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# Testosterone level and the effect of levodopa and agonists in early Parkinson disease: results from the INSPECT cohort

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## Abstract

**Background:** To determine if testosterone levels are influenced by dopaminergic therapy in Parkinson disease (PD) patients. Testosterone level has been reported to be low in patients with PD and other neurodegenerative diseases. In this study, we sought to determine whether dopaminergic therapy (i.e. levodopa and dopamine agonist) influenced testosterone levels. We used a cohort of consecutive male patients from the INSPECT trial—a multi-center, prospective, study that primarily investigated the effects of short-term treatment with pramipexole or levodopa on [<sup>123</sup>I] B-CIT SPECT imaging in early PD.

**Methods:** Testosterone levels were drawn on consenting male subjects with early PD who enrolled in the INSPECT trial at three study visits (baseline, 12 weeks post-treatment, and 8–12 weeks post-washout). Subjects were randomized to: no treatment, pramipexole (up to 3 mg) or levodopa (up to 600 mg). Testosterone levels were obtained twice (prior to 10 AM) and averaged for each of three study visits.

**Results:** Thirty two male patients participated in this sub-study and there were no significant differences in disease characteristics in the 3 groups at baseline. Twenty-nine patients completed the follow-up visits and were suitable for analysis. There were statistically significant differences in the change in free testosterone level, increased in both the levodopa group and pramipexole group but decreased in the untreated group at 12-weeks post-treatment. There were no significant differences in the changes of UPDRS total or motor scores, although there was a strong trend toward improvement in motor scores. The testosterone level persisted in its increase only in the pramipexole group at the end of the washout period.

**Conclusion:** These preliminary data support the premise that dopaminergic medications do not reduce testosterone levels in early PD patients.

**Keywords:** Testosterone, Parkinson's disease, Levodopa, Agonist, Medications, LH

## Background

There has been mounting evidence suggesting that inappropriately low plasma testosterone levels commonly exist in male patients with Parkinson disease (PD) [1-6]. The relevance and underlying cause of this endocrine disturbance remain unknown. Additionally, replacement of testosterone has not to date been proven to significantly improve the motor and non-motor symptoms of these patients, though there have been anecdotal successes

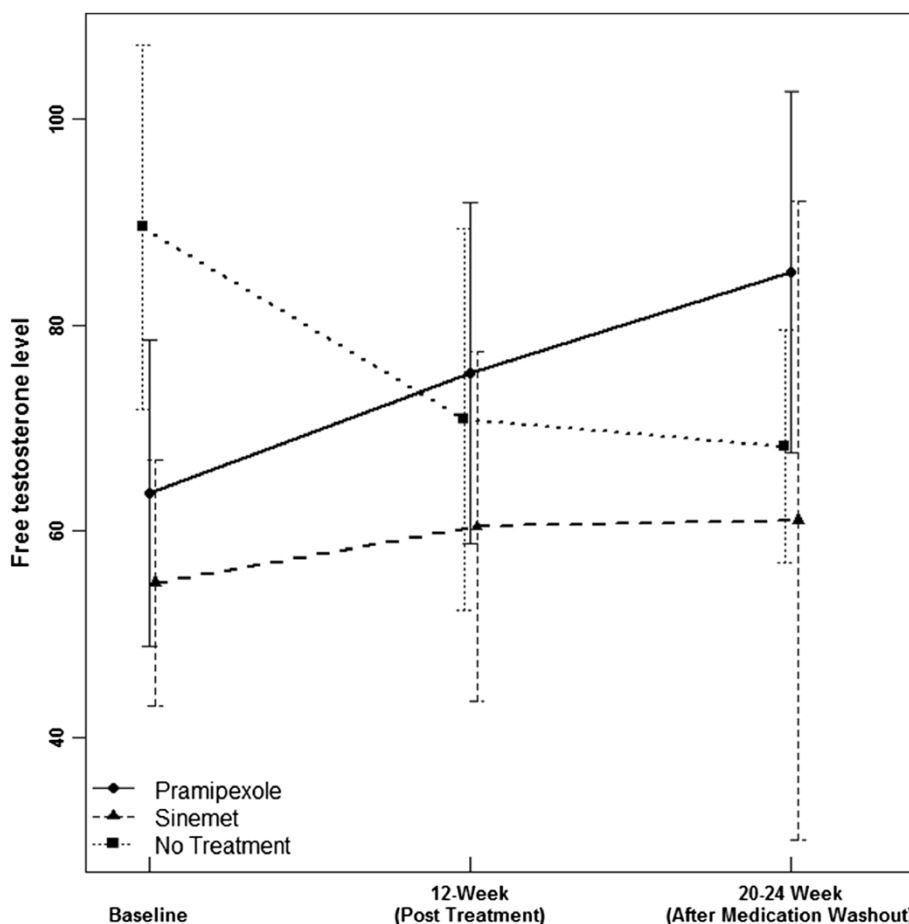
[4-7]. Two main hypotheses have been proposed to explain the low testosterone levels: the levels are reduced by dopaminergic medications, or the testosterone level is a surrogate marker for pathology known to occur in the hypothalamus and in other relevant regions of the PD brain [4]. We sought to examine the former hypothesis that dopaminergics may lower testosterone. In this study we utilized the INSPECT cohort of early PD subjects.

## Methods

Consecutive male PD patients (who fulfilled the UK Parkinson's Disease Brain Bank Criteria [8]) enrolled in the INSPECT study had plasma free and total testosterone

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**Figure 2** Mean and 95% confidence interval of the free testosterone level by time and group.

dopamine agonist group post-washout. Dopamine agonists have been used in the treatment of prolactinoma, because dopamine is a natural inhibitor of prolactin [9,10]. Prolactin lowers leutenizing hormone (LH) which in turn lowers testosterone level [11-16]. Thus, dopamine agonists may theoretically increase testosterone levels by inhibiting prolactin. This point will need further clarification.

Sinhamahapatra and Kirschner in 1971 published a detailed analysis of the effect of levodopa on testosterone

level [17]. They sought in their study to answer the question as to whether levodopa stimulated LH production and Leydig cell activity. They utilized an electron capture gas liquid chromatograph, an older technique now considered less accurate when compared to more modern techniques for measuring testosterone. Seven PD men staged using an older system devised by Leon were included in the analysis. Very high doses of levodopa were used (2–6 grams/day). There were other methodological

**Table 2** Summary of changes from baseline to 12 weeks post treatment

Group	N	Total T		UPDRS M		UPDRS T	
		Mean	SD	Mean	SD	Mean	SD
Pramipexole	10	34.80	87.33	-4.27	6.15	-5.91	7.34
Sinemet	9	-34.17	59.79	-6.11	6.77	-9.11	10.62
NoTreatment	10	21.80	74.71	0.90	6.64	-0.50	8.87
		p = 0.12		p = 0.06		p = 0.12	

Legend: Total T - total testosterone level. UPDRS M- Unified Parkinson Disease Rating Scale Motor Subsection; UPDRS T- Unified Parkinson Disease Rating Scale total score. Free testosterone measured in pg/ml, and total testosterone in ng/dl.

**Table 3** Summary of changes from baseline to the end of washout period

Group	N	Total T		UPDRS M		UPDRS T	
		Mean	SD	Mean	SD	Mean	SD
Pramipexole	7	103.79	49.47	0.89	5.62	1.56	5.29
Sinemet	7	-13.21	40.27	1.86	6.54	1.71	7.93
NoTreatment	9	100.78	104.58	0.78	8.63	-0.22	11.39
		p = 0.01		p = 0.95		p = 0.88	

Legend: Total T - total testosterone level. UPDRS M- Unified Parkinson Disease Rating Scale Motor Subsection; UPDRS T- Unified Parkinson Disease Rating Scale total score. Free testosterone measured in pg/ml, and total testosterone in ng/dl.

limitations including baseline normal levels in all patients enrolled (>325 ng/ml), and 2/7 PD patients who did not improve on levodopa. One interesting aspect of their study was the calculation of testosterone production and metabolism, as well as the measurement of LH. The study concluded that levodopa did not have an impact on plasma testosterone or LH [17]. Despite methodological limitations this data is supportive of our findings.

We suspect based on our results that the finding of low testosterone in PD patients is indicative of intrinsic PD pathology. It is well known that Lewy Body pathology is present in PD patients at post-mortem examination, and lesions includes hypothalamic involvement [18-22]. Braak has shown that this hypothalamic pathology may be present relatively early in the course of PD [18-21]. We propose this as a plausible explanation for the low testosterone levels.

There were several limitations in this study that should be addressed in future investigations. These limitations included a small sample size, the lack of non-PD controls, the use of early PD patients, differences between free and total testosterone levels, and observed changes in testosterone level were small and not likely clinically relevant. There were changes seen between free testosterone and total testosterone and this highlighted difficulties in laboratory measurements. Most experts use a free or bioavailable testosterone level as the gold standard rather than utilizing both a free and total testosterone level [23-25]. Despite these limitations we conclude as did Sinhamahapatra, that dopaminergics are probably not the cause of low testosterone in PD. Clinicians should not assume that low testosterone levels are an effect of PD medications. There is currently no evidence that checking a testosterone level prior to dopaminergic therapy will be clinically useful. We suggest that future research on this topic should focus on disease related factors as the potential culprits in the low testosterone PD story, however a larger study of the effects of medication can confirm our results.

#### Competing interests

Dr. Okun serves as a consultant for the National Parkinson Foundation, and has received research grants from NIH, NPF, the Michael J. Fox Foundation, the Parkinson Alliance, Smallwood Foundation, the Bachmann-Strauss Foundation, the Tourette Syndrome Association, and the UF Foundation. Dr. Okun has previously received honoraria, but in the past >60 months has received no support from industry. Dr. Okun has received royalties for publications with Demos, Manson, Amazon, Smashwords, Books4Patients, and Cambridge (movement disorders books). Dr. Okun is an associate editor for New England Journal of Medicine Journal Watch Neurology. Dr. Okun has participated in CME and educational activities on movement disorders (in the last 36 months sponsored by PeerView, Prime, Quantia, Henry Stewart, and by Vanderbilt University. The institution and not Dr. Okun receives grants from Medtronic, Abbvie, and ANS/St. Jude, and the PI has no financial interest in these grants. Dr. Okun has participated as a site PI and/or co-I for several NIH, foundation, and industry sponsored trials over the years but has not received honoraria. The other authors report no other relevant competing interests.

#### Authors' contributions

MSO participated in study conception. MSO, SSW, DK, JM, RLR and HHF participated in study design. MSO wrote the first draft of the manuscript. MSO, SSW, DK, JM, RLR and HHF added critical revisions to the manuscript. All authors have read and approved the final manuscript.

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