Effects of two-year testosterone replacement therapy on cognition, emotions and quality of life in young and middle-aged hypogonadal men

L. Lašaitė | J. Čeponis | R. T. Preikša | B. Žilaitienė

Summary
The aim of the study was to examine the effects of two-year testosterone replacement therapy on cognitive functioning, emotional state and quality of life in young and middle-aged men with hypogonadotropic hypogonadism. Nineteen males diagnosed with hypogonadotropic hypogonadism participated in the study. Cognitive functions were assessed by Trail Making Test and Digit Span Test of Wechsler Adult Intelligence Scale. Emotional state was evaluated by Profile of Mood States. Quality of life was evaluated by WHO Brief Quality of Life Questionnaire. Changes after two-year testosterone replacement therapy were detected in Trail Making A (42.9 ± 22.3 vs. 36.2 ± 22.5, \(p = .050\)) and B (90.6 ± 55.3 vs. 65.6 ± 21.4, \(p = .025\)) tests, showing improvement in attention and visual scanning abilities, executive function and psychomotor speed, as well as in Digit Span Test forward score (5.4 ± 2.0 vs. 6.1 ± 2.6, \(p = .046\)), showing improvement in attention capacity and psychomotor speed. No significant differences were observed in emotional state and quality of life. In conclusion, beneficial effect in cognitive functioning (improved attention and visual scanning ability, executive function and psychomotor speed), but not in emotional state and quality of life, was observed in young and middle-aged hypogonadal men after two-year testosterone replacement therapy.

KEYWORDS
cognitive functioning, emotional state, quality of life, testosterone replacement therapy, young and middle-aged hypogonadal men

1 | INTRODUCTION
Hypogonadism can be diagnosed in all age groups, but is most prevalent in older males (Araujo et al., 2007). Hypogonadism manifests itself with a variety of symptoms, which can be of psychological, cognitive, sexual and/or somatic nature (Zitzmann & Nieschlag, 2006). The most prominent symptoms of hypogonadism are loss of libido, erectile dysfunction (Araujo et al., 2007), decreased muscle mass and strength, increased abdominal fat, depressed mood, fatigue (Bhattacharya et al., 2011). Symptomatic presentation tends to vary depending on the patient’s age (Basaria, 2014).

Young adult patients with hypogonadism not only have erectile dysfunction and loss of libido, but may also have other problems such as fatigue, increased body fat, osteoporosis, mild anaemia, gynaeecomastia, sleep disturbances, hair and skin changes (Araujo et al., 2007; Blute et al., 2009; Wang et al., 2004). Young hypogonadal men, especially treatment naïve, have symptoms of anxiety, depression, worse quality of life (Amiaz & Serdman, 2008; Aydogan et al., 2012). In our previous study, we found young hypogonadal men to have impaired emotional state (higher depression–dejection, fatigue–inertia, confusion–bewilderment, and lower vigour–activity) and quality of life (worse psychological health and social relations), but the greatest
impairment was found in cognitive functions (attention and visual scanning abilities, executive functions and psychomotor speed) when compared to healthy age-matched control men (Lašaitė, Čeponis, Preikša, & Žilaitienė, 2014).

After establishing the diagnosis of hypogonadism, testosterone replacement treatment is usually recommended after consideration of absolute and relative contraindications (Zitzmann & Nieschlag, 2006). Testosterone was first synthesised approximately 80 years ago and since then a number of different modalities of testosterone preparations have become available, offering patients various benefits, including enhancements in mood and sexual functioning, among others (Wynia & Kaminetsky, 2015).

Burris, Banks, Carter, Davidson, and Sheris (1992) has shown that in self-reported forms, hypogonadal men scored significantly higher ratings of depression, anger, fatigue and confusion than did normal men. After androgen replacement, these mood scores improved, although hypogonadal men continued to score higher in depression scale than did normal men. This led the authors to conclude that testosterone replacement had some capacity to improve mood. These findings were not confirmed by another study (Morales, Johnston, Heaton, & Clark, 1994) using methyltestosterone in hypogonadal men. Visual analogue scales did not show increases in levels of energy/mood or feeling of well-being between pre- and post-treatment periods. However, men with the most profound deficiency of testosterone were noted to show the most positive response to testosterone (Morales et al., 1994).

Data of different studies on effects of testosterone replacement on emotional state, symptoms of depression and anxiety, quality of life are not consistent. With regard to emotional state, several studies have found testosterone replacement to substantially reduce negative mood states relating to fatigue, depression and self-esteem and suggest that prolonged treatment is likely to maintain these mood benefits (Anderson et al., 1999; O’Connor, Archer, Hair, & Wu, 2001a; Wang et al., 2000). Results of another double-blind, placebo-controlled study have shown that elevation of testosterone to supraphysiological or high normal levels for 2–4 weeks in young hypogonadal men had minor effects (decreased fatigue–inertia and increased anger–hostility remaining well within the normal range), but none on aggressive tendencies or other aspects of behaviour such as assertiveness, irritability, self-esteem or sexual functioning (O’Connor, Archer, & Wu, 2004). No beneficial effects of parenteral testosterone on depression rating scale compared to placebo in hypogonadal men with major depressive disorder were found in randomised, placebo-controlled clinical trial (Seidman, Spatz, Rizzo, & Roose, 2001). In other meta-analysis of trials with depressed hypogonadal patients, testosterone replacement did increase the response on depression rating scales to testosterone treatment versus placebo (Zarrouf, Artz, Griffith, Sirbu, & Kommor, 2009).

Several studies have shown that testosterone replacement therapy improved metabolic state, vitality, libido, ability to concentrate, social functioning and emotional state, quality of life and mental health in hypogonadal men (Andrade, Clapauch, & Buksman, 2009; Aydogan et al., 2012; Moncada, 2006; Yassin et al., 2015; Zitzmann et al., 2013).

Few placebo-controlled randomised studies have reported on testosterone effect on quality of life in men, and the results have been inconsistent (English, Steeds, Jones, Diver, & Channer, 2000; Reddy, White, Dunn, Moyna, & Thompson, 2000). A recent study has found that gonadotrophin treatment for young adult males with hypogonadotropic hypogonadism was associated with significant improvements in quality of life, and these changes were particularly noticeable in the psychological domains (Shiraishi, Okas, & Matsuyama, 2014).

Existing studies on the effect of testosterone on cognitive functions have also produced inconsistent results and have mostly demonstrated only moderate improvement in visuospatial cognition, but not in other domains. Borst et al. (2014), Cherrier et al. (2005) and Janowsky, Ovian, and Orwell (2010) have found improved spatial and visuospatial cognition after testosterone replacement treatment in older hypogonadal men. However, Gray et al. (2005), Haren, Wittert, Chapman, Coates, and Morley (2005), Vaughan, Goldstein, and Tenover (2007) and Young, Neiss, Samuels, Roselli, and Janowsky (2010) have found no changes in cognitive functioning after treatment with testosterone.

So, data on the effect of testosterone replacement therapy on emotional state, quality of life and cognitive functioning in hypogonadal men are quite controversial. Most of the studies have been performed in patients with hypogonadism of different aetiologies, having comorbidities and taking a wide range of medications. Also scientific research on different aspects of hypogonadism in men is focused on the middle-aged and older groups of age, as hypogonadism usually can be diagnosed in those age groups (Mulligan, Frick, Zurrow, Stemhagen, & McWhirter, 2006). The impact of hypogonadism and the effect of testosterone replacement therapy on somatic and psychosocial state, and quality of life in young adult men have not been fully evaluated.

The aim of the study was to examine the effect of two-year testosterone replacement therapy on cognitive functioning, emotional state and quality of life in young and middle-aged men with hypogonadotropic hypogonadism.

## 2 | SUBJECTS AND METHODS

### 2.1 | Subjects

The study was performed in the Department of Endocrinology of Lithuanian University of Health Sciences in Kaunas, Lithuania. The study was approved by Kaunas Regional Ethics Committee of Biomedical Research (No. BE-2-38). All procedures were carried out with adequate understanding and written consent of the subjects.

Twenty-three males diagnosed with hypogonadotropic hypogonadism were recruited for the study, and 19 of them (82.6%) completed through the study (2 years long), showing an excellent retention rate. Of the 19 researched patients, 11 had isolated hypogonadism and 8 had multiple impairments in hypothalamic–pituitary axis. Of the researched patients, 12 were treatment naïve, while 7 had received the first injection of testosterone undecanoate within a period of 6 weeks prior to the analysis. At the time of enrolment, 1 of the...
participants had testosterone concentration in the upper normal range (46 nmol L⁻¹). A different assay was used for testosterone measurement prior to commencing therapy in those subjects, which may not be directly compared to that used throughout our study.

None of them had either comorbid psychiatric disorders (such as major depressive disorder, dementia or anxiety disorder), or any organic cerebral disorder, or any chronic uncontrolled, untreated somatic disease at the period of the study (as evaluated by treating physician).

Baseline anthropometric and hormonal characteristics of the participants are presented in Table 1. Age of the participants was 30.5 ± 12.7 (18–56) years. Of the studied hypogonadal men, 15 were younger than 30 years, and 4 were older than 30 years of age (one of them was 56 years of age and 3 of them were between 30 and 40). Despite the age, based on the clinical features, the oldest subject had pre-pubertal onset hypogonadism, however has never been diagnosed and treated.

Social status of the participants (education, marital state and employment state) was evaluated. Education of participants was evaluated as: (i) secondary or lower, (ii) special professional and (iii) university. Of the 19 subjects, 12 (63.1%) had secondary or lower education, 4 (21.1%) had special professional education, and 3 (15.8%) had university education. Marital status was evaluated as: (i) married or cohabitating, (ii) single. Of the 19 patients, 5 (26.3%) were married or cohabitating, 4 (21.1%) had special professional education, and 14 (73.7%) were single. Employment state was evaluated as: (i) still studying, (ii) employed, (iii) unemployed and (iv) disabled. Of the 19 patients, 3 (15.8%) were still studying, 8 (42.1%) were employed, 2 (10.5%) were unemployed, and 6 (31.6%) were disabled.

### 2.2 Objective data

Anthropometrical measurements were performed according to WHO guidelines (World Health Organization, 1995). Body mass index (BMI) was calculated as weight (kg) per height (metres) squared (Garrow & Webster, 1985).

### 2.3 Testosterone replacement therapy

All patients underwent regular replacement therapy with testosterone undecanoate (TU) 1,000 mg – 4 ml intramuscular injections every 10–14 weeks with interval titrated to optimal testosterone serum levels (17.6–34.1 nmol L⁻¹; Čeponis, 2014). The time of an upcoming TU injection was determined based upon serum testosterone level prior to previous injection. As per label recommendations, a booster dose at 6 weeks after initiation was given to subjects so that optimal testosterone levels were achieved sooner.

### 2.4 Psychological assessment

Cognitive functions were assessed by Trail Making Test (Retain & Tarshes, 1959) and Digit Span Test (DST) of Wechsler Adult Intelligence Scale (Wechsler, 1981). Trail Making Test is a timed test in which the subject connects an altering sequence of numbers (Trail Making A) or numbers and letters (Trail making B) in ascending order. The score on the Trail Making A test, which is based on time required to complete the sequence, is a measure of attention and visual scanning abilities. Trail Making B is a test of executive function and psychomotor speed. Executive function includes those brain processes that guide action in accordance with internally generated ideas (i.e. planning and strategising; Kortte, Horner, & Windham, 2002). A higher score denotes a worse cognitive functioning.

Digit Span Test is a test in which the subject repeats sequences of numbers in a given order. The score of the test is a number of repeated number sequences in forward order and backward order. The test shows attention capacity and psychomotor speed. A higher score denotes a better cognitive functioning.

Emotional state was evaluated by means of Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1992). It measures total score and six subscales: tension–anxiety, depression–dejection, anger–hostility, vigour–activity, fatigue–inertia and confusion–bewildermend. A higher score represents a higher level of certain emotion.

Quality of life was evaluated by WHO Brief Quality of Life Questionnaire (WHOQoL; World Health Organization, 1998). It measures four domains: physical, psychological, social and environmental. A higher score represents a better quality of life.
2.5 | Statistical analysis

Analysis was performed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). The values are given as mean ± standard deviation also median and 25th, 75th percentile. The differences between the baseline values and those after 2 years of treatment were calculated using Wilcoxon test. Associations between somatic and psychological data were determined using Pearson correlation coefficient. The limit of significance was defined as a two-sided p-value lower than .05.

3 | RESULTS

Comparison of cognitive functioning data before and after two-year testosterone replacement therapy in young and middle-aged hypogonadal men is presented in Table 2. Significant differences were detected in Trail Making B test (p = .025), showing improvement in executive function and psychomotor speed, as well as in Digit Span Test forward score (p = .046), showing improvement in attention capacity and psychomotor speed. Borderline significance was found in Trail Making A test (p = .050), showing improvement in attention and visual scanning abilities.

Comparison of emotional state before and after 2-year testosterone undecanoate replacement therapy in young and middle-aged hypogonadal men is presented in Table 3. No significant difference was observed in any of POMS domains.

Comparison of quality of life data before and after 2-year testosterone undecanoate replacement therapy in young and middle-aged hypogonadal men is presented in Table 4. No significant difference was observed in any of Quality of Life Questionnaire domains.

The following significant correlations between hormone concentrations and psychological factors (Table 5) were detected: negative moderate correlation between FT4 concentration and Trail Making B test (r = -.415, p = .023); positive moderate correlations between PRL concentrations and Digit Span Test forward score (r = .373, p = .025), POMS total score (r = .407, p = .015), POMS confusion–bewilderment (r = .336, p = .049), positive strong correlation between PRL concentrations and POMS depression–dejection (r = .527, p = .001), negative moderate correlations between PRL concentrations and quality of life psychological (r = -.343, p = .044) and social (r = -.485, p = .003) domains; positive moderate correlation between SHBG concentration and quality of life social domain (r = .335, p = .049); negative moderate correlation between BMI and quality of life social domain (r = -.307, p = .045).

4 | DISCUSSION

The data of our study revealed that two-year testosterone replacement therapy had beneficial effect only on cognitive functioning (attention and visual scanning abilities, executive function and psychomotor speed), but not on emotional state and quality of life in relatively young hypogonadal men.

Data of several studies have shown that testosterone supplementation slightly improves visuospatial cognition (Borst et al., 2014; Janowsky et al., 2010) and working memory (Janowsky, Chavez, & Orwell, 2000), although other (Gray et al., 2005; Haren et al., 2005; Vaughan et al., 2007; Young et al., 2010) have found no changes in cognitive functions after testosterone treatment in elderly men. Alexander (Alexander et al., 1998) have found only enhancement of verbal fluency in hypogonadal men after androgen replacement. Several studies have found increased testosterone level to have an effect on cognitive functions, inhibiting spatial abilities and improving verbal fluency, slowing psychomotor speed and reaction time (O’Connor, Archer, Hair, & Wu, 2001b; Salminen, Portin, Koskinen, Helenius, & Nurmi, 2004). It was shown that visuospatial cognition improves in a dose-dependent manner (Gray et al., 2005). But, similar effects were not found in younger healthy men (Bhasin et al., 2001).

Differences in results among studies could be due to the age of participants, their cognitive status, severity of hypogonadism, the degree to which testosterone levels were replaced by the treatment and the small sample size possibly resulting in sample bias. The cognitive measures and processes assessed varied in sensitivity and differed from study to study. The definition of hypogonadal and exclusion of subjects with depression or cognitive impairment

<table>
<thead>
<tr>
<th>TABLE 2 Differences of cognitive functions at baseline and after 2 years of testosterone replacement therapy in young and middle-aged hypogonadal men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Trail Making Test—Aa</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Trail Making Test—Bb</td>
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<tr>
<td></td>
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<tr>
<td>Digit Span Test, forwards scorec</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Digit Span Test, backwards scored</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*a A higher score denotes a worse cognitive function.  
*b A higher score denotes a better cognitive function.
varied widely among studies. Any one of these factors might have been crucial for finding effects of testosterone replacement treatment (Janowsky, 2006).

Christiansen (1993) found that serum concentrations of total testosterone in saliva exhibited a positive relation to tactual-spatial tests. Celec, Ostatnikova, Putz, and Kudela (2002) have revealed significant differences between visuospatial test performances during high-testosterone compared to low-testosterone phases in both genders. In our previous study, we provided some evidence that endogenous testosterone level is related to attention, visual scanning abilities, executive function and psychomotor speed in a cohort of young adult healthy males (Žilaitienė, Lašaitė, Žilaitytė, & Matulevičius, 2006).

In our other study, in a cohort of young adult hypogonadal men, we found testosterone level to be correlated only to psychological domain of quality of life (Lašaitė et al., 2014).

Studies on effects of current free testosterone have variously reported either linear (Christiansen, 1993), quadratic (Celec et al., 2002) or no association (Alexander et al., 1998) with perceptual and cognitive abilities. Findings of Falter (Falter, Arroyo, & Davis, 2006) and Manning and Taylor (2001) suggested a substantial role for prenatal testosterone but not current testosterone in determining cognitive performance, although Rahman, Wilson, and Abrahams (2004) did not confirm it. Beneficial cognitive effects of testosterone may result directly via androgen receptor-depending mechanism or indirectly following conversion of testosterone to dihydrotestosterone (DHT) by 5-alpha reductase and to estradiol by aromatase (Giatti, Boraso, Melcangi, & Viviani, 2012; Lim, Flicker, Dharamarajan, & Martins, 2003). There is evidence that DHT specifically reduces neuroinflammation (Giatti et al., 2012).

Androgen receptors (ARs) are present throughout life in cortical regions that are crucial for learning and memory including hippocampus (Beyenburg et al., 2000), pre-frontal cortex (Finley & Kritzer, 1999) and amygdala (Abdelgadir, Roselli, Choate, & Resko, 1999), but are not found in other cortical regions of the brain (Kritzer, 2004).

It has been demonstrated that AR polymorphism is related to emotional state of ageing males. Patients with psychosomatic and andrological disorders have significantly longer AR CAG repeats, higher depression and anxiety levels, if compared to the subjects from the general population. At the same time, their testosterone levels did not differ significantly (Schneider et al., 2011a, 2011b). So, sensitivity of AR should be taken into the consideration along with the other factors.

### TABLE 3 Differences of emotional state at baseline and after 2 years of testosterone replacement therapy in young and middle-aged hypogonadal men

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Minimum-maximum values</th>
<th>Median (25–75 percentile)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>POMS total score†</td>
<td>Baseline 28.2 ± 29.7</td>
<td>-23 to 91</td>
<td>28 (4–47)</td>
<td>.653</td>
</tr>
<tr>
<td></td>
<td>After 2 years 25.4 ± 29.2</td>
<td>-26 to 105</td>
<td>28 (5–39)</td>
<td></td>
</tr>
<tr>
<td>POMS tension–anxiety†</td>
<td>Baseline 7.7 ± 5.8</td>
<td>0–21</td>
<td>8 (3–13)</td>
<td>.948</td>
</tr>
<tr>
<td></td>
<td>After 2 years 7.4 ± 4.8</td>
<td>0–22</td>
<td>7 (5–9)</td>
<td></td>
</tr>
<tr>
<td>POMS depression–dejection†</td>
<td>Baseline 11.2 ± 9.2</td>
<td>0–34</td>
<td>9 (5–15)</td>
<td>.842</td>
</tr>
<tr>
<td></td>
<td>After 2 years 10.6 ± 8.7</td>
<td>0–35</td>
<td>9 (4–15)</td>
<td></td>
</tr>
<tr>
<td>POMS anger–hostility†</td>
<td>Baseline 11.2 ± 8.4</td>
<td>1–29</td>
<td>11 (3–15)</td>
<td>.586</td>
</tr>
<tr>
<td></td>
<td>After 2 years 9.6 ± 5.9</td>
<td>2–25</td>
<td>9 (5–13)</td>
<td></td>
</tr>
<tr>
<td>POMS vigour–activity†</td>
<td>Baseline 15.2 ± 5.2</td>
<td>27–1</td>
<td>15 (18–14)</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>After 2 years 15.4 ± 5.1</td>
<td>28–6</td>
<td>16 (18–12)</td>
<td></td>
</tr>
<tr>
<td>POMS fatigue–inertia†</td>
<td>Baseline 9.1 ± 5.9</td>
<td>0–19</td>
<td>8 (5–14)</td>
<td>.628</td>
</tr>
<tr>
<td></td>
<td>After 2 years 8.8 ± 5.6</td>
<td>0–18</td>
<td>8 (5–14)</td>
<td></td>
</tr>
<tr>
<td>POMS confusion–bewildement†</td>
<td>Baseline 4.3 ± 4.5</td>
<td>3–13</td>
<td>4 (1–7)</td>
<td>.306</td>
</tr>
<tr>
<td></td>
<td>After 2 years 5.2 ± 4.8</td>
<td>4–15</td>
<td>5 (2–10)</td>
<td></td>
</tr>
</tbody>
</table>

POMS, Profile of Mood States.
†A higher score denotes a worse emotional state.
‡A higher score denotes a better emotional state.

### TABLE 4 Differences of quality of life at baseline and after 2 years of testosterone replacement therapy in young and middle-aged hypogonadal men

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Minimum-maximum values</th>
<th>Median (25–75 percentile)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical domain†</td>
<td>Baseline 15.7 ± 2.6</td>
<td>10–19</td>
<td>16 (14–18)</td>
<td>.393</td>
</tr>
<tr>
<td></td>
<td>After 2 years 15.2 ± 2.2</td>
<td>11–19</td>
<td>16 (13–17)</td>
<td></td>
</tr>
<tr>
<td>Psychological domain†</td>
<td>Baseline 13.5 ± 2.8</td>
<td>9–17</td>
<td>14 (11–16)</td>
<td>.490</td>
</tr>
<tr>
<td></td>
<td>After 2 years 13.3 ± 2.6</td>
<td>9–19</td>
<td>14 (11–15)</td>
<td></td>
</tr>
<tr>
<td>Social domain†</td>
<td>Baseline 14.1 ± 2.4</td>
<td>11–19</td>
<td>13 (12–15)</td>
<td>.240</td>
</tr>
<tr>
<td></td>
<td>After 2 years 13.6 ± 2.8</td>
<td>9–20</td>
<td>13 (12–16)</td>
<td></td>
</tr>
<tr>
<td>Environmental domain†</td>
<td>Baseline 14.3 ± 1.9</td>
<td>12–18</td>
<td>14 (13–16)</td>
<td>.156</td>
</tr>
<tr>
<td></td>
<td>After 2 years 14.6 ± 1.9</td>
<td>11–19</td>
<td>15 (14–16)</td>
<td></td>
</tr>
</tbody>
</table>

†A higher score denotes a better quality of life.
TABLE 5  Significant correlations between hormone concentrations and psychological evaluations in young and middle-aged hypogonadal men

<table>
<thead>
<tr>
<th>Significant correlations between</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT₅ concentration (pmol L⁻¹)</td>
<td>Trail Making Test, B</td>
<td>−.415</td>
</tr>
<tr>
<td>PRL concentration (mU L⁻¹)</td>
<td>Digit Span Test, forward score</td>
<td>.373</td>
</tr>
<tr>
<td>PRL concentration (mU L⁻¹)</td>
<td>POMS total score</td>
<td>.407</td>
</tr>
<tr>
<td>PRL concentration (mU L⁻¹)</td>
<td>POMS depression-dejection</td>
<td>.527</td>
</tr>
<tr>
<td>PRL concentration (mU L⁻¹)</td>
<td>POMS confusion-bewilderment</td>
<td>.336</td>
</tr>
<tr>
<td>PRL concentration (mU L⁻¹)</td>
<td>Quality of life, psychological domain</td>
<td>−.343</td>
</tr>
<tr>
<td>PRL concentration (mU L⁻¹)</td>
<td>Quality of life, social domain</td>
<td>−.485</td>
</tr>
<tr>
<td>SHBG concentration (nmol L⁻¹)</td>
<td>Quality of life, social domain</td>
<td>.335</td>
</tr>
<tr>
<td>BMI, kg m⁻²</td>
<td>Quality of life, social domain</td>
<td>−.307</td>
</tr>
</tbody>
</table>

as assessed by the Beck Depression Inventory, and men reporting a higher number of adverse life events in the previous 6 months had low PRL levels (Corona et al., 2014). PRL is involved in response to stress. It has been demonstrated that intraventricular administration of PRL in rats is able to reduce anxiety-related behaviours (Torner, Toschi, Pohlunger, Landgraf, & Neumann, 2001). Serum PRL levels change during different psychosocial conditions; in particular, higher PRL levels are found when stressful events are faced with a passive coping attitude, whereas during active coping, lower PRL levels are observed (Theorell, 1992). While a direct role for impaired PRL function in the pathogenesis of the reproductive, sexual, metabolic and psychological disorders is conceivable, the possibility that low PRL is a mirror of a decreased serotonergic tone can be ruled out. Indeed, a hyposerotonergic tone fits well with the clinical features associated with low PRL, and there is significant evidence supporting the hypothesis that PRL could be a mirror of serotonin in the brain (Rastrelli et al., 2015).

Our study also revealed negative correlation between BMI and quality of life social domain. There is an increasing body of evidence indicating a beneficial effect of testosterone treatment on visceral fat and other components of the metabolic syndrome in hypogonadal men (Jones et al., 2011). Part of the beneficial effects of testosterone on mental well-being and sexual well-being may be mediated through weight reduction and a change in the distribution of body fat (Giltay et al., 2010). As shown in long-term registries (Saad, Yassin, Doros, & Haider, 2016), weight loss is more pronounced, the more obese subjects are at baseline. In our study, we did not find significant reduction of BMI after 2 years of testosterone replacement, even in three participants with BMI higher than 25 kg m⁻².

Data of our study did not show any significant improvement in quality of life after 2-year testosterone replacement therapy. Similarly, as in our previous study on psychological state and quality of life in hypogonadal men in comparison with healthy age-matched men (Lašaitė et al., 2014), the baseline quality of life evaluation of this study showed that relatively young hypogonadal men have impaired psychological and social domains, but not impaired physical and environmental domains. Unfortunately, we found no significant improvement, even in the most significantly impaired domains after 2 years of testosterone replacement in this group of relatively young hypogonadal men. Although results of our studies indicate that testosterone is associated with a decreased serotonergic tone,
were mostly middle-aged or elderly. But in the study with young adult men taking a wide range of medications, also the subjects of the studies of hypogonadism of different aetiologies, having several comorbidities on depression symptoms compared with placebo in hypogonadal men, improvement was also observed in depression and anxiety scores after testosterone replacement therapy (Aydogan et al., 2012). In an animal model, it was revealed that effect of testosterone on depression is dose dependent (Buddenberg, Komorowski, Ruocco, Silva, & Topic, 2009).

The anxiety seems to be most sensitive to testosterone. It was shown in several experiments that testosterone, either endogenous or exogenous, decreased anxiety in animal models; this anxiolytic effect of testosterone was shown to be dose dependent (Aikey, Nyby, Annuth, & James, 2002). Similar anxiolytic effect of single testosterone administration resulted in reduced fear of healthy women (Van Honk, Peper, & Schutter, 2005). In rats, single testosterone injection did not reduce anxiety; however, a repeated administration had anxiolytic effect (Fernandez-Guasti & Martinez-Mota, 2005). Association between testosterone and anxiety might be not linear (Celec, Ostatnikova, & Hodosy, 2015). An important determinant of the postnatal association between anxiety and testosterone or its metabolites might be prenatal stress. Stress induced during gestation resulted in both reduced testosterone level and increased anxiety of the adult offspring (Walf & Frye, 2012).

Testosterone concentration has been linked particularly to risky decision-making. Some data indicate (Stanton, Mullette-Gillman, & Huettel, 2011) that females and males with high testosterone levels show more risky behaviour than those with low testosterone concentrations, with a more pronounced effect in women. Moreover, individuals with higher levels of endogenous testosterone are not only more likely to demonstrate tendencies towards dominance, aggression and risk-taking but also less likely to appreciate potential dangers to their physical well-being (Mehta & Josephs, 2011; Ristvedt, Josephs, & Liening, 2012). A recent study (Reimers & Diekhof, 2015) provided evidence that testosterone does not only promote antisocial behavioural tendencies, but also facilitates altruism. This was shown to be specifically the case during an inter-group competition in human males. In this context, testosterone was predictive of parochial altruism (i.e. the favourable treatment of in-group members, whereas aggression was directed towards the out-group) and thus was associated with both aggressive and cooperative behaviour depending on group membership and competition. Results of this study are in line with previously stated theories on male coalition building (i.e. “male warrior hypothesis”); Van Vugt, De Cremer, & Janssen, 2007) and evolutionary theories on the development of altruism and parochialism (Choi & Bowles, 2007). They propose testosterone to play a key role in these social mechanisms.

Elevation of testosterone to supraphysiological or high normal values for 2–4 weeks was shown to have significant, although minor effects on mood, but none on aggressive tendencies, irritability and self-esteem. Specifically, testosterone undecanoate administration was associated with significant increases in POMS anger–hostility scores from baseline to week 2, compared with a reduction in anger–hostility over the same time period in the placebo phase, but the magnitude of the observed change in the study was comparatively minor and remaining within the normal range (O’Connor et al., 2004). Testosterone undecanoate was also found to have positive effect on overall POMS fatigue–inertia with participants reporting significantly lower levels on placebo (O’Connor et al., 2004). However, other studies using other testosterone preparations (e.g. testosterone enanthate) have not found any effect of testosterone on fatigue in healthy normal men (Alexander et al., 1997), although effects of testosterone replacement on mood (reduced fatigue and improved vigour) have been found in hypogonadal men (O’Connor et al., 2001a). It is possible that the absent effect of testosterone enanthate on fatigue could be a result of the wide fluctuations of testosterone levels generated by short-acting injections in contrast to testosterone undecanoate.

Testosterone replacement in hypogonadal men has shown to improve some of their positive mood parameters (friendliness, energy levels) and decrease their negative mood parameters (anger, irritability, sadness, tiredness). Improvement in mood was present early in 3-week course of testosterone replacement. Prolonged treatment (up to 6 months) maintained but did not further improve these mood changes (Wang et al., 1996).

The time-course of the spectrum of effects of testosterone shows considerable variation, probably related to pharmacodynamics of the testosterone preparation, genomic and nongenomic effects, androgen receptor polymorphism and intracellular steroid metabolism (Saad et al., 2011).

Several studies have reported an improvement in depression after 3 weeks (Jockenhövel et al., 2009) or 1 month (Malkin et al., 2004) or after 6 weeks (Perry et al., 2002) or 8 weeks (Pope et al., 2003) of testosterone replacement in hypogonadal men. A number of psychological variables (increase in sociability, decrease in anxiety, increase in concentration and self-confidence) were apparent after 3 weeks (Jockenhövel et al., 2009). A decrease in fatigue and listlessness was found after 1 month (Boyano, Bonova, & Christov, 2003) or 6 weeks (Jockenhövel et al., 2009). Improvement in quality of life was noted after 1 month of testosterone treatment (Malkin et al., 2004). A transient increase in anger–hostility was found in eugonadal men whose testosterone levels were raised above normal after 3 weeks (O’Connor et al., 2004).

Similarly, effects of testosterone administration in hypogonadal men on the ability to process spatial data of visual content were observed within 2 weeks of treatment (Zitzmann et al., 2001). These effects are directly related to testosterone and not its aromatisation product estradiol as it was later confirmed in a placebo-controlled study involving aromatase inhibitor combined with testosterone administration in hypogonadal men. These patients exhibited a markedly improved spatial memory within 3 weeks, improving further until week 6 (Cherrier et al., 2005).
It is likely that the positive effects of testosterone on emotional state start as early as after 3–6 weeks, but will most likely take 18–30 weeks to find a patient with significant improvement (Saad et al., 2011). So, effects on psychological variables, as well as on libido and on vasculature, occur rather rapidly. It may well be that these effects are not mediated via the classical androgen receptor but through other mechanisms like effects on membranes (Foradori, Weiser, & Handa, 2008; Malkin, Jones, Jones, & Channer, 2006). It may also be possible that effects on psychosexual variables are secondary to changes in body composition and anthropometry (weight loss, reduction of waist circumference; Giltay et al., 2010), and this may take more time than the short-term effects mentioned in the review by Saad et al. (2011).

This study may have several limitations. The main limitation is that numerous variables were examined in a small sample size. Besides, there was lack of data regarding concomitant medication use for other health problems or diseases as some of the patients had impairments of other pituitary axes. Despite the limitations, our data are important in gaining a better understanding of the testosterone replacement therapy effects on psychological aspects associated with hypogonadism in relatively young men. As advantages of the study we could mention an excellent retention rate (82.6%), the fact that all testosterone replacement injections were performed by the investigators at the study site, therefore providing full medication adherence, as well as the long duration of the study, becoming one of the longest studies performed on the effect of testosterone replacement on psychological state. The homogeneity of our study population regarding relatively young age of participants could be seen as main advantage, as most of the previous studies, except few (Aydogan et al., 2012; Jockenhövel et al., 2009), were focused on testosterone replacement effects in the middle-aged or elderly hypogonadal men.

In conclusion, beneficial effect in cognitive functioning (improved attention and visual scanning ability, executive function and psychomotor speed) but not in emotional state and quality of life was observed in young and middle-aged hypogonadal men after 2-year testosterone replacement therapy.

Evaluation of men suffering from hypogonadism (not only elderly, but also young adults) and undergoing testosterone replacement therapy should not be limited to metabolic and functional parameters alone, but should also address psychological aspects and quality of life; if any psychological problems are found, they should be managed and followed up by a specialists.

REFERENCES


