Testosterone Therapy in Men With Parkinson Disease

Results of the TEST-PD Study

Michael S. Okun, MD; Hubert H. Fernandez, MD; Ramon L. Rodriguez, MD; Janet Romrell, PA-C; Michele Suelter, BS; Sarah Munson, BS; Elan D. Louis, MD; Thomas Mulligan, MD; Paul S. Foster, PhD; Brian V. Shenal, PhD; Sheyan J. Armaghani, BS; Charles Jacobson, BS; Samuel Wu, PhD; Gregory Crucian, PhD

Background: Testosterone deficiency has been reported in patients with Parkinson disease (PD), Alzheimer disease, and Huntington disease. It is not known whether testosterone therapy (TT) in men with borderline hypogonadism and neurodegenerative diseases will be of substantial benefit. Previously, we reported that testosterone deficiency is more common in patients with PD compared with age-matched control subjects, and we also reported in 2 small open-label studies that some nonmotor symptoms responded favorably to TT.

Objective: To define the effects of TT on nonmotor and motor symptoms in men with PD and probable testosterone deficiency.

Design: Double-masked, placebo-controlled, parallel-group, single-center trial.

Patients: Two experimental groups: patients with PD who were receiving either TT or placebo.

Interventions: Participants received either the study drug by intramuscular injection (200 mg/mL of testosterone enanthate every 2 weeks for 8 weeks) or placebo (isotonic sodium chloride solution injections). In patients in each group, the testosterone serum concentration was obtained at each study visit. During 2 study visits, testosterone levels were blindly evaluated and the intramuscular testosterone dose was increased by 200 mg/mL if the free testosterone value failed to double from the baseline value.

Main Outcome Measures: The primary outcome variable was the St Louis Testosterone Deficiency Questionnaire, and secondary outcome measures included measures of mood, cognition, fatigue, motor function, and frequency of adverse events. At the end of the double-blind phase, all patients were offered open-label TT and were followed up after 3 and 6 months.

Results: Fifteen patients in the placebo group (mean age, 69.9 years), receiving a mean total levodopa equivalent dose of 924 mg/d, had a baseline free testosterone level of 47.91 pg/mL, compared with 15 patients in the TT group (mean age, 66.7 years), receiving an average total levodopa equivalent dose of 734 mg/d, who had a baseline free testosterone level of 63.49 pg/mL. Testosterone was generally well tolerated. More subjects in the TT group experienced lower extremity edema (40% vs 20%). In 2 patients, 1 in each group, prostate-specific antigen levels were elevated from baseline. The improvement in the TT group compared with the placebo group (1.7 vs 1.1) on the St Louis Testosterone Deficiency Scale was not statistically significant. In addition, there were no significant differences in motor and nonmotor features of PD between the 2 groups, although a few subscales showed improvements (Hopkins Verbal Learning Test, $P<.04$; and Backward Visual Span subtrial, $P<.03$). However, long-term open-label TT resulted in delayed but sustained improvement in subjects in the TT group who continued to receive treatment (n=6) compared with subjects in the placebo group who elected not to receive TT (n=3).

Conclusions: Testosterone therapy was generally well tolerated in elderly men with PD and probable testosterone deficiency. While there was no significant difference in the motor and nonmotor scales between the TT and placebo groups at the end of 8 weeks compared with baseline, this may be due to several study limitations, including small sample size, a strong placebo effect with intramuscular therapy, and short follow-up that did not allow measurement of delayed effects of TT in some subjects. Until more definitive studies are reported, practitioners should be particularly cautious in treatment of low testosterone concentrations in men with PD and borderline testosterone deficiency, and careful consideration should be given to the risks vs the benefits of TT.

Arch Neurol. 2006;63:729-735

T ESTOSTERONE DEFICIENCY may be important in patients with Parkinson disease (PD),[1] Alzheimer disease, and Huntington disease.[2-5] It is not known, however, whether replacement of testosterone in men with borderline hypogonadism and neurodegenerative diseases is of substantial benefit. Parkinson disease is commonly associated with motor symptoms (eg, bradykinesia, rigidity, tremor, and gait or balance difficulties) and nonmotor symptoms (eg, fatigue, depressive symptoms, anxiety, reduced libido, sexual dysfunction, and cognitive difficulty). The motor dysfunction in PD can typically be treated with a variety of pharmacologic strategies.[6] The nonmotor manifestations
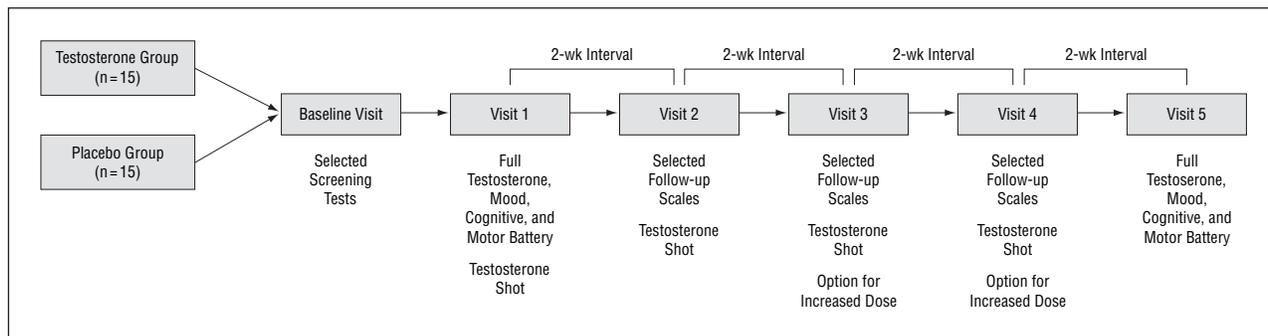
Author Affiliations are listed at the end of this article.

Figure 1. Flowchart shows study visits.

Table 1. Characteristics of Study Participants*

Variable	Placebo Group	TT Group	P Value†
Age, y	69.9 ± 9.41	66.7 ± 10.26	.38
Hoehn and Yahr Parkinson stage	2.5	2.5	.99
Levodopa equivalent dose, mg/d	924.41 ± 524.36	734.43 ± 382.55	.27
Free testosterone level, pg/mL			
Pretreatment	47.91 ± 20.48	63.49 ± 17.44	.03
Posttreatment	53.06 ± 26.69	333.72 ± 389.08	.009
Total testosterone level, ng/dL			
Pretreatment	273.14 ± 133.00	375.50 ± 104.55	.03
Posttreatment	333.04 ± 161.11	1029.92 ± 413.49	.000
St Louis Testosterone Deficiency Questionnaire score	7.00 ± 1.51	7.73 ± 1.44	.19
Geriatric Depression Scale score	9.47 ± 7.70	11.0 ± 6.03	.55
UPDRS off score‡	26.71 ± 9.94	26.87 ± 9.43	.97

Abbreviations: TT, testosterone therapy; UPDRS, Unified Parkinson Disease Rating Scale.
SI conversion factor: To convert total testosterone to nanomoles per liter, multiply by 0.0347.
*Data are given as mean ± SD unless otherwise indicated.
†Based on 2-sample *t* tests between the 2 groups.
‡UPDRS off indicates at least 12 hours without any Parkinson disease medications.

have been more therapeutically challenging.[7] Previously, we reported that testosterone deficiency was more common in patients with PD compared with age-matched control subjects.[3] We also reported in 2 small open-label studies that some nonmotor symptoms respond favorably to testosterone therapy (TT).[8] We endeavored in this study (the Testosterone Therapy in PD Trial [TEST-PD]) to conduct a double-masked, placebo-controlled, parallel-group, single-center trial to define the effects of TT on nonmotor and motor symptoms in men with PD and probable testosterone deficiency.

METHODS

Patients for the study were recruited from the University of Florida Movement Disorders Center, Gainesville. All patients signed an institutional review board–approved informed consent form before participation. Inclusion criteria were age older than 45 years, male sex, diagnosis of idiopathic PD by a movement disorders specialist using published criteria, and free testosterone level less than 100 pg/mL (borderline testosterone deficiency range). Criteria for exclusion included prostate-specific antigen level greater than 4.0 ng/mL; history of prostate cancer; abnormal findings at digital rectal examination; hematocrit higher than 49% (elevated); liver enzyme (alanine aminotransferase and aspartate aminotransferase) levels more than 2 times the upper limit of normal; abnormal thyrotropin, prolactin, or morning cortisol levels; Mini-Mental State Ex-

amination score less than 26; poorly controlled diabetes mellitus (glycosylated hemoglobin level >7.5 or taking insulin); sleep apnea; congestive heart failure; and any neurologic or neuromuscular disorder other than PD.

Subjects were divided into 2 experimental groups: patients with PD who were receiving TT (n = 15) and patients with PD who were receiving placebo (n = 15). Subjects received either the study drug by intramuscular injection (200 mg/mL of testosterone enanthate every 2 weeks for 8 weeks) or placebo (saline injections), administered by a nurse who was not involved in data collection for the study. A summary of the study visits for both the TT group and the placebo group is shown in **Figure 1**. Serum testosterone concentrations were obtained in patients in each group at each study visit (before 10 AM). During 2 study visits, testosterone levels were blindly evaluated and the intramuscular testosterone dose was increased by 200 mg/mL if the free testosterone level, measured at the baseline visit, failed to double (doubling of the level was chosen to ensure that clinically relevant changes in testosterone occurred in the treatment group). Testosterone levels at each study visit were measured twice, 30 minutes apart, and the average of the 2 values was used to make study-related decisions about dosage increases.

Each subject participated in the study for 8 weeks. At the baseline visit, all blood samples were drawn, including blood for determination of testosterone level. Screening questionnaires were completed. The remainder of the double-blind portion of the study was divided into 5 study visits at 2-week intervals. Testosterone was administered at the end of each study visit (visits 1-4). To assess the general testosterone deficiency features and func-

tional well-being, the following questionnaires were administered serially at various times: the St Louis Testosterone Deficiency Questionnaire[9] (primary outcome measure), the Massachusetts Male Aging Study Questionnaire,[10] the Multidimensional Fatigue Inventory,[11] the Sickness Impact Profile,[12] and the Parkinson's Disease Questionnaire (PDQ-39).[13] To assess behavioral features, the Geriatric Depression Scale (GDS),[14,15] the State-Trait Anxiety Inventory,[15] and the Visual Analog Mood Scale[16] were administered. To assess motor function, all subjects underwent a videotaped Unified Parkinson's Disease Rating Scale (UPDRS)[17] evaluation (UPDRS off, ie, at least 12 hours without any PD medications, and UPDRS on, ie, 1 hour after taking usual PD medications) with blind ratings by a neurologist trained in movement disorders. To track cognitive status, a comprehensive neuropsychologic battery of tests[18] was administered, including the Mini-Mental State Examination[19]; controlled oral word association task[18,20]; block design subtest of the Wechsler Adult Intelligence Scale; Mental Rotations Test; digit span subtest of the Wechsler Memory Scale; visual span subtest of the Wechsler Memory Scale (3rd ed)[21-24]; and the Subject Ordered Pointing Task,[25-27] Trail Making Test,[18,28] Stroop task test,[29] and Hopkins Verbal Learning Test.[30] Each test administered was analyzed using means (SDs) for each group. Simple repeated analysis of variance measures were calculated, with the testing time (before and after study drug) used as the within-subjects variable and the treatment group (testosterone vs placebo) as the between-subjects variable. Following the blinded portion of the study, all patients were offered open-label TT and were followed up clinically at 3-month intervals.

RESULTS

DEMOGRAPHICS

A summary of patient characteristics is given in **Table 1**. There were no significant differences between the TT and control groups except that, although both groups were testosterone deficient, the placebo group had lower baseline levels.

SAFETY

A summary of adverse events comparing the TT vs the control group is given in **Table 2**. The most frequent adverse event was a change or worsening of motor symptoms of PD, but there was no statistically significant difference between the TT and placebo groups (23.3% vs 26.7%). Testosterone was generally well tolerated. More subjects in the TT group compared with the placebo group had lower extremity edema (40% vs 20%). Other notable adverse effects between groups included epistaxis (13% vs 0%), falling (20% vs 7%), increased libido (20% vs 7%), and increased dyskinesia (13% vs 0%). In 2 patients, 1 in each group, prostate-specific antigen levels were elevated from baseline beyond the 4.0 ng/mL required for study enrollment; elevated absolute levels were 4.6 ng/mL in the patient in the TT group and 5.5 ng/mL in the patient in the placebo group.

PRETREATMENT VS POSTTREATMENT DATA IN THE STUDY AND PLACEBO GROUPS

A summary of pretreatment data vs posttreatment data in both the TT and placebo groups is given in **Table 3**.

Table 2. Adverse Events in the Testosterone Therapy (TT) Group Compared With the Placebo Group

Adverse Event	TT Group, No. (%)	Placebo Group, No. (%)
Worsening of dyskinesias*	2 (6.7)	0
Increase in PSA†	1 (3.3)	1 (3.3)
Change or worsening of PD	7 (23.3)	8 (26.7)
Edema	6 (20)	3 (10)
Worsening of gait	5 (16.7)	5 (16.7)
Fatigue	3 (10)	3 (10)
Increased libido	3 (10)	1 (3.3)
Sleep disturbance	2 (6.7)	2 (6.7)
Bleeding	2 (6.7)	1 (3.3)
Change in behavior	2 (6.7)	1 (3.3)
Coryza	2 (6.7)	0
Increased perspiration	2 (6.7)	0
Numbness	2 (6.7)	0
Pain	1 (3.3)	3 (10)
Cramps	1 (3.3)	2 (6.7)
Flulike symptoms	1 (3.3)	1 (3.3)
Constipation	1 (3.3)	1 (3.3)
Visual changes	1 (3.3)	1 (3.3)
Hypertension	1 (3.3)	1 (3.3)
Increased salivation	1 (3.3)	1 (3.3)
Restless leg syndrome	1 (3.3)	1 (3.3)
Nausea	1 (3.3)	1 (3.3)
Angular cheilitis (recurrence)	1 (3.3)	0
Asthenia	1 (3.3)	0
Chipped tooth	1 (3.3)	0
Dizziness	1 (3.3)	0
Hallucination	1 (3.3)	0
Increased sensitivity to temperature	1 (3.3)	0
"Medicine" taste in mouth	1 (3.3)	0
Vivid dreaming	1 (3.3)	0
Arthralgia	0	3 (10)
Headache	0	3 (10)
Rash	0	3 (10)
GI tract disturbance	0	2 (6.7)
Worsening of cognition	0	2 (6.7)
Dry mouth	0	2 (6.7)
Arrhythmia	0	1 (3.3)
Diarrhea	0	1 (3.3)
Dysphagia	0	1 (3.3)
Difficulty with speech	0	1 (3.3)
Drowsiness	0	1 (3.3)
Dry eyes	0	1 (3.3)
Cough	0	1 (3.3)
Shortness of breath	0	1 (3.3)
Hirsutism	0	1 (3.3)

Abbreviations: GI, gastrointestinal; PD, Parkinson disease; PSA, prostate-specific antigen.
*Dyskinesias were rated moderate to severe and required change in PD medication regimen.
†Asymptomatic elevation in PSA level resulted in referral to a urologist for full evaluation.

TESTOSTERONE SERUM CONCENTRATIONS

Study subjects enrolled in the TT arm had a significant increase in testosterone levels from baseline to final visit ($P<.02$). A dosage increase was required in 15 patients in the TT group at visit 3 and in 4 patients at visit 4. The dosage was adjusted to ensure a minimum doubling of the free testosterone level in all subjects assigned to the TT group.

Table 3. Results of Baseline Measurements Compared With Posttreatment Measurements*†

Examination/Test	Control Group		TT Group		P Value‡
	Pretreatment	Posttreatment	Pretreatment	Posttreatment	
St Louis Testosterone Deficiency Scale, total score	7.00 ± 1.51	5.87 ± 2.95	7.62 ± 1.50	5.92 ± 2.29	.56
PDQ-36, mobility score	36.33 ± 30.06	27.50 ± 28.32	32.68 ± 25.52	33.93 ± 27.17	.02
SIP, sleep score	29.12 ± 21.31	20.07 ± 17.42	23.86 ± 25.68	33.77 ± 21.77	.006
SIP, home score	22.16 ± 22.22	14.16 ± 13.90	25.07 ± 21.58	32.80 ± 29.95	.08
HVLT score	−0.998 ± 1.10	−1.22 ± 0.66	−0.51 ± 1.11	−0.05 ± 0.85	.04
Backward Visual Span subtest score	54.53 ± 28.98	38.93 ± 27.92	50.00 ± 28.53	57.07 ± 20.51	.03

Abbreviations: HVLT, Hopkins Verbal Learning Test; PDQ-36, Parkinson's Disease Questionnaire; SIP, Sickness Impact Profile; TT, testosterone therapy.

*Table gives the results of the primary outcome variable, the St Louis Testosterone Deficiency Scale score, and the results of any subscale that showed a significant change. These included the scores for the following: PDQ-39 subscale for mobility, the SIP subscales for sleep and home functioning, the HVLT, and the Backward Visual Span subtest. Simple repeated analysis of variance measurements were calculated with the testing time (before study drug and after study drug) used as the within-subjects variable and TT group (TT group vs placebo group) as the between-subjects variable.

†Data are given as mean ± SD.

‡Based on 2-sample t tests (based on the difference between the TT and placebo groups for improvements that were defined as the arithmetic difference of pretreatment and posttreatment data).

TESTOSTERONE DEFICIENCY SCALES

The study was powered to determine a 25% difference between the scores on the St Louis Testosterone Deficiency Scale before and after treatment between the TT and placebo groups. No significant change was detected between the groups. There was a significant improvement in question 5 ($P<.007$) (Have you noticed decreased enjoyment in your life?) and question 9 ($P<.04$) (Have you noted a recent deterioration in your ability to play sports?) in the TT group compared with the placebo group. There were no significant changes before or after treatment in the Massachusetts Male Aging Study Questionnaire.

QUALITY OF LIFE AND FATIGUE SCALES

No significant changes on the PDQ-39 were noted in the TT group. The placebo group demonstrated improvement in the mobility subscale of the PDQ-39 ($P<.02$). The TT group exhibited worsening in both the Sickness Impact Profile sleep and home functioning subsections, whereas the placebo group showed improvements in the same 2 subscales ($P<.006$ and $P<.02$, respectively). No significant changes were seen in the subscales of the Multidimensional Fatigue Inventory.

MOOD AND COGNITIVE TESTING

No significant changes were noted in any mood scales (Geriatric Depression Scale, State-Trait Anxiety Inventory, and Visual Analog Mood Scale). Scores on the Hopkins Verbal Learning Test initial encoding trial 1 were significantly improved in the TT group compared with the placebo group ($P<.03$), as was the backward visual span (Corsi blocks) ($P<.03$). No significant changes were found in any of the remaining cognitive scales (Controlled Oral Word Association task; block design subtest of the Wechsler Adult Intelligence Scale; Mental Rotations Test; digit span subtest of the Wechsler Memory Scale; visual span subtest of the Wechsler Memory Scale [3rd ed]; and Subject Ordered Pointing Task, Trail Making Test, and Stroop test).

MOTOR TESTING

No significant changes were seen in the UPDRS testing (blinded video review of on-off evaluations before and after treatment).

OTHER ANALYSES

Repeated-measures analyses of variances and linear regression analyses were performed on all scales administered at each of the 5 study visits, and no significant changes were identified. A subanalysis (repeat analysis of the entire study data set) was also performed in patients in both groups with the lowest baseline testosterone levels (<330 ng/dL [<11.4 nmol/L]), and no significant changes were found (this subanalysis was underpowered because of small sample size).

OPEN-LABEL FOLLOW-UP

Subjects in the TT group in the open-label phase of the study who elected to continue TT (n=6) showed a delayed, but sustained, improvement in the St Louis Testosterone Deficiency Scale at the end of 3 and 6 months compared with subjects in the placebo group who chose not to receive TT (n=3) (**Figure 2**). In addition, analysis of the subjects who were originally randomized to the placebo group who later chose to receive TT in the open-label phase (n=3) showed further improvement in the St Louis Testosterone Deficiency Scale at 3- and 6-month follow-up visits (**Figure 3**).

COMMENT

Testosterone therapy was administered safely and was generally well tolerated by the elderly male subjects with PD in this study. There was no sustained elevation of prostate-specific antigen levels, prostate cancer, or seri-
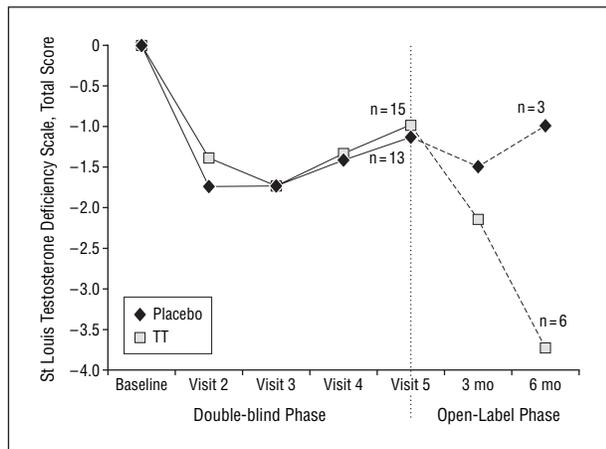
Figure 2. Open-label follow-up phase of patients after the 8-week study (completed at visit 5) shows that patients who continued to receive testosterone therapy (TT) (n=6) continued to demonstrate a downward trend at the 3- and 6-month data points. The graph displays the change from baseline in the St Louis Testosterone Deficiency Questionnaire.
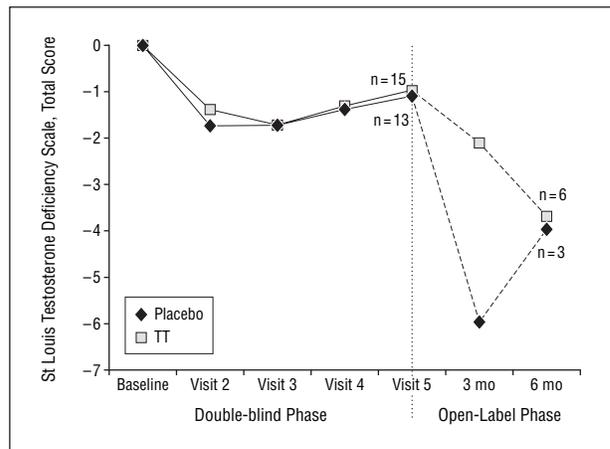

Figure 3. After visit 5 (8-week study completion point), both the testosterone therapy (TT) group (n=6) and the group who switched to testosterone therapy during an open-label phase (n=3) showed improvement in St Louis Testosterone Deficiency Questionnaire scores.

ous adverse events in either the TT or the placebo group.

The results of this study reveal an improvement in the TT group compared with the placebo group (1.7 vs 1.1) on the St Louis Testosterone Deficiency Scale; however, it was not statistically significant. There were no significant differences in motor and nonmotor features of PD in men with possible testosterone deficiency who received TT. Because large numbers of statistical tests were conducted in a small sample, the few significant differences that were found between groups were likely chance findings, especially since there was no clear direction of effects. There is a possibility that, given a larger number of study subjects, quality-of-life measures such as those for sleep and home functioning may worsen with TT, and this will require a better-powered study. These results raise an important question as to why testosterone levels in patients with PD who are possibly testosterone deficient fail to improve with TT, whereas similar groups of elderly patients seem to demonstrate improvement.[31-33] Potential explanations include small sample size; strong placebo effect, especially with intramuscular delivery of TT; heterogeneous speed of response to TT in patients with PD; and short duration of follow-up. The continued improvement in the St Louis Testosterone Deficiency Scale scores in subjects in the TT group during the long-term, open-label phase suggests a delay in response in at least some patients with PD. The self-selected group in the open-label phase may have exhibited a strong placebo effect because of their awareness that they were receiving active treatment. Thus, future testosterone studies in this population might benefit from a longer duration of observation. On the other hand, analysis of the subjects who were originally randomized to receive placebo who later chose to receive TT in the open-label phase showed immediate and sustained improvement in the St Louis Testosterone Deficiency Scale, which suggests heterogeneity in the rapidity of response to TT in this population.

Another potential explanation for these findings is the recent and significant pathologic changes seen in postmortem hypothalamic analysis of brains from patients with PD.[34-39] These pathologic changes may affect both dis-

ease symptoms and potential treatments such as TT; however, the relationship between pathologic findings, symptoms, and response to therapy remains to be investigated.

The diagnosis of hypogonadism in older men is controversial and could have affected the results of this study. The American Association of Clinical Endocrinologists defines definite testosterone deficiency as an early morning serum total testosterone level less than 200 ng/mL (<6.9 mmol/L) with symptoms typical of hypogonadism (eg, loss of libido, erectile dysfunction, and loss of energy).[40] The standard accepted by the US Food and Drug Administration for the administration of TT is a serum total testosterone concentration less than 300 ng/dL (10.4 mmol/L).[41] The patients in the TT arm of our study had a baseline mean serum total testosterone concentration of 375 ng/dL (13.0 mmol/L). Thus, patients in our TT group had borderline hypogonadism. Bioavailable testosterone is the most accurate measurement,[42] and future studies of testosterone in PD should consider using a bioavailable marker and selecting subjects with testosterone levels clearly in the deficient range.

Testosterone levels decline with normal aging, even in healthy men.[43] Cross-sectional and longitudinal studies have confirmed this decline, although the rate of decline can differ among individuals.[43-50] Twenty percent or more of elderly men will experience a decline in testosterone level to the extent that symptoms of testosterone deficiency develop that may include frontal lobe dysfunction, memory impairment, depressed mood, and fatigue or apathy.[43,49] The Rancho-Bernardo Study[51] was performed using a cross-sectional design and examined age-associated variations in total and bioavailable testosterone. Samples from 810 men aged 24 to 90 years were examined for testosterone deficiency. Bioavailable testosterone decreased significantly with age, independent of covariates.[52] In a longitudinal analysis, Harman et al[43] examined testosterone levels in 890 men in the Baltimore Longitudinal Study on Aging. Independent, age-invariant, longitudinal effects of age on testosterone level were found. Several studies have shown improvements in elderly men with TT; however, when examining only

placebo-controlled studies in patients older than 65 years, TT failed to show significant improvements in mood, cognition, or sexual function.[53] Age may also have affected the results of our study.

Other limitations of this study include the following: other scales were underpowered to detect changes on scales other than the St Louis Testosterone Deficiency Scale; the stage of disease was not considered carefully in the inclusion criteria; testosterone interaction with dopaminergic medications was not considered; and 2 averaged free testosterone levels were used rather than a bioavailable level.

Future directions for the study of testosterone deficiency in PD will need to include investigations of epidemiology, the role of hormones in neurodegeneration, and the effects of pathologic findings and hypothalamic function in PD on testosterone. The results of this study can be used in construction of a larger placebo-controlled study of TT in PD. This potential study should have a longer follow-up period to avoid placebo effects and should use bioavailable testosterone levels, which are a more reliable blood marker for testosterone deficiency. Testosterone therapy should not be routinely administered in patients with PD with symptoms of probable testosterone deficiency. Suspicion of testosterone deficiency in this population should be followed up by obtaining a bioavailable testosterone level and referring the patient to a medical expert for an examination and discussion of the substantial risks of TT.

Author Affiliations: Departments of Neurology (Drs Okun, Fernandez, Rodriguez, Foster, Shenal, and Crucian, Messrs Armaghani and Jacobson, and Mss Romrell, Suelter, and Munson), Neurosurgery (Dr Okun), and Psychiatry (Dr Okun), University of Florida Movement Disorders Center, McKnight Brain Institute, Gainesville; Gertude H. Sergievsky Center, College of Physicians and Surgeons, Columbia University Medical Center, New York, NY (Drs Okun and Louis); Departments of Medicine and Geriatrics, Geriatric Research, Education, and Clinical Center, Malcolm Randall Veterans Affairs Hospital and University of Florida (Dr Mulligan); and Division of Biostatistics, College of Medicine, University of Florida (Dr Wu).
Correspondence: Michael S. Okun, MD, Department of Neurology, University of Florida Movement Disorders Center, McKnight Brain Institute, PO Box 100236, Gainesville, FL 32610 (okun@neurology.ufl.edu).

REFERENCES

1. Harman SM, Tsitouras P. Reproductive hormones in aging men, I: measurement of sex steroids, basal luteinizing hormone, and Leydig cell response to human chorionic gonadotropin. *J Clin Endocrinol Metab*. 1980;51:35-41.
2. Okun MS, DeLong MR, Hanfelt J, Gearing M, Levey A. Plasma testosterone levels in Alzheimer and Parkinson diseases. *Neurology*. 2004;62:411-413.
3. 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.
4. Hogervorst E, Bandelow S, Combrinck M, Smith AD. Low free testosterone is an independent risk factor for Alzheimer's disease. *Exp Gerontol*. 2004;39:1633-1639.
5. Markianos M, Panas M, Kalfakis N, Vassilopoulos D. Plasma testosterone in male patients with Huntington's disease: relations to severity of illness and dementia. *Ann Neurol*. 2005;57:520-525.
6. Nutt JG, Wooten GF. Clinical practice. Diagnosis and initial management of Parkinson's disease. *N Engl J Med*. 2005;353:1021-1027.
7. Lang AE, Obeso JA. Challenges in Parkinson's disease: restoration of the nigrostriatal dopamine system is not enough. *Lancet Neurol*. 2004;3:309-316.
8. Okun MS, Walter BL, McDonald WM, et al. Beneficial effects of testosterone replacement for the nonmotor symptoms of Parkinson disease. *Arch Neurol*. 2002;59:1750-1753.
9. Morley JE, Charlton E, Patrick P, et al. Validation of a screening questionnaire for androgen deficiency in aging males. *Metabolism*. 2000;49:1239-1242.
10. Smith KW, Feldman HA, McKinlay JB. Construction and field validation of a self-administered screener for testosterone deficiency (hypogonadism) in ageing men. *Clin Endocrinol (Oxf)*. 2000;53:703-711.
11. Zenzola A, Masi G, De Mari M, Defazio G, Livrea P, Lamberti P. Fatigue in Parkinson's disease. *Neurol Sci*. 2003;24:225-226.
12. Bergner M, Bobbitt RA, Pollard WE, Martin DP, Gilson BS. The Sickness Impact Profile: validation of a health status measure. *Med Care*. 1976;14:57-67.
13. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The Parkinson's Disease Questionnaire (PDQ-39): development and validation of a Parkinson's disease summary index score. *Age Ageing*. 1997;26:353-357.
14. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res*. 1982;17:37-49.
15. Vedana L, Baiardi P, Sommaruga M, et al. Clinical validation of an anxiety and depression screening test for intensive in-hospital rehabilitation. *Monaldi Arch Chest Dis*. 2002;58:101-106.
16. Stern RA. Assessment of mood states in neurodegenerative disease: methodological issues and diagnostic recommendations. *Semin Clin Neuropsychiatry*. 1996;1:315-324.
17. Martinez-Martin P, Gil-Nagel A, Gracia LM, Gomez JB, Martinez-Sarries J, Bermejo F; the Cooperative Multicentric Group. Unified Parkinson's Disease Rating Scale characteristics and structure. *Mov Disord*. 1994;9:76-83.
18. Lezak MD, Howieson DB, Loring DW. *Neuropsychological Assessment*. New York, NY: Oxford University Press; 2004.
19. Tinklenberg J, Brooks JO III, Tanke ED, et al. Factor analysis and preliminary validation of the Mini-Mental State Examination from a longitudinal perspective. *Int Psychogeriatr*. 1990;2:123-134.
20. Eslinger PJ, Damasio AR, Benton AL, Van Allen M. Neuropsychologic detection of abnormal mental decline in older persons. *JAMA*. 1985;253:670-674.
21. Amolsch TJ, Henrichs TF. Behavioral correlates of WAIS profile patterns: an exploratory study. *J Pers Assess*. 1975;39:55-63.
22. Howard AR. Further validation studies of the Wechsler Memory Scale. *J Clin Psychol*. 1954;10:164-167.
23. Leli DA, Filskov SB. Actuarial assessment of Wechsler Verbal-Performance Scale

differences as signs of lateralized cerebral impairment. *Percept Mot Skills*. 1981; 53:491-496.

24. Wechsler D. *Wechsler Memory Scale, Manual*. 3rd ed. San Antonio, Tex: Psychological Corp; 1997.

25. Petrides M. Frontal lobes and behavior. *Curr Opin Neurobiol*. 1994;4:207-211.

26. Petrides M. Impairments on nonspatial self-ordered and externally ordered working memory tasks after lesions of the mid-dorsal part of the lateral frontal cortex in the monkey. *J Neurosci*. 1995;15:359-375.

27. Petrides M, Pandya DN. Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. *Eur J Neurosci*. 1999;11:1011-1036.

28. Spreen O, Strauss E. *A Compendium of Neuropsychological Tests*. 2nd ed. New York, NY: Oxford University Press; 1998.

29. Rubino IA, Fedeli B, Zanna V, Fortuna E. A multivariate study of the Serial Color-Word Test. *Percept Mot Skills*. 1997;84:275-282.

30. Hogervorst E, Combrinck M, Lapuerta P, Rue J, Swales K, Budge M. The Hopkins Verbal Learning Test and screening for dementia. *Dement Geriatr Cogn Disord*. 2002;13:13-20.

31. Tenover JL. Experience with testosterone replacement in the elderly. *Mayo Clin Proc*. 2000;75(suppl):S77-S82.

32. Tenover JS. Prevalence and management of mild hypogonadism: introduction. *Int J Impot Res*. 2003;15(suppl 4):S1-S2.

33. Tenover JL. Testosterone replacement therapy in older adult men. *Int J Androl*. 1999;22:300-306.

34. Braak H, Ghebremedhin E, Rub U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. *Cell Tissue Res*. 2004;318: 121-134.

35. Braak H, Braak E. Pathoanatomy of Parkinson's disease. *J Neurol*. 2000;247(suppl 2):II3-II10.

36. Wakabayashi K, Takahashi H. Neuropathology of autonomic nervous system in Parkinson's disease. *Eur Neurol*. 1997;38(suppl 2):2-7.

37. Nakamura S, Ohnishi K, Nishimura M, et al. Large neurons in the tuberomammillary nucleus in patients with Parkinson's disease and multiple system atrophy. *Neurology*. 1996;46:1693-1696.

38. Kremer HP, Bots GT. Lewy bodies in the lateral hypothalamus: do they imply neuronal loss? *Mov Disord*. 1993;8:315-320.

39. Kremer HP. The hypothalamic lateral tuberal nucleus: normal anatomy and changes in neurological diseases. *Prog Brain Res*. 1992;93:249-261.

40. American Association of Clinical Endocrinologists. American Association of Clinical Endocrinologists Medical Guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients–2002 update. *Endocr Pract*. 2002;8:440-456.

41. Hanna KE. No fountain of youth: FDA and NIH review off-label use of hormones. *Hastings Cent Rep*. 2003;33:8-9.

42. Morley JE, Patrick P, Perry HM III. Evaluation of assays available to measure free testosterone. *Metabolism*. 2002;51:554-559.

43. 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. *J Clin Endocrinol Metab*. 2001;86:724-731.

44. Gray A, Berlin JA, McKinlay JB, Longcope C. An examination of research design effects on the association of testosterone and male ageing: results of a meta-analysis. *J Clin Epidemiol*. 1991;44:671-684.

45. Vermeulen A. Clinical review 24: androgens in the aging male. *J Clin Endocrinol Metab*. 1991;73:221-224.

46. Vermeulen A. Environment, human reproduction, menopause, and andropause. *Environ Health Perspect*. 1993;101(suppl 2):91-100.

47. Vermeulen A, Kaufman JM. Ageing of the hypothalamo-pituitary-testicular axis in men. *Horm Res*. 1995;43:25-28.

48. Tal S, Berner Y, Levy S. Influence of estrogen replacement therapy on cognitive function and dementia in postmenopausal women [in Hebrew]. *Harefuah*. 1999; 137:636-639.

49. Tenover JS, Matsumoto AM, Plymate SR, Bremner WJ. The effects of aging in normal men on bioavailable testosterone and luteinizing hormone secretion: response to clomiphene citrate. *J Clin Endocrinol Metab*. 1987;65:1118-1126.

50. Tenover JS, Bremner WJ. The effects of normal aging on the response of the pituitary-gonadal axis to chronic clomiphene administration in men. *J Androl*. 1991;12:258-263.

51. Barrett-Connor E, Von Muhlen DG, Kritz-Silverstein D. Bioavailable testosterone and depressed mood in older men: the Rancho Bernardo Study. *J Clin Endocrinol Metab*. 1999;84:573-577.

52. Ferrini RL, Barrett-Connor E. Sex hormones and age: a cross-sectional study of testosterone and estradiol and their bioavailable fractions in community-dwelling men. *Am J Epidemiol*. 1998;147:750-754.

53. Krause W, Mueller U, Mazur A. Testosterone supplementation in the aging male: which questions have been answered? *Aging Male*. 2005;8:31-38.

Call for Papers

ARCHIVES Express

ARCHIVES EXPRESS

The ARCHIVES launched a new *ARCHIVES Express* section in the September 2000 issue. This section will enable the editors to publish highly selected papers within approximately 2 months of acceptance. We will consider only the most significant research, the top 1% of accepted papers, on new important insights into the pathogenesis of disease, brain function, and therapy. We encourage authors to send their most exceptional clinical or basic research, designating in the cover letter a request for expedited *ARCHIVES Express* review. We look forward to publishing your important new research in this accelerated manner.

Roger N. Rosenberg, MD