Beneficial Effects of Testosterone Replacement for the Nonmotor Symptoms of Parkinson Disease

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Objective: To investigate whether a single daily dose of testosterone replacement gel has beneficial effects on testosterone deficiency symptoms, cognitive function, nonmotor symptoms of Parkinson disease (PD), and motor symptoms of PD.

Background: Recently it has been observed that testosterone replacement therapy improves refractory nonmotor symptoms in testosterone-deficient men with PD. Many of the symptoms of testosterone deficiency are nonspecific and overlap with the nonmotor symptoms of PD, such as decreased enjoyment of life, lack of energy, sexual dysfunction, and depression. Replacement therapy for men with PD and comorbid testosterone deficiency may be an important addition to antiparkinsonian management strategies.

Methods: A prospective open-labeled pilot study of testosterone topical gel (5 g of AndroGel; Unimed Pharmaceutical Inc, Deerfield, Ill) administered daily to testosterone-deficient (free testosterone <80 pg/mL) men with PD. All 10 patients were followed up for 1 month and 6 patients were followed up for a total of 3 months. Patients were administered a battery of testosterone deficiency questionnaires, cognitive studies, and scales of PD nonmotor and motor function at baseline, 1, and 3 months.

Results: With the daily transdermal testosterone gel, patients had an average increase in levels of free testosterone from baseline (53 pg/mL) to a 1-month follow-up visit (131 pg/mL; $P=.06$) and to a 3-month follow-up visit (98 pg/mL; $P=.04$). Testosterone deficiency symptoms improved in these patients (St Louis Testosterone Deficiency Questionnaire) from baseline (7.9 deficiency symptoms) to 1 month (5.6 deficiency symptoms, $P=.04$) and 3 months (5.8 deficiency symptoms, $P=.08$). The Unified Parkinson's Disease Rating Scale IV showed improvement at 1 month ($P=.008$). Additionally, there were trends toward improvement in the following scales: Unified Parkinson's Disease Rating Scale I at the 3-month follow-up ($P=.09$), Letter Fluency at the 3-month follow-up ($P=.08$), and the Hamilton Anxiety Scale at the 1-month follow-up ($P=.09$).

Conclusions: A daily dose of transdermal testosterone gel improved testosterone deficiency symptoms in men with PD. Although there were trends in improvement in other nonmotor and motor symptoms of PD, future placebo control studies will need to be powered to answer these important questions. Whether testosterone deficiency is simply a comorbidity in PD or whether it plays a role in the pathogenesis of disease also remains for future study.

Arch Neurol. 2002;59:1750-1753

TESTOSTERONE levels decline with normal aging, even in healthy men. Although the rate of decline can vary between individuals, both cross-sectional and longitudinal studies have confirmed this decline.[1-3] Some older men (20% or more depending on age) will experience a decline in testosterone levels to the extent that they will develop symptoms of testosterone deficiency, such as decreased libido, lack of energy, fatigability, and depression.[4] We recently found that similar to the general population, a large proportion of patients with Parkinson Disease (PD) in our registry had low levels of testosterone.[5] Although it has long been known that treatment of low testosterone levels can improve deficiency symptoms in men, it has not been previously appreciated that the nonmotor symptoms in PD may also respond to replacement therapy. In a small sample of patients with low testosterone levels, we observed that some of the refractory nonmotor symptoms of PD did respond to testosterone replacement therapy.[5] In this pilot study, we aimed to investigate further the effects of testosterone replacement on testosterone deficiency symptoms, cognitive and emotional function, as well as the motor and nonmotor symptoms of PD.

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The study was open labeled and prospective. Ten men with idiopathic PD defined by the United Kingdom Brain Bank Criteria,[6] who met clinical criteria for testosterone deficiency and who had low morning plasma testosterone levels (free testosterone <80 pg/mL), were enrolled in the study. The validated St Louis Testosterone Deficiency Questionnaire was used as the screening tool for testosterone deficiency symptoms.[7] This instrument requires a simple yes or no answer to questions regarding decreased libido, lack of energy, decreased strength, loss of height, decreased enjoyment in life, sadness or irritability, erectile dysfunction, falling asleep after dinner, deterioration in the ability to play sports or perform activities, and recent deterioration in work performance.

All patients signed an informed consent prior to enrollment in the study. Patients were screened for medical disorders that may have biased the results or put participants at increased risk for adverse events from testosterone therapy. Screening for endocrinopathies included thyroid function tests (free thyroxin, thyrotropin) and obtaining levels of hemoglobin A_1c, fasting blood glucose, cortisol, prolactin, follicle stimulating hormone, luteinizing hormone, sex hormone binding globulin, and prolactin. Serum hematocrit, aspartate aminotransferase, alanine aminotransferase, and prostate-specific antigen levels were evaluated to screen for factors related to treatment safety.

To be included in the study, patients had to meet the following criteria: (1) age 45 years or older, (2) male sex, (3) diagnosis of idiopathic Parkinson disease by a movement disorders specialist using UK Brain Bank Criteria,[6] (4) 5 or more St Louis Testosterone Deficiency Criteria, (5) free testosterone level less than or equal to 80 pg/mL. Patients were excluded if they had: (1) a prostate-specific antigen greater than 4.0 ng/mL, (2) a history of prostate cancer, (3) abnormal results of digital rectal examination, (4) an elevated serum hematocrit level (>49%), (5) liver enzymes (aspartate aminotransferase or alanine aminotransferase) greater than 2× normal, (6) an abnormal thyroid-stimulating hormone, prolactin, or morning cortisol level, (7) a Mini-Mental State score less than 26, (8) poorly controlled diabetes mellitus (hemoglobin A_1c >7.5% or taking insulin), (9) or the possibility of significant sleep apnea by history.

All 10 patients received a single daily dose of testosterone topical gel (5 g/d of Androgel [equivalent to 5 mg/d of testosterone]) for 1 month. Patients were instructed to apply the gel to the skin of the shoulders, chest, and abdomen. Six of the 10 patients were also followed-up for 3 months. Of the 4 patients who did not receive the 3-month follow-up, 1 was lost to follow-up, 2 discontinued the study because of unrelated medical reasons (bacterial pneumonia, new diagnosis of Hodgkin lymphoma), and 1 patient developed congestive heart failure. It is unknown whether the congestive heart failure was a result of the testosterone treatment or whether it was due to worsening of underlying coronary heart disease. The study medication in that patient was stopped as a precautionary measure.

Outcome measures included (1) testosterone deficiency symptoms by the St Louis Testosterone Deficiency Questionnaire; (2) PD motor and nonmotor symptoms as measured by the Unified Parkinson's Disease Rating Scale (UPDRS); (3) Obeso dyskinesia rating scale; (4) Parkinson's Disease 39 Quality of Life Questionnaire (PDQ39) (5) depression and anxiety as determined by the Hamilton Depression and Anxiety Questionnaires; (6) neuropsychologic function as measured by Word and Animal Fluency tests and Letter-Number Sequencing and Digit Span tests; and (7) Epworth Sleepiness Scale. These tests were administered at baseline and at 1 month and 3 months following treatment.

Average Laboratory and Clinical Scale Values at Baseline, 1-Month, and 3-Month Follow-up After Initiation of Testosterone Replacement Therapy*

Measures	Baseline	1 mo	3 mo
Testosterone, pg/mL			
Free	53.19	130.67†	97.93‡
Total	303.20	583.80‡	432.50‡
Hematocrit, %	43.02	. . .	46.57
St Louis	7.90	5.60†	5.83‡
UPDRS			
I	4.60	3.00	2.83‡
II	17.80	16.50	15.83
III	35.00	32.30	31.83
IV	3.80	2.80†	3.50
Dyskinesias	0.56	0.44	0
PDQ39	57.40	56.30	53.33
Schwab & England			
Patient	62.22	63.00	70.00
Investigator	63.00	64.00	68.33
Letter Fluency			
Correct	28.00	26.20	30.67‡
Error	3.50	3.60	2.50
Animal Fluency	15.10	13.80	14.33
Letter-Number Sequencing	5.40	5.40	6.33
Digit Span	15.44	16.78	16.33
Hamilton			
Depression			
Inclusive	13.60	12.00	10.00
Etiologic	10.40	8.10	15.00
Anxiety			
Inclusive	17.90	15.00	14.00
Etiologic	13.80	10.00‡	11.33
Epworth	12.60	11.20	13.67

*St Louis indicates St Louis Testosterone Deficiency Questionnaire; UPDRS, Unified Parkinson's Disease Rating Scale; and PDQ39, Parkinson's Disease Questionnaire 39.
†$P<.05$.
‡$P<.10$.

RESULTS

STUDY POPULATION AND TESTOSTERONE LEVELS

Ten nondemented men with PD with an average age of 70.8 years met the study screening criteria and were enrolled. Patients had an average Hoehn and Yahr "on" score of 2.7 and an average Mini-Mental State score of 28.2. Patients who took a single daily dose of testosterone replacement gel had an average increase in levels of free testosterone from baseline (53 pg/mL) to a 1-month follow-up visit (131 pg/mL, $P=.06$) and a 3-month follow-up visit (98 pg/mL, $P=.04$) (**Table 1**).

ST LOUIS TESTOSTERONE DEFICIENCY QUESTIONNAIRE

Testosterone deficiency symptoms improved from baseline (7.9 deficiency symptoms) to a 1-month follow-up visit (5.6 deficiency symptoms, $P=.04$) and a 3-month follow-up visit (5.8 deficiency symptoms, $P=.08$) (Table 1). An analysis of the responses to individual questions administered (**Figure**) revealed 20% or greater reported improvement in 7 of 10 categories.
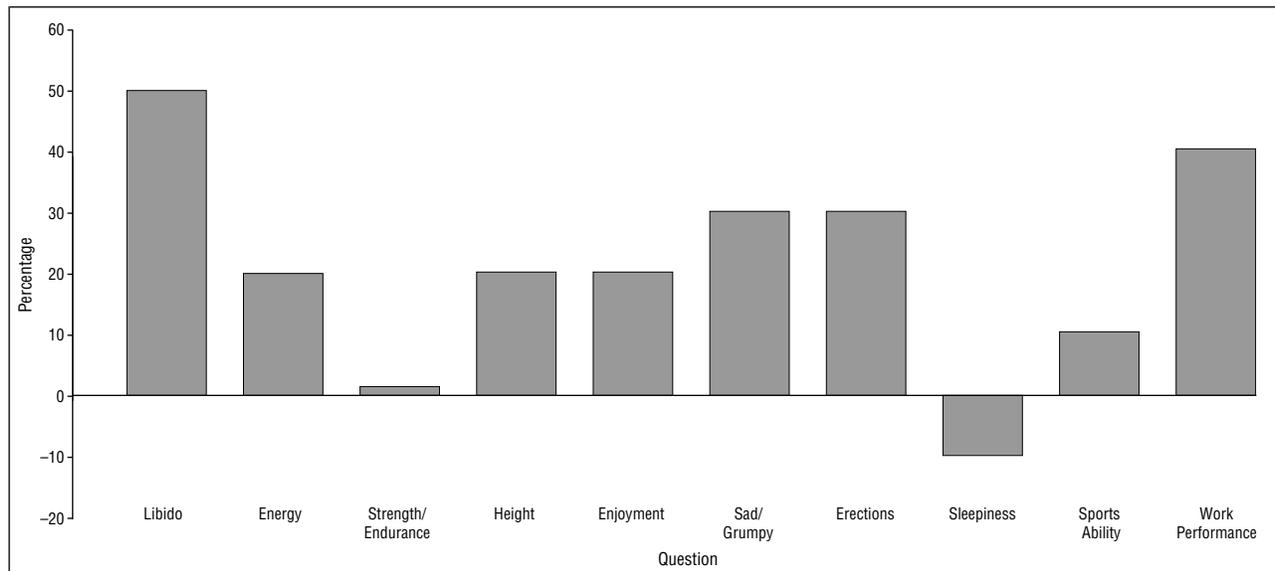
St Louis Testosterone Deficiency Scale: percentage of patients improved from baseline to 1 month, by question.

PD SYMPTOMS: UPDRS, DYSKINESIAS, PDQ39

Of the instruments used (the UPDRS scale [I, Intellectual Function/Psychosis; II, Activities of Daily Living; III, Motor; IV, Fluctuations], the Obeso dyskinesia rating scale, the Schwab and England rating scale, and the PDQ39 to measure possible changes in PD features or quality of life, only the UPDRS IV showed improvement ($P<.05$) at 1 month but did not show sustained improvement at the 3-month follow-up visit. The UPDRS I showed improvement at the 3-month follow-up visit ($P<.1$). There were no other significant changes seen on these tests (Table 1).

NEUROPSYCHOLOGIC FUNCTION, NEUROPSYCHIATRIC FUNCTION, AND SLEEP

Of the instruments used (the Letter Fluency test, Animal Fluency test, Letter-Number Sequencing test, Digit Span, Hamilton Anxiety Questionnaire, Hamilton Depression Questionnaire, and the Epworth Sleepiness scale) to measure possible changes in neuropsychologic function, neuropsychiatric function, and sleep, the Letter Fluency test showed improvement at the 3-month follow-up visit ($P<.1$), and the Hamilton Anxiety Scale (etiologic) showed improvement at the 1-month follow-up ($P<.1$). The improvement detected by the Hamilton scales was not sustained at the 3-month follow-up visit.

COMMENT

The results in this pilot study provide further evidence[5] that testosterone therapy in testosterone-deficient men with PD improves testosterone deficiency symptoms as measured by the St Louis Testosterone Deficiency Questionnaire. These symptoms are virtually identical to the nonmotor symptoms of PD. Although there was a lack of effect seen on cognition, sleep, depression, and PD symptoms, patients in this study reported improvements in categories such as energy level, enjoyment in life, and libido. These data indicate that perhaps testosterone replacement in PD has an effect on "depressive symptoms" but not on depression and cognitive symptoms as measured by the other questionnaires in this study. Future studies will need to focus on achieving better measurements of improvement in these categories. Conceivably beneficial effects on these symptoms may be seen with a longer duration of treatment or with higher levels of testosterone replacement.

One potential reason for the lack of response of the UPDRS, the quality of life scales, and the neuropsychological, psychiatric, and sleep symptoms in this pilot study may have been related to the inability to significantly increase plasma testosterone levels in several study participants. All patients were surveyed for compliance and proper application technique of the gel during the protocol and at the completion of the protocol. Although there was no evidence of poor compliance or technique of application, only 4 of 10 patients had a doubling of the plasma-free testosterone level, raising 2 important issues: (1) whether more improvement in some scales would have been evidenced with a higher dose of the medication and consequently a larger increase in the plasma testosterone level and (2) whether the benefits seen in this study were the result of a placebo effect. Serum hematocrit levels, which usually rise after administration of testosterone, were increased in 5 of 6 patients, supporting the notion that some testosterone was absorbed, albeit not enough to double the level in all patients. Future studies of the testosterone gel preparation should establish an adequate dose that achieves a desired blood level for each patient prior to follow-up testing.

It is unknown whether testosterone deficiency and PD represent independent entities that overlap and whose symptoms are simply additive, or whether testosterone deficiency is a factor in age at onset, rate of progression,

severity, and selected nonmotor and motor features of the disease. Future studies should address this concern. The failure of other PD-related scales and cognitive studies to demonstrate a response to replacement therapy may indicate that (1) these symptoms are not amenable to testosterone therapy, (2) the daily dose was inadequate, or (3) the treatment and follow-up intervals were too short. Additionally, the best vehicle for administration (gel vs intramuscular injection) was not addressed by this study. Although there were trends in improvement in other nonmotor and motor symptoms of PD, future placebo control studies will need to be powered to answer these important questions.

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