Effect of 12 month oral testosterone on testosterone deficiency symptoms in symptomatic elderly males with low–normal gonadal status

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Abstract

Background: relative androgen deficiency in ageing males is assumed to have adverse health effects. This study assessed the effect of 12 months’ standard dose, oral testosterone, on symptoms attributed to testosterone deficiency in older men with plasma testosterone levels in the low–normal range for young men.

Methods: testosterone undecanoate (TU, 80 mg bid) or placebo was administered for one year to 76 healthy men, 60 years or older, with a free testosterone index (FTI) of 0.3–0.5 and significant symptoms on a questionnaire designed to evaluate androgen deficiency (ADAM). The ADAM was completed at baseline, 6 and 12 months. Hormone and safety data were collected at baseline, 1, 3, 6 and 12 months.

Results: after 12 months, plasma total testosterone was unchanged in both groups and sex hormone binding globulin decreased in the testosterone group (P=0.01). FTI and calculated bioavailable testosterone (cBT) were greater in the testosterone group as compared with the placebo group (P=0.021 and 0.025, respectively). There was no significant difference in total symptom score between testosterone and placebo groups after 12 months of oral TU. However, there were trends toward improvements in sadness/grumpiness (P=0.063), reduced erection strength (P=0.059) and decreased work performance symptoms (P=0.077), particularly in men with baseline cBT levels below 3.1 nmol/l.

Conclusions: this study concludes that 80 mg bid oral TU does not improve overall ADAM questionnaire scores in older men with low–normal gonadal status. Oral TU may preserve mood and erectile function, as assessed by this questionnaire, particularly in men with the lowest testosterone levels.

Keywords: testosterone, ageing, men, androgen deficiency, randomised controlled trial, elderly

Introduction

Plasma total testosterone (TT) levels decline progressively, but variably, over the male lifespan [1–5]. A concomitant increase in plasma sex hormone binding globulin (SHBG) concentration results in an even greater decline in the plasma free and bioavailable fractions of testosterone [6, 7]. Relative androgen deficiency in ageing males is often assumed to have adverse health effects. Efforts to identify the symptom complex associated with low testosterone in older men, if one exists, have been made but are complicated by the slow rate of decline in testosterone levels, concomitant disease, changes in dietary and exercise habits, and the multitude of other physiological changes that occur along a similar time course [8, 9].

In order to identify clinical signs and symptoms of relative androgen deficiency, various screening questionnaires have been proposed. The ADAM (Androgen Deficiency in the Ageing Male) questionnaire was reported to have 88% sensitivity and 60% specificity in identifying Canadian physicians with bioavailable testosterone (BT) <70 ng/dl (2.43 nmol/l) [10]. Furthermore, treatment with testosterone cypionate (200 mg i.m.) improved ADAM questionnaire scores in men with borderline low BT levels (<85 ng/dl (2.95 nmol/l))
was to assess the effect of 12 months of treatment with oral ADAM questionnaire [13, 14]. The aim of the present study was to identify androgen deficiency (plasma testosterone concentration not specified) when a questionnaire score of 18 was used as the cut-off in 32 Lebanese men [12]. These authors further reported that questionnaire scores improved from baseline after 8 months of oral testosterone undecanoate (TU) treatment (120 mg/day) in 76 out of 87 men aged 50–70 years [12]. This study was, however, open and non-comparative in design, thereby limiting interpretation of the data. The Ageing Male Symptoms Scale (AMS) has been also used to evaluate the symptoms of relative hypogonadism in ageing men with comparable performance to the ADAM questionnaire [13, 14]. The aim of the present study was to assess the effect of 12 months of treatment with oral TU on symptoms of testosterone deficiency, in elderly men with two or more symptoms on the St Louis University ADAM questionnaire and a testosterone level in the low–normal range relative to young men.

Materials and methods

Subjects

Seventy-six healthy men aged 60 years or older (68.5 ± 6 years, range 60–86) were recruited by community advertisement. Men were included if they had at least two symptoms on the St Louis University ADAM questionnaire [10], a free testosterone index (FTI) between 0.3 and 0.5 (based on a single value obtained while fasting between 08.00 and 10.00 hours) and TT greater than 8 nmol/l. These cut-offs were established in a series of preliminary studies in which we determined that in men with unequivocal hypogonadism (TT < 8 nmol/l), the FTI was always less than 0.3, and in young (aged 20–30 years) healthy Red Cross blood donors the FTI was greater than 0.5. A second value was obtained at baseline and we have reported the mean of these two values. Exclusion criteria included: a history or presence of prostate cancer or a PSA > 5 ng/ml (the upper limit of normal for men aged 60, as recommended by our institutional laboratory at the time the study commenced); a score of greater than 20 on the International Prostate Symptom Score (IPSS), suggesting significant urinary obstruction [15], and an abnormal prostate on digital rectal examination. Subjects were also excluded if they had a history of testicular, liver or renal disease, diabetes mellitus, cardiac failure, a score of greater than 15 on the Geriatric Depression Scale, significant joint pain, prior use of androgen, bisphosphonates, oral, intravenous or intraarticular glucocorticoid within the preceding 6 months or an haematocrit greater than 50%. The baseline hormonal characteristics of these subjects have been reported previously [16].

The Research Ethics Committee of the Royal Adelaide Hospital approved the study. Informed consent was obtained from all subjects. The study was performed according to International Conference on Harmonisation (ICH)/Good Clinical Research Practice (GCRP).

Study design

Subjects were treated for 12 months with either TU (Andró®, Organon, Oss, The Netherlands) 80 mg orally, twice daily, or identical placebo, in a randomised, double-blind manner. The testosterone or placebo was taken prior to the onset of breakfast and dinner. Assessments were performed at baseline, 1, 3, 6 and 12 months. The dose of testosterone was halfed if the haematocrit increased above 50%.

Randomisation was done using a block design of four in the Almedica Drug Labeling System (Version 5). The drug was well tolerated; there were no serious adverse events. There were 12 withdrawals in the placebo group and six in the testosterone group. Of the subjects completing the study, 69.7% in the testosterone group and 80% in the placebo group took 90% or more of their tablets; 27.3% took between 51 and 89% of their dose in the testosterone group, and 20% did the same in the placebo group.

Measurements

St Louis University ADAM questionnaire

Androgen deficiency symptoms were assessed using the St Louis University ADAM questionnaire [10] at screening, 6 and 12 months.

Laboratory assays

Assay protocols for this study have been reported previously [16]. Briefly, blood was drawn from a forearm vein at baseline between 08.00 and 09.00 hours, prior to the morning dose of testosterone or placebo and after an overnight fast. Serum TT concentration was determined by chemiluminescent immunoassay (Elecsys, Roche, Indianapolis, USA). The inter-assay coefficient of variation (CV) for this assay was 9.3% at a concentration of 10.7 nmol/l. SHBG was analysed in subject serum diluted to 1:21 with SHBG product diluent (DPC IMMULITE SHBG, Diagnostic Products Corporation, Los Angeles, CA). The inter-assay CV was 4.0% at 32.3 nmol/l.

Calculated bioavailable testosterone (cBT)

Bioavailable testosterone was calculated from TT and SHBG concentrations using an equilibrium dissociation constant ($K_d$) of $5.88 \times 10^{-9}$ M [17]. The correlation between cBT values and BT values obtained by the ammonium sulphate precipitation method was 0.96 in 143 healthy male blood donors aged 19–65 years and 0.79 in 131 clinical patients aged 60–88 years, self-selected for symptoms of androgen deficiency [17].

Statistical analyses

Data are reported as mean ± SE, except where otherwise specified. Analyses for the primary outcome measures (St Louis University ADAM symptoms) were performed using an intent-to-treat approach. Where patients had discontinued, their last observations were carried forward in analyses of
subsequent time points to prevent bias due to differential drop-out. All other analyses were performed for all subjects treated. The mean change over time between the treatment and placebo groups for total St Louis University ADAM score was compared using a two-tailed independent sample t-test. The effect of treatment on individual symptoms was analysed using chi-squared tests. Within the Andriol-treated group, the effect of low (<3.1 nmol/l) or normal (≥3.1 nmol/l) baseline cBT levels on each individual symptom was also analysed using chi-squared tests. P < 0.05 was considered significant.

This study was sponsored by Organon Pty Ltd and the University of Adelaide. Organon Pty Ltd was involved in the study design.

**Results**

**At baseline**

There were no differences in TT or cBT between those answering positively and those answering negatively to particular symptoms on the ADAM questionnaire, with the exception that those who were sad and/or grumpy tended to have a higher cBT (P = 0.052) and those falling asleep after dinner had lower TT (P = 0.006) (Table 1). Total ADAM scores were slightly, but not significantly, higher in men with cBT < 3.1 nmol/l at baseline (Table 2).

The frequency of positive ADAM symptoms was similar between the testosterone and placebo groups, with the exception that decreased libido was greater in the placebo group (P = 0.009) and lack of energy tended to be more common in the testosterone group (Table 1).

**Discussion**

This study shows that the overall symptom complex as defined by the St Louis University ADAM questionnaire was not greatly improved by 12 months of oral TU treatment in older men with low–normal testosterone levels. Some

### Table 1. Mean TT and cBT levels for ‘yes’ and ‘no’ responses to symptoms at baseline and the percentages of positively reported ADAM symptoms at baseline (BL) and month 12 (M12), in the testosterone and placebo groups for all subjects and for those with baseline cBT < 3.1 nmol/l

<table>
<thead>
<tr>
<th>St Louis University ADAM Questions</th>
<th>Yes</th>
<th>No</th>
<th>Testosterone</th>
<th>Placebo</th>
<th>Testosterone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TT</td>
<td>cBT</td>
<td>BL M12</td>
<td>BL M12</td>
<td>BL M12</td>
<td>BL M12</td>
</tr>
<tr>
<td>1. Do you have a decrease in libido (sex drive)?</td>
<td>16.3</td>
<td>2.98</td>
<td>15.7</td>
<td>3.08</td>
<td>77%</td>
<td>59%</td>
</tr>
<tr>
<td>2. Do you have a lack of energy?</td>
<td>15.9</td>
<td>3</td>
<td>17.2</td>
<td>3</td>
<td>82</td>
<td>54</td>
</tr>
<tr>
<td>3. Do you have a decrease in strength and/or endurance?</td>
<td>16.2</td>
<td>2.97</td>
<td>16.8</td>
<td>3.2</td>
<td>90</td>
<td>51</td>
</tr>
<tr>
<td>4. Have you lost height?</td>
<td>17.1</td>
<td>3</td>
<td>10.9</td>
<td>15.8</td>
<td>2.96</td>
<td>11</td>
</tr>
<tr>
<td>5. Have you noticed a decreased ‘enjoyment of life’?</td>
<td>15.6</td>
<td>3</td>
<td>16.6</td>
<td>3</td>
<td>30.2</td>
<td>28</td>
</tr>
<tr>
<td>6. Are you sad and/or grumpy?</td>
<td>15.1</td>
<td>3.28</td>
<td>16.6</td>
<td>2.92*</td>
<td>26</td>
<td>11</td>
</tr>
<tr>
<td>7. Are your erections less strong?</td>
<td>16.3</td>
<td>3</td>
<td>29.9</td>
<td>14.6</td>
<td>3.19</td>
<td>95</td>
</tr>
<tr>
<td>8. Have you noted a recent deterioration in your ability to play sports?</td>
<td>15.6</td>
<td>2.93</td>
<td>16.9</td>
<td>3.08</td>
<td>49</td>
<td>48</td>
</tr>
<tr>
<td>9. Are you falling asleep after dinner?</td>
<td>14.8</td>
<td>3</td>
<td>17.4</td>
<td>2.91</td>
<td>38</td>
<td>46</td>
</tr>
<tr>
<td>10. Has there been a recent deterioration in your work performance?</td>
<td>15.8</td>
<td>2.86</td>
<td>16.5</td>
<td>3.08</td>
<td>44</td>
<td>24</td>
</tr>
</tbody>
</table>

Data presented are mean hormone levels and percentages of those who responded ‘yes’ to the question. At BL, decreased libido was less in the testosterone (30/39) than in the placebo (36/37) group (chi-squared = 6.9, P = 0.009). There was a trend towards a difference between the testosterone (32/39) and placebo (24/37) groups for lack of energy (chi-squared = 2.9, P = 0.089). All other individual symptoms of the ADAM were reported with similar proportions. At month 12, decreased libido was less in the testosterone (22/37) than in the placebo (25/30) group (chi-squared = 4.51, P = 0.034), but the proportion of subjects experiencing ADAM symptoms 2–10 were similar. In subjects with cBT < 3.1 nmol/l at baseline, there were trends towards reduction in the number reporting decreased performance at work (P = 0.077) and decreased penile erection strength (P = 0.092) with testosterone treatment at month 12.

*P = 0.052, †P = 0.034, ‡P = 0.006, ¶P = 0.009.
changes in individual symptoms occurred in both placebo and testosterone-treated subjects.

The present study enrolled subjects who had at least two positive symptoms on the ADAM questionnaire at screening rather than the criteria set by Morley et al. [10]. Morley et al. observed that 18 out of 21 patients experienced improvement in ADAM symptoms after 3–4 months of testosterone treatment (TC 200 mg i.m.) [10]. While these men had similar testosterone levels and similar total ADAM scores (5.8 ± 0.5) to the men in the present study, they were younger (57.5 ± 1.6 years), a much higher dose of testosterone was used and this was an uncontrolled, single-group, observational study. In a group of men with much lower TT levels (mean of 7.07 nmol/l) Ghanem et al. [12] showed improvement in similar symptoms in 71 out of 86 men aged 50–70 years, but once again this was an uncontrolled observational study. Improvements in scores obtained on the Aging Male Symptoms Scale (AMS), which has been used to evaluate the symptoms of relative hypogonadism in ageing men, have been noted in uncontrolled studies [13, 14]. Similarly, the study of Park et al. [18], which reported improved St Louis University ADAM scores after 3 months of oral TU treatment (160 mg/day) in 10 men with primary hypogonadism and 29 older men with relative androgen deficiency, was single-blind as opposed to the present study’s double-blind, placebo-controlled design.

The differences at month 12 in sadness/grumpiness and strength of penile erections between the testosterone- and placebo-treated groups in the present study was primarily due to the increased incidence of the symptoms in the placebo group after 12 months, rather than a decreased prevalence due to improvement in the testosterone group. There was, however, a trend to an absolute improvement in erectile strength and work performance, as determined by a change in response to the questions relating to erectile function and work performance on the ADAM questionnaire, in testosterone-treated men with a baseline cBT < 3.1 nmol/l. There was, however, no improvement in any other symptom on the questionnaire with testosterone as opposed to placebo treatment regardless of the baseline testosterone level.

Aversa et al. [19] showed that in men with erectile dysfunction, low free testosterone levels, independent of age, correlated with impaired relaxation of cavernous endothelial and corporeal smooth muscle cells. Moreover, a follow-up study in men with arteriogenic erectile dysfunction, testosterone levels in the lower quartile of the normal range, and who were non-responsive to sildenafil treatment after six attempts, demonstrated that 1 month of transdermal testosterone supplementation improved erectile response to sildenafil [20]. Tariq et al. [21] have also reported reversal of sildenafil failure following testosterone therapy. A number of other studies have suggested enhanced strength and/or maintenance of erections following testosterone or dihydrotestosterone replacement [22–24]. It is therefore plausible that men exposed to testosterone supplementation over the 12 month period of this study may have been protected from decreased cavernosal blood flow and decreased erection strength. Furthermore, a meta-analysis of the usefulness of androgen replacement for erectile dysfunction showed that testosterone-treated patients improve significantly more than placebo-treated patients and that patients with primary testicular failure respond better to treatment than those with secondary testicular failure. Moreover, transdermal therapy is more effective than oral or i.m. therapy [25].

Novak et al. [26] reported that both patients and physicians considered that decreased energy levels and impaired sexual performance had the greatest adverse effect on well-being and quality of life. Moreover, patients generally felt that testosterone replacement led to improvements in energy levels in addition to improvements in libido and erectile function, albeit to a lesser degree. Unlike other studies [22, 23, 27–29], we did not observe enhanced libido with testosterone replacement in older males. Whether the improvement in feelings of sadness and grumpiness in the testosterone-treated subjects is directly related to improvements in erectile function or an independent effect of testosterone cannot be determined from these data. Testosterone supplementation has been reported to decrease anger, irritability, sadness, tiredness and nervousness, and to increase energy level, friendliness and sense of well-being in younger hypogonadal men after 6 months of various modes and doses of testosterone supplementation [30]. We did not observe any benefit on energy levels, strength and endurance, enjoyment of life or ability to play sports, although a small but non-significant improvement in performance at work was observed.

It is important to note that over the treatment period there was also a trend for some of the responses on the questionnaire to improve on placebo alone, highlighting the importance of appropriate placebo-controlled trials in this field. It also suggests that many purported relative androgen deficiency symptoms may be driven by psychosocial factors rather than by low plasma testosterone. There is potential for depression to lead to positive answers on the ADAM questionnaire, particularly for lack of energy, decreased enjoyment of life and sad and/or grumpy items. Tan et al. [31] report the confounding nature of depressive symptoms and concurrent medical conditions in determining whether low androgen levels are responsible for symptoms such as loss of libido, erectile dysfunction and fatigue, in a primary care setting. Mood disorders may be a major reason for the low specificity of the ADAM questionnaire. The confounding effect of depression in the present study is likely to be minimal as depression, as defined by a GDS > 15, was a criterion for exclusion.

The methods used to measure plasma testosterone and the cut-offs that are used to identify low testosterone levels

### Table 2. Mean total ADAM scores in all subjects, testosterone and placebo groups by baseline cBT

<table>
<thead>
<tr>
<th>Baseline cBT</th>
<th>Mean total ADAM score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3.1 nmol/l</td>
<td>≥23.1 nmol/l</td>
</tr>
<tr>
<td>All subjects</td>
<td>5.8</td>
</tr>
<tr>
<td>Testosterone group</td>
<td>5.89</td>
</tr>
<tr>
<td>Placebo group</td>
<td>5.73</td>
</tr>
</tbody>
</table>

There were no differences in total ADAM score within or between the two groups at baseline.
differ widely and potentially affect the outcomes of replacement studies. More sophisticated methods such as the measurement of free testosterone by equilibrium dialysis are not in clinical use.

In general, oral testosterone had no significant effect on symptoms of hypogonadism as evaluated by the ADAM questionnaire in this group of men with borderline-low testosterone levels. The data do indicate relationships between erectile strength as assessed by the ADAM questionnaire and some aspects of mood, androgen levels and responses to androgen supplementation in some men. Nevertheless, taken together, these data do not support the use of the ADAM questionnaire in the evaluation of any particular testosterone level in ageing men and, moreover, do not support a positive ADAM questionnaire as an indication for testosterone replacement therapy in older men with low-normal testosterone levels.

**Key points**
- Standard-dose oral TU supplementation does not improve overall ADAM symptom score.
- Oral TU in older men may preserve mood and erectile function.
- Beneficial responses to oral TU are most likely to occur in men with the lowest bioavailable testosterone levels.

**References**

**Symptomatic impact of testosterone therapy**
Use of the QOL-AD for measuring quality of life in people with severe dementia—the LASER-AD study

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Abstract

Background: health-related quality of life (HR-QOL) scales are particularly important in older people as global outcome measures for interventions. It is known that people with mild to moderate dementia can provide valid assessments of their own QOL, but it is unclear whether these instruments are useful in those with severe dementia.

Objective: we examined the usefulness of the QOL scale in Alzheimer’s disease (QOL-AD) in people with severe dementia by considering the ability of older people with a Mini-Mental State Examination (MMSE) score of <12 and their caregivers to complete this scale, as well as its construct validity and internal consistency.

Methods: data were collected from people with Alzheimer’s disease and their caregivers using a range of instruments measuring cognition, mood, behaviour, QOL and functional ability.

Results: of 79 participants and their caregivers, 41 (52%) could complete the QOL-AD. Cognition and functional abilities were significantly higher in the completers than in the non-completers (P < 0.001). The QOL-AD showed internal consistency and construct validity as it correlated with ability to look after self, fewer limitations due to physical health, positive mood status and low levels of apathy.

Conclusions: there is evidence for the validity and reliability of the QOL-AD in people with MMSE scores of 3–11, as well as the practicality of administering the scale in this population. The scale is unlikely to generate useful information for people with MMSE scores of <3. QOL does not decrease as cognition worsens. This throws into question most people’s assumption that decreasing cognition worsens QOL. We consider that it may be important to inform the public of this, as living wills are used increasingly in our culture.

Keywords: quality of life, dementia, Alzheimer’s disease, outcome measures, reliability and validity, elderly