A, et al. A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: the Baltimore Longitudinal Study of Aging. Neurology 1998;48:1517–1521.
4. Miller MM, Monjan AA, Buckholtz NS. Estrogen replacement therapy for the potential treatment or prevention of Alzheimer's disease. Ann NY Acad Sci 2001;949:223–234.
5. Green PS, Simpkins JW. Estrogens and estrogen-like non-feminizing compounds. Their role in the prevention and treatment of Alzheimer's disease. AnnN Y Acad Sci 2000;924:93–98.
6. Wang PN, Liao SQ, Liu RS, et al. Effects of estrogen on cognition, mood, and cerebral blood flow in AD: a controlled study. Neurology 2000;54:2061–2066.
7. Gandy S, Duff K. Post-menopausal estrogen deprivation and Alzheimer's disease. Exp Gerontol 2000;35:503–511.
8. Gouras GK, Xu H, Gross RS, et al. Testosterone reduces neuronal secretion of Alzheimer's beta-amyloid peptides. Proc Natl Acad Sci USA 2000;97:1202–1205.
9. Gandy S, Petanceska S. Regulation of Alzheimer beta-amyloid precursor trafficking and metabolism. Biochim Biophys Acta 2000;1502:44–52.
10. Gandy S, Almeida OP, Fonte J, et al. Chemical andropause and amyloid-beta peptide. JAMA 2001;285:2195–2196.
11. Almeida OP, Waterreus A, Spry N, et al. Effect of testosterone deprivation on the cognitive performance of a patient with Alzheimer's disease. Int J Geriatr Psychiatry 2001;16:823–825.
12. Tan RS, Culberson JW. An integrative review on current evidence of testosterone replacement therapy for the andropause. Maturitas 2003;45:15–27.
13. Olanow CW, Watts RL, Koller WC. An alorithim (decision tree) for the management of Parkinson's disease 2001: treatment guidelines. Neurology 2001;56:S52–S53.
14. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR, Baltimore Longitudinal Study of Aging. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab 2001;86:724–731.
15. Tenover JL. Testosterone replacement therapy in older adult men. Int J Androl 1999;22:300–306.
16. Hogervorst E, Williams J, Budge M, et al. Serum total testosterone is lower in men with Alzheimer's disease. Neuroendocrinol Lett 2001;22:163–168.