

Serum total testosterone is lower in men with Alzheimer's Disease

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Submitted: May 18, 2001
Accepted: May 18, 2001

Key words: **testosterone; hormones; Alzheimer's disease; dementia; cognition**

Neuroendocrinology Letters 2001; 22:163-168 pii: NEL220301A01 Copyright © Neuroendocrinology Letters 2001

Abstract

OBJECTIVES: The purpose of this study was to determine whether the level of serum total testosterone (TT) was different in cases of Dementia of the Alzheimer's Type (DAT) than in controls.

SETTING AND DESIGN: We included 83 referred DAT cases and 103 cognitively screened volunteers (aged 75 ± 9 years) from the Oxford Project To Investigate Memory and Ageing.

METHODS: Information was obtained about potential confounds in the relation of DAT with testosterone, including age, gender, education, body mass index, smoking, (ab)use of alcohol, diabetes mellitus, endocrine therapy, and having undergone hysterectomy. TT was measured in non-fasting serum obtained between 10 and 12 a.m. using a competitive enzyme immunoassay.

RESULTS: Men with DAT ($n=39$) had lower levels ($p=0.005$) of total serum testosterone ($TT=14 \pm 5$ nmol/L) than controls ($n=41$, $TT=18 \pm 6$ nmol/L). Lower TT was more likely in men with DAT, independent of potential confounds (Odds Ratio=0.78, 95% C.I.=0.68 to 0.91). In women there was no difference in TT levels between cases ($n=44$) and controls ($n=62$).

MAIN FINDINGS: Our results suggested that low TT may be a co-morbid feature of DAT in men. However, low TT levels could also exacerbate the disease.

CONCLUSIONS: Prospective longitudinal studies should investigate whether low TT levels precede or follow the onset of DAT (209 words).

Abbreviations:

DAT	Dementia of the Alzheimer's Type
AD	Alzheimer's Disease
TT	Total Testosterone
FT	Free Testosterone
β APP	Beta-Amyloid Precursor Protein
OPTIMA	Oxford Project To Investigate Memory and Ageing
NINCDS/ADRDA	National Institute of Neurological Disorders and Stroke / Alzheimer's Disease and Related Disorders Association
CERAD	Consortium to Establish a Registry for AD
CAMCOG	Cambridge Examination for Mental Disorders of the Elderly-Cognitive Section
MMSE	Mini-Mental Status Examination
TSH	Thyroid Stimulating Hormone
B.M.I.	Body Mass Index
HRT	Hormone Replacement Therapy
C.V.	Coefficient of Variation
O.R.	Odds Ratio
SHBG	Sex Hormone Binding Globulin
LH	luteinizing hormone
FSH	Follicle Stimulating Hormone

Introduction

It is biologically plausible that testosterone affects brain structures and functional systems which degenerate in Dementia of the Alzheimer's Type (DAT) or Alzheimer's disease (AD) [1, 2]. AD is characterised by depositions of neurofibrillary tangles and senile plaques, which are composed of hyperphosphorylated tau and aggregated β -amyloid ($A\beta$) 40/42 peptides, respectively [3]. Potential protective mechanisms of testosterone in the brain could be preventing hyperphosphorylation of tau [4], altering the β APP metabolism [5], affecting nerve growth factor [6], and indirectly, through its conversion to estradiol in the brain [7, 8]. Low levels of testosterone could theoretically lead to a decline in neuronal plasticity, structural neuronal loss and modifications of neurotransmitter functions [2–8]. These findings suggest that low levels of testosterone could be associated with AD and cognitive impairment.

Previous studies have related low levels of testosterone to cognitive dysfunction in the elderly [9, 10 but see 11]. One large study in healthy community dwelling men [10] and women [12] reported that both low total testosterone (TT) and free testosterone (FT) related to lower performance on several cognitive tests. Abassi et al. [9] found that levels of TT and FT were lower in institutionalised men than healthy, community dwelling men. However, of 13 principal diagnostic groups, only 'dementia' correlated with TT. The criteria for classifying subjects as having 'dementia (organic brain disorder)' in this study were unclear, but the other neurological diagnoses (e.g. 'cerebrovascular accident', Parkinson's disease' and

'other neurological disorders') did not correlate with TT or FT. The previous studies [9, 10] both reported that the associations of TT and FT with cognition [9] and dementia [10] were similar.

No previous study has actually tested whether patients with AD, the most common form of dementia, have lower levels of testosterone than controls. The goal of the present exploratory study was to test if patients with clinical DAT and histopathologically proven AD had lower levels of TT than cognitively screened controls and whether this association was independent of potential confounds.

Materials and methods

The present cross-sectional case-control study initially consisted of 197 participants aged 51 to 95 years from the Oxford Project To Investigate Memory and Ageing (OPTIMA) cohort [13] from whom serum was available. We excluded 11 subjects with endocrinological or related problems, i.e. those who had undergone oophorectomy (n=5 controls and n=1 DAT) or orchidectomy (n=1 DAT); those (n=1 control and n=1 DAT) with abnormal thyroid (TSH > 8 mU/L, total thyroxine > 200) or liver function (n=1 DAT) and those using medication that could interfere with gonadal steroid function (tamoxifen, n=1 DAT). No-one in this study had been diagnosed with prostate cancer, Cushing's or Addison's disease.

We thus included 56 living cases of DAT who had initially been referred by general practices because dementia was suspected. These patients had been diagnosed clinically using the National Institute of Neurological Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria (NINCDS/ADRDA [14], 'possible' and 'probable' Alzheimer's disease). We also included 27 AD cases who had met histopathological criteria of the Consortium to Establish a Registry for AD (CERAD [15] 'probable' or 'definite' AD). The accuracy of our clinical diagnoses of DAT compared to histopathologically confirmed diagnoses of AD has been found to be substantial [16]. We compared the in total 83 DAT cases with 103 elderly screened controls. These were community dwelling volunteers who had no progressive cognitive impairment. All patients and their closest relatives gave informed consent to the study, which had local ethics committee approval.

Assessments used the Cambridge Examination for Mental Disorders of the Elderly [17], which yields measures of demographic and medical variables and which also has a cognitive section: the 'CAMCOG' and the Mini-Mental Status Examination (MMSE). The CAMDEX also has a global Dementia Severity Scale, which was scored by a clinician and is a clinical judgment of the gradation of dementia. This scale

ranges from '0' no dementia to '4' severe dementia. Patients with DAT may differ from healthy aged controls in ways that can affect their testosterone levels, such as smoking habits [18–20]. Our study adjusted for demographic and medical factors that could modulate testosterone and mediate or confound the relationship between DAT and testosterone, including age [21]; weight or body mass index (B.M.I.) [22, 23]; smoking ('ever'/'never') [18–24]; the (ab)use of alcohol (regular and heavy or problem drinking either currently or in the past) [25]; endocrine treatment (all types of hormone replacement treatment; e.g. HRT, glucocorticoid (prednisone and dexamethasone) and thyroid treatment); diabetes mellitus (self-report, checked with the use of insulin) and (for women) having undergone hysterectomy [1, 26–28]. For cases, we used the response of the carer. Finally, since more DAT cases died earlier in the OPTIMA study, their serum had been stored longer. Hence, we adjusted TT data for duration of storage (in years).

We analyzed total testosterone (TT) using a competitive enzyme immunoassay (Bayer®, Bayer Corporation, 511 Benedict Avenue, Tarrytown, N.Y. 10591–5097 U.S.A.) in non-fasting blood serum samples that had been obtained between 10:00 and 12:00 hours a.m. and stored at -70°C . Inter-assay reliability for the assay was good (correlation with DPC Coat-a-Count TT radio-immunoassay=0.99). The within-run Coefficient of Variation (C.V.) varied between 1–8% and the between-day C.V. varied between 2–5% for TT in the ranges from 2 to 67 nmol/L. The minimum sensitivity for this assay was 0.17 nmol/L [29]. In men over 50 years of age the normal range for TT is 5.73–28.80 nmol/L. In post-menopausal women, the ovary and adrenal glands secrete small amounts of testosterone (normal range: 0.28–2.12 nmol / L).

We compared demographic and medical characteristics between cases and controls using non-parametric Wilcoxon Mann-Whitney z-tests and Chi-square tests. We performed stepwise linear regression analyses to investigate which demographic and medical variables predicted serum TT levels. In this analysis we also entered variables that we did not want to enter in the logistic regression, i.e. 'storage of samples' which we knew had been longer in cases and 'dementia severity' which naturally explained most of the variance of DAT presence. To assess the Odds Ratio (O.R.) and the predictive value of serum TT levels with reference to the presence of DAT, we performed stepwise backward conditional logistic regression analyses with the potential mediators or confounds. All analyses used SPSS 8.0 for Windows [30].

Results

Table I (next page) lists the characteristics of the study population. Cases and controls were matched for age and gender. Most cases had minimal (40%) to mild (20%) dementia severity and only 12.5% had dementia of a severe degree (table I). Serum TT levels were lower in male cases with clinically diagnosed DAT ($n=39$, $z=-2.835$, $p=0.005$, including the histopathologically confirmed cases) compared to male controls ($n=41$). Also men with histopathologically-proven AD ($n=20$) had lower levels of TT compared to male controls ($z=-2.773$, $p=0.006$). There were no differences in TT levels between women who had clinical DAT ($n=44$) and controls ($n=62$) ($z=1.682$, $p=0.092$), or between histopathologically confirmed women cases ($n=7$) versus controls ($z=0.73$, $p=0.465$).

Linear regression showed that the main predictors of low serum TT were female gender and DAT. None of the other variables was significant to enter the model (see table II). Since TT levels in women were low, floor effects might complicate or obscure any overall associations with DAT. To avoid this, we stratified the analyses by gender. Among men, stepwise logistic regression analyses showed that DAT related to lower serum TT, controlling for confounds (table II). For women, no variables entered the regression model.

To further investigate the association between DAT and TT, we performed post hoc Spearman's rank correlations. These showed that TT levels related positively to CAMCOG and MMSE scores in men with or without DAT ($\rho=0.355$, $p=0.001$; $\rho=0.345$, $p=0.002$) and inversely to dementia severity ($\rho=-0.318$, $p=0.004$) but not to any of the demographic or medical variables. In men with DAT, TT levels were associated with MMSE performance ($\rho=0.379$, $p=0.002$) but not with general dementia severity ($\rho=-0.131$, $p=0.43$). No associations of TT were seen with the MMSE performance or dementia severity in control men or women or in women with DAT.

Discussion

Our findings show that men with AD have lower levels of TT than controls. Our results confirm and extend the findings of previous studies relating low levels of testosterone to cognitive dysfunction in older men [9, 10]. The strength of this study is that we showed lower TT levels in histopathologically-confirmed AD cases compared with cognitively-screened controls. In the earlier studies [9, 10] no valid criteria were used to classify subjects as 'demented'. We

Table I. Characteristics at presentation in controls (Con), all patients with DAT (Cases), and histopathologically confirmed AD (Hist .AD) separately

Variable	Con (n=103)	Cases (n=83)	Hist. AD(n=27)
Demographic variables			
Age, mean (SD)	75.1 (8.9)	73.8 (8.8)	74.4 (8.0)
Years of education, mean (SD)	13.8 (3.4)	11.7 (3.4)***	12.0 (4.0)
Gender, % male	40%	47%	71%**
Current smokers, %	18%	24%	22%
Regular alcohol drinkers, %	22%	25%	30%
Heavy and problem drinkers, %	9%	18%	21%
Cognitive decline			
CAMCOG (max 107), mean (SD)	99.3 (5.6)	44.8 (26.7)***	32.7 (23.8)***
MMSE score (max 30), mean (SD)	28.1 (2.0)	12.7 (7.9)***	10.2 (7.4)***
Dementia severity (0-4) mean (SD)	0 (0)	2.0 (1.2)***	2.8 (1.1)***
Medical variables			
Hysterectomy (ovaries intact), %	13%	11%	4%
HRT never users, % (women only)	87%	93%	100%
HRT current users, % (women only)	10%	5%	0%
Thyroid medication users,%	9%	12%	13%
Anti-thyroid medication, %	2%	1%	0%
Glucocorticoid users, %	4%	0%	0%
Diabetes Mellitus, %	4%	4%	4%
Body Mass Index (kg/m2) Mean (SD)	25.8 (3.8)	25.0 (3.8)	24.2
Biochemical variables, mean (SD)			
Duration of sample storage	1.6 (1.1)	3.1 (2.6)**	5.6 (2.3)**
Testosterone (men), nmol /L	18.0 (6.0)	14.3 (5.2)**	14.0 (5.2)*
Testosterone (women), nmol /L	0.88 (0.56)	0.97 (0.46)	1.0 (0.63)

*: P<0.05
 ** P<0.01
 ***P<0.001

Table IIa. Stepwise linear regression analyses showing the variables that predicted the level of serum TT (including duration of sample storage, age, B.M.I., dementia severity, alcohol (ab)use, moking, HRT use, glucocorticoid and thyroid medication, diabetes and hysterectomy)

		B	SE	95% C.I.	R ²
step 1	Gender	16.295	0.692	14.925 to 17.665	0.823
step 2.	Gender	16.462	0.663	15.149 to 17.774	0.839
	AD	-2.497	0.711	-3.905 to -1.089	

Table IIb. Stepwise backward conditional logistic regression analyses showing the variables that predicted the presence of DAT in men (including age, B.M.I., alcohol (ab)use, thryoid and glucocorticoid medication).

	B	SE	O.R.	95% C.I.
TT (nmol/L)	-0.242	0.076	0.785	0.676 to 0.911
Smoking	1.467	0.775	4.337	0.945 to 19.908

diagnosed DAT using NINCDS/ADRDA criteria and have shown earlier that our clinical diagnoses were accurate compared to the histopathologically confirmed CERAD diagnosis of AD [16]. The present results therefore seem to indicate that lower TT may be a co-morbid feature of AD in men. In women, we found no difference in TT levels nor an effect of TT on cognition, which is in agreement with the recent report of Yaffe et al. [31] but in contrast with the findings of Barrett-Connor et al. [12]. The latter authors reported that community dwelling women with low MMSE scores (below 23, the cut-off point for dementia) had lower levels of testosterone. It is possible that our study did not detect differences because of a floor effect. However, we think it unlikely that our failure to confirm the results of Barrett-Connor et al. was due merely to insufficient power in our study because there was a trend for higher TT levels in our female DAT cases.

The present results cannot determine whether our DAT cases had functionally less testosterone. Two factors could lower FT while TT remains normal overall. These are (i) an increase in sex hormone binding globulin (SHBG); or (ii) a change in the pattern of testosterone secretion. Firstly, FT is the active fraction of TT, most of which is inactive (being bound to SHBG). SHBG increases with age [32] and is lower in obesity, type II diabetes, and hypothyroidism [28]. According to a large ageing study [33], age and B.M.I. were the major determinants of SHBG concentrations in older men. Controlling for age, B.M.I., diabetes and thyroid function did not alter the association between serum TT levels and DAT in the present study. However, if SHBG is lower in DAT, then TT would be lower although FT could remain the same. Against this possibility, Abbasi et al. [9] found that both TT and FT levels were lower in institutionalized men with dementia. Also Barrett-Connor et al. [10] found that both lower TT and FT were associated with low cognitive function in men. Second, testosterone has a circadian rhythm and levels are higher in the morning [25]. Although Barrett-Connor stated that the circadian rhythm has less effect on TT levels in the old [10], patients with DAT lack circadian rhythms, so they may not have the morning peaks of TT. The OPTIMA serum samples were obtained in the morning, so apparent lower levels of TT in AD cases could just reflect the disruption of their circadian rhythm. To test this possibility would require repeated measures of TT over the 24-hour cycle and/or taking into account levels of luteinizing hormone (LH).

Our study could also not determine whether the lower TT in men with AD was a cause or an effect of the disorder. Indirect evidence from the literature

suggests that changes in the brain in DAT may cause low TT. This evidence relates to measures of pituitary function. In the study by Abbasi et al. [9], 80% of the elderly men with low FT and TT also had low serum LH and low Insulin-like Growth Factors. These findings could suggest that their low TT was due to hypothalamo-pituitary dysfunction (since primary hypogonadism should raise LH levels, due to failure of negative feedback). Normal ageing decreases hypothalamo-pituitary function and lower levels of testosterone (TT and FT) are found in older men compared to young men [9]. It is unclear whether AD further decreases hypothalamo-pituitary function as an early effect of brain degeneration. For instance, one recent study reported higher levels of FSH and LH in institutionalized demented men compared to age-matched controls [34]. To test this would require long-term prospective assessments of serum TT and LH in subjects before they begin to develop AD. In addition, it is unclear whether lower TT is specific to AD or relates to cognitive impairment in general. Further studies should test whether TT is also lower in men with other types of dementia or neurological degenerative disease.

Even if human studies were to indicate that lower TT results from cognitive impairment in general, there may still be a case for testing whether testosterone protects against AD. Currently, this case rests on data from animal and *in vitro* studies [4–6, 8, 35]. In theory, low testosterone levels could exacerbate the neuronal destruction seen in AD. In practice, however, the evidence that testosterone, or more potent androgens like dehydroepiandrosterone, can preserve cognitive function in healthy older men is still inconclusive [36–39].

In sum, we found that levels of serum TT were lower in men with DAT compared to controls. Our results suggested that low TT may be a co-morbid feature of DAT in men. However, low TT levels could also exacerbate the disease. Prospective longitudinal studies should investigate whether low TT levels precede or follow the onset of DAT.

Acknowledgments

The authors would like to thank members and participants of OPTIMA for making this study possible. Also we would like to thank the staff of the biochemistry laboratory at the John Radcliffe hospital, Oxford, for performing the testosterone assay. This work was supported by a grant from Bristol-Myers Squibb and the Blascko Scholarship.

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